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Alzheimer's Disease: Recent Advancements in Therapeutics and Screening

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Abstract

Alzheimer's disease is the leading cause of dementia and has a current global prevalence of over 55 million individuals. Despite its high prevalence, there is currently no cure for the neurodegenerative disease. AD is characterized by an accumulation of the misfolded amyloid-beta protein, forming Aβ plaques and an abundance of the hyperphosphorylated tau protein in the brain. The accumulation of these abnormal proteins in the brain leads to synaptic dysfunction, neuronal death, and brain tissue degradation. These studies lead to symptoms such as loss of memory, language, and intellectual thinking, eventually leading to the patient being bedridden, and eventually, death. Another detrimental effect of Alzheimer's is the negative financial and emotional effect on caregivers. Because of these issues, there is a drive to better understand the pathology of AD and find a cure. Recent studies have aimed to find a connection between Alzheimer's and other chronic illnesses, as well as find an encompassing treatment for AD. Studies have shown efficacy using various therapies involving stem cells, lithium, gut microbiota, and genetic targets. Recent advancements in screening techniques such as plasma-based biomarkers and neuroimmune infiltration could allow earlier detection of AD, and therefore a better chance at preventing or postponing clinical onset. All these studies and recent developments will be discussed in this paper.

Keywords: Alzheimer's disease, Dementia, Treatments

1. Introduction

1.1 Overview of Alzheimer's Disease

Despite Alzheimer's Disease being the leading cause of dementia and the 6th leading cause of death in the United States, there is currently no encompassing treatment or cure for the progressive disease [1]. Globally speaking, there is a current prevalence of over 55 million people who have been diagnosed with the disease, with about 10 million new cases arising annually [2]. Demographically, Alzheimer's is more common in men than women and is most common in Native Americans and people of European descent [3].

APOE Pair	African Americans	European Americans	American Indians †
e3/e3	45.2	63.4	71.6–73.2
e3/e4	28.6	21.4	22.7–23.9
e3/e2	15.1	10.2	2.6–3.0
e2/e4	5.7	2.4	0.5
e4/e4	4.5	2.4	1.0–1.2
e2/e2	0.7	0.2	0.0–0.1

Figure 1: An analysis of the prevalence of certain APOE pairs in individuals of different racial backgrounds [3].

(a) (b)

Figure 2: Comparisons of the prevalence of AD onset between (a) men and women and by (b) age [3].

Along with causing issues for patients, Alzheimer's and associated dementia also cause dilemmas and financial burdens for the healthcare field and for caregivers, as there is currently a $339 million unpaid dementia care deficit. Caring for somebody with AD also comes with emotional distress, negative emotional and physical health, and loss of time, as patients tend to require around the clock care [1].

For the patients, Alzheimer's exhibits a variety of symptoms, and the onset of these symptoms varies greatly from patient to patient. Symptoms can be dependent on the age of onset, genetic factors, overall health, smoking, traumatic brain injuries, and other factors [1]. Since AD is a progressive disease, these symptoms can accumulate over time in an individual and tend to worsen as the disease develops. The first symptoms that a patient displays tend to be related to a general loss of memory, language, and intellectual thinking. The patient can exhibit changes in mood, personality, and behavior that can include depression, apathy, and aggression that was previously uncharacteristic for them [3]. Another symptom that may arise during this time is wandering, which can be dangerous for the individual. Later symptoms may include issues with walking and swallowing, leaving them bedridden and in need of continuous care. These patients also have difficulty speaking or communicating with others. Alzheimer's disease tends to lead to death, and in most cases, tends to occur between 4-8 years after diagnosis [3].

Due to the emotional and financial burden on the healthcare system and on caregivers as well as the detrimental nature of the disease on the patients themselves, there is a dire need for an effective treatment or cure for Alzheimer's disease.

1.2 Pathophysiology of AD

Alzheimer's disease is characterized by an accumulation of abnormal proteins in the brain, including beta-amyloid and hyperphosphorylated tau, which leads to neuronal death and damage to brain tissue [2]. Over the course of time, this causes inflammation and atrophy of the brain, leading to the characteristic symptoms that were previously discussed.

The amyloid cascade hypothesis is described as when neuronal deposition of **Aβ** peptides misfold into amyloid plaques [2]. Amyloid plaques come in many morphological forms, but generally are formed when the amyloid precursor protein is cleaved by proteolytic enzymes [1]. Specifically, when the amyloid precursor protein (APP) is cleaved by a **β**-secretase, it forms the C99 fragment and soluble APP. This C99 fragment is further cleaved by **γ**-secretase to form **Aβ** and APP intracellular domain (AICD) [4]. It is believed that this accumulation of the amyloid-beta protein and amyloid plaques in the brain leads to the hyperphosphorylation of the tau protein [2].

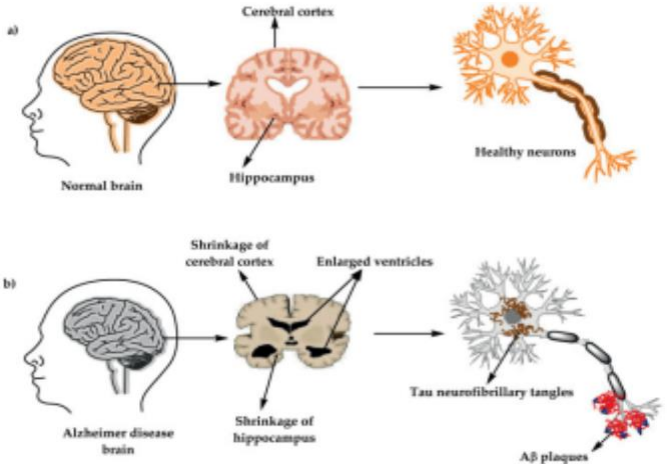

Figure 3: The physiological structure of the brain and neurons in (a) healthy brain and (b) Alzheimer's disease brain [1].

Neurofibrillary tangles (NFTs) occur when the tau protein, which is essential for microtubule assembly, gets hyperphosphorylated and accumulates intracellularly. NFTs are one of the main pathological signs of AD. Due to the hyperphosphorylation, tau no longer displays strong affinity towards microtubules and loses some resistance to calcium-activated neutral proteases. Due to the intracellular accumulation of NFTs and the extracellular accumulation of amyloid plaques, synaptic dysfunction within the nervous system begins to occur [1].

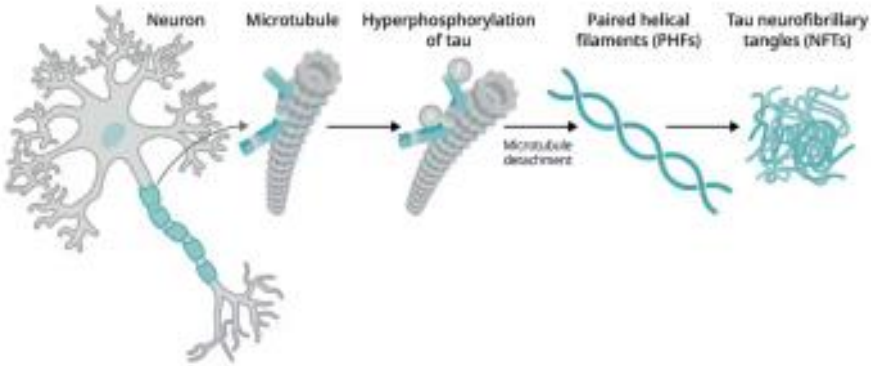

Figure 4: Formation of Neurofibrillary Tangles (NFTs) by the tau protein in tauopathies such as Alzheimer's disease. Under pathological conditions, tau becomes hyperphosphorylated and detaches from microtubules. Phosphorylated tau then aggregates to form paired helical filaments (PHFs) and NFTs [1].

1.3 AD History

Alzheimer's disease was first brought to light by Alois Alzheimer in 1906, who discovered the abnormal symptoms in the cerebral cortex in one of his patients. Despite this discovery, the first hypotheses about AD did not come out until the 1980s, when probable Alzheimer's disease was characterized as a condition that shows association between amnestic dementia and the presence of neurotic plaques containing A**β** and neurofibrillary tangles including tau [1]. This gap in information is because researchers at the time had not yet recognized AD as its own entity [5]. Towards the end of the 20th century, components of pathological hallmarks and genetic subtypes were identified. In recent years, biomarkers and new technologies have changed the view on Alzheimer's from a basic idea of an amnestic dementia to a disease that could be clinically manifested as a normal cognition or as different types of dementia [5]. Currently, there are two pharmacologic therapy classes that do not cure or reverse the effects of Alzheimer's, but can alleviate some symptoms of AD. These two classes are cholinesterase inhibitors and N-Methyl-D-aspartate receptor antagonists. These two drugs can work when taken together to deliver neuroprotection in patients with mild to severe Alzheimer's disease [1].

Although the current treatments for AD can help alleviate some symptoms, there is a worldwide drive to create a cure that targets amyloid-beta plaques and NFTs and a need for a screening method that can help catch the disease before clinical onset [1].

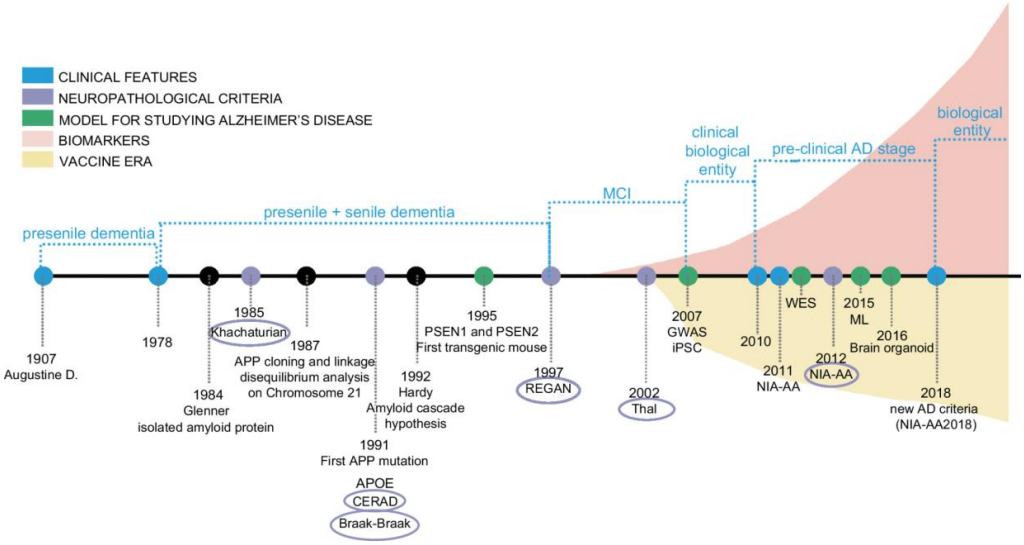

Figure 5: The milestones of AD history [5].

2. Discussion

2.1 Lithium Therapies and Ties to Bipolar Disease

A field of study that has come to light in the last few years is the correlation between Alzheimer's and bipolar disorder and the potential use of lithium as a therapy for AD. It has been seen that patients with BPD have an increased chance of receiving a dementia diagnosis compared to other patients of the same age, so much that individuals aged 65-84 with BPD may have double the likelihood of developing AD compared to their non-BPD counterparts [1].

Despite this trend, patients who have consistently been taking lithium to treat BPD for many years did not have this problem. Dementia is characterized by a degradation of brain tissue, primarily in the hippocampus region. Patients who have been receiving constant lithium treatment did not display this same degradation as much as those who had not been taking lithium, leaving scientists to wonder if lithium possessed neuroprotective properties [1].

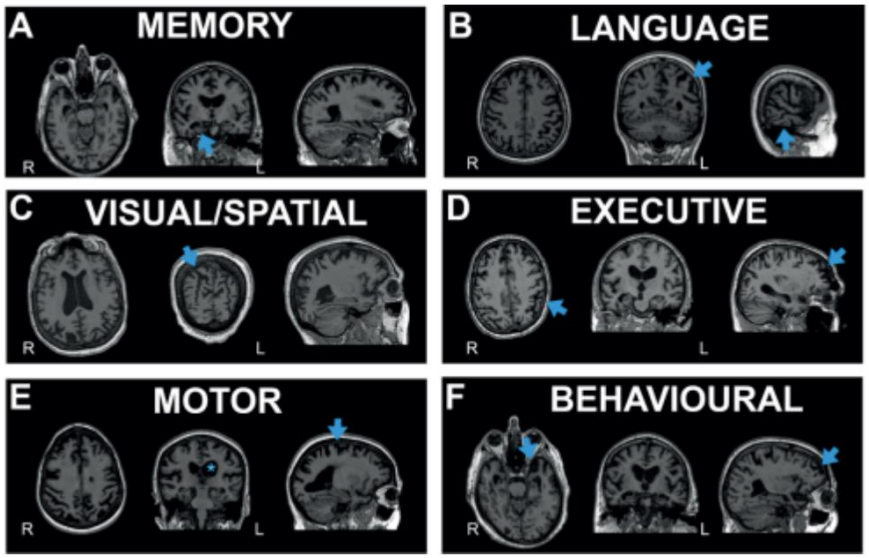

Figure 6: MRI across AD phenotypes; blue arrows indicate atrophy regions [1].

Many studies have now revealed that lithium has the ability to inhibit enzymes that are related to neurodegeneration and has also been shown to correspond with the formation of stem cells in the brain, potentially helping with overall volumetric expansion [1]. Evidence has also shown that the benefits of lithium extend to promoting neuroprotection, brain plasticity, remyelination, telomere length maintenance, and mitochondrial function [6].

Experimental studies have modified many intracellular signaling pathways, primarily glycogen synthase kinase-3**β** (GSK-3**β**), to evaluate the effects of lithium and its potential neuroprotective properties [6]. GSK-3**β** has been identified in previous research as a molecular link to the hyperphosphorylation of tau that is indicative of AD [1].

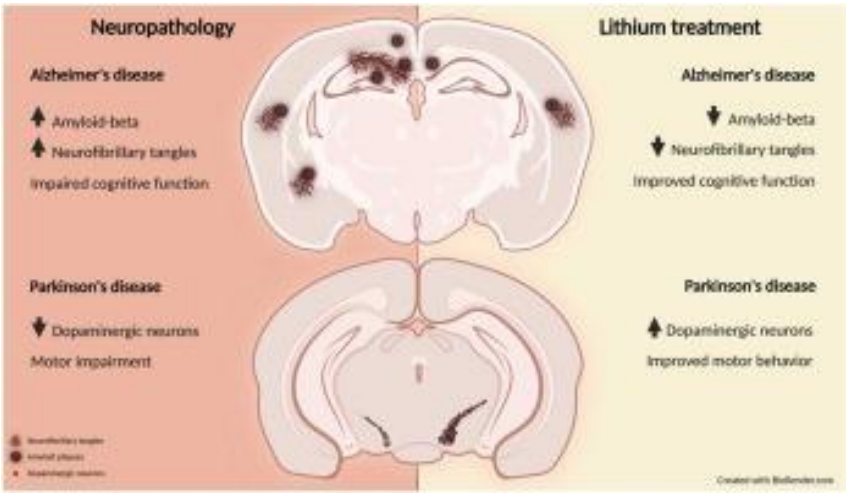

Figure 7: Graphical abstract showing the neuropathology of AD and Parkinson's disease and how lithium treatments potentially affect atrophy regions [6].

Due to the GK-3β inhibitory properties of lithium, there is a possibility that its neuroprotective and regenerative effects could influence the activity of mesenchymal stem cells (MSCs). Studies have shown that when lithium is administered at low doses, it can promote MSC proliferation and enhance the efficacy of MSC transplantation therapy in AD patients [1].

Due to these recent discoveries, there is a lot of interest in chronic lithium use and its role in the prevention of neurodegenerative diseases like AD, most likely through the inhibition of the protein GSK-3β [1]. Findings from preclinical research using lithium have provided foundation for potential clinical trials and effective treatments of AD using lithium [6] and also the promise of using it with stem cells [1].

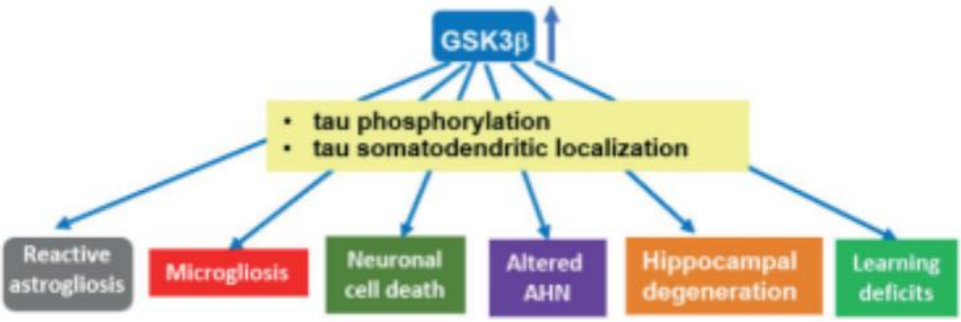

Figure 8: Overexpression of GSK-3β induces tau-dependent AD-like pathology [1].

2.2 Current Lithium Studies for AD Treatment

There are many pre-clinical and clinical trials and studies currently underway with lithium use for Alzheimer's disease. A recent meta-analysis study has shown the effectiveness of lithium in enhancing cognitive function in patients that are struggling with mild cognitive impairment and AD. One thing being done in this study is comparing lithium to current FDA-approved drugs, like aducanumab, lecanemab, and donanemab, and it has been found that lithium may be superior in improving cognitive symptoms. Lithium is also safer to administer at lower doses and much less costly [7].

Current studies are also evaluating the mechanism of how lithium activates autophagy. These studies aim to prove that lithium is capable of degrading misfolded proteins and damaged organelles, therefore degrading amyloid-beta, p-tau, and damaged mitochondria that lead to the pathogenesis of AD [7].

Research is also proving that lithium can reduce inflammation, which is a large factor in the clinical onset of AD symptoms. Studies are trying to prove that lithium can attenuate inflammatory responses of microglia and astrocytes, as well as reduce production of pro-inflammatory factors. A new drug, called Nanolithium, is an experimental product that is using a form of encapsulated lithium to reduce toxicity, but also gives it unique absorption and distribution characteristics [7].

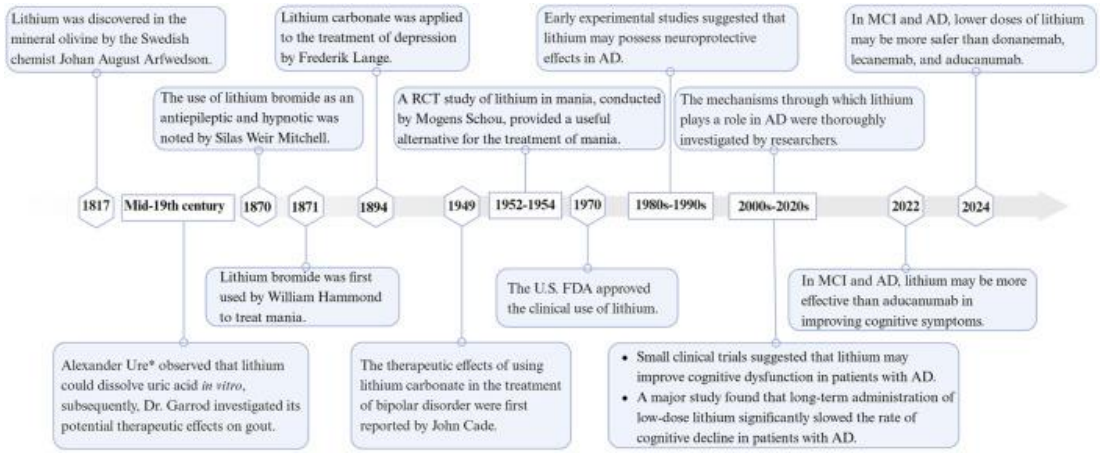

Figure 9: Timeline of lithium in medical research [7].

2.3 Combination of Lithium and Stem Cells

Due to its use in psychiatric treatments for the past 70 years, lithium is well studied as a mood-modulating drug but is understudied in its other effects on the human body. Studies as far back as 60 years ago have tested the effect of chronic lithium use on hematopoietic stem cells. Lithium has been shown to improve the proliferation and homing of stem cells, the ability for stem cells to form colonies, and aid in HSC self-renewal. Recently, research has been done to see if these benefits extend to mesenchymal and neural stem cells as well [8].

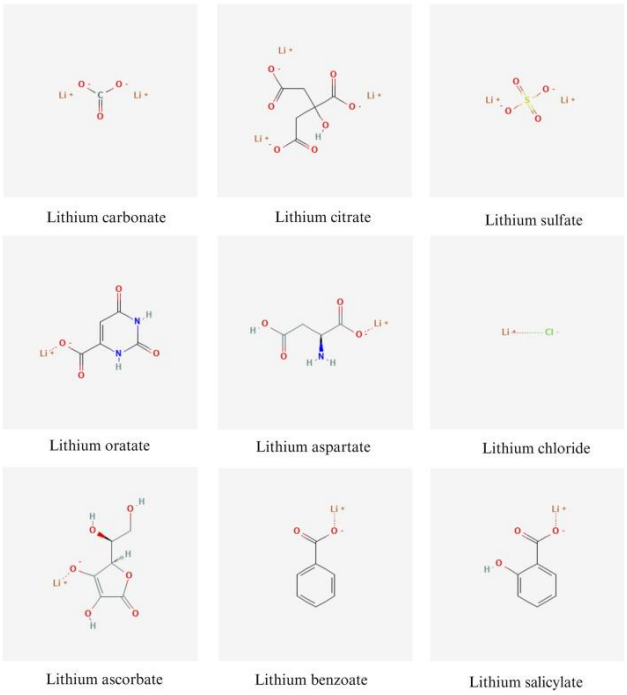

Figure 10: Chemical structures of various lithium salts [7].

When studies were done to determine the effect of lithium on neurogenesis, it was found that lithium is associated with increased proliferation of progenitor cells in the hippocampus and increased mitotic ability of Schwann cells. It is believed that this behavior is connected to the neuroprotective effects of lithium and the improvement of brain cell plasticity that is seen when patients take lithium regularly [8]. These findings have been leading scientists to study how chronic lithium use could positively impact stem cell transplantation in Alzheimer's disease [1].

When the effect of varying lithium doses was tested on stem cell proliferation, it was found that lithium, when administered at a concentration of 0.1mM, enhanced MSC viability. Another study showed that lithium at a concentration of 5mM increased cell growth without causing cell death in *vitro*. This was linked to an increase of cells in S phase, most likely caused by the mechanism that inhibits GSK-3**β** by lithium. These studies, along with others, have shown that applying select low doses of lithium, and therefore inhibiting GSK-3**β**, could potentially increase the effectiveness of MSC transplantation therapy for the treatment of AD [1].

2.4 Pancreatic Beta-Cell Secreted Factors and Ties to Diabetes

Diabetes mellitus is a chronic disease classified by hyperglycemia that is caused by insufficient insulin secretion by pancreatic **β**-cells. Patients with diabetes have a higher risk of developing Alzheimer's than other patients without diabetes, as shown in epidemiological analyses [2]. Type 2 diabetes is also increasing in prevalence worldwide, particularly in well-industrialized countries, which is only enhancing the rising cases of AD [9]. This has led scientists to study whether there is a causal relationship between insulin production, and therefore **β**-cell function, and onset of AD. In a study, insulin's neuroprotective properties were tested to see if pancreatic **β**-cell-derived insulin could modulate neuronal activity, therefore mitigating the onset of Alzheimer's [2].

The study showed that there were peripheral organ-derived factors that were defective when the individual had diabetes, which made the patient more susceptible to AD. These findings indicate that effectively functioning pancreatic **β**-cells may secrete other neuroprotective factors that are not insulin. One of the identified factors in this study, FGF23, may be capable of alleviating A**β** toxicity, allowing for potential for neuroprotection against AD [2].

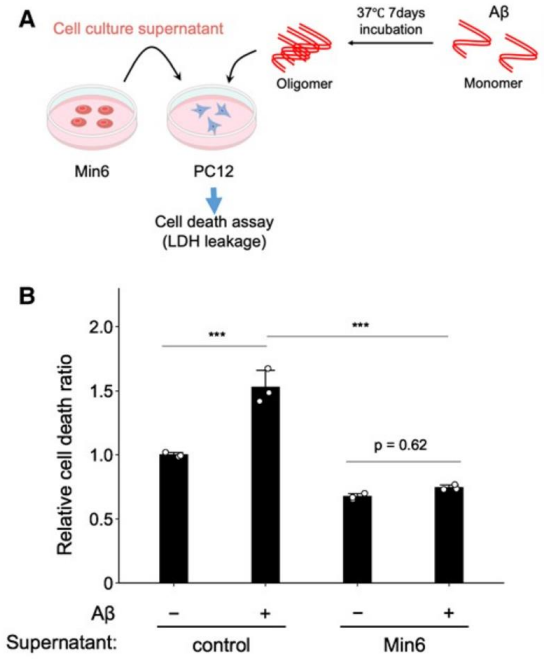

Figure 11: Protection against aggregated A**β**-induced neuronal cell death by culture supernatant of pancreatic **β**-cell. (**a**) Schematic representation of experimental conditions. (**b**) Cell death measured by LDH assay [2].

2.5 Gut-Brain Axis and its Connection to AD

Another potential connection to Alzheimer's pathology has been found in the gut-brain axis and gut microbiota. It has been seen in past experimentation that gut microbiota changes can cause accumulation of microbial metabolites in peripheral regions, which can be a contributor for Alzheimer's associated neuroinflammation. Studies suggest that the gut microbiome and the metabolites that the organisms produce can be responsible for regulation of microglial maturation, showing that metabolic products derived from microorganisms can influence glial cell homeostasis and other complex behaviors seen in AD [10].

In a recent study, it was found that treatment with *Bacteroides ovatus* and its associated secondary metabolite, lysophosphatidylcholine, also known as LPC, reduces A**β** load in the brain and reduces cognitive impairment. It was also found that AD patients have diminished levels of *B. ovatus* and LPC in their gut when fecal analyses were run, further strengthening this correlation [10].

This study began with using germ-free transgenic mice, as they have significantly reduced amyloid plaque deposition compared to other mice. It was seen that transferring the gut bacteria of amyloidosis mice into germ-free mice increased their A**β** pathology. This data shows that the gut and its microbiota can have an impact on brain health and AD, as patients with AD have lower levels of *B. ovatus* in their gut [10]. The data also shows that treatment with *B. ovatus* and LPC could reduce amyloid plaque load in the brain, reduce myelin degeneration, and rescue some synaptic function. This suggests that *B. ovatus* and LPC interventions could hold promise as potential therapeutic agents for AD [10].

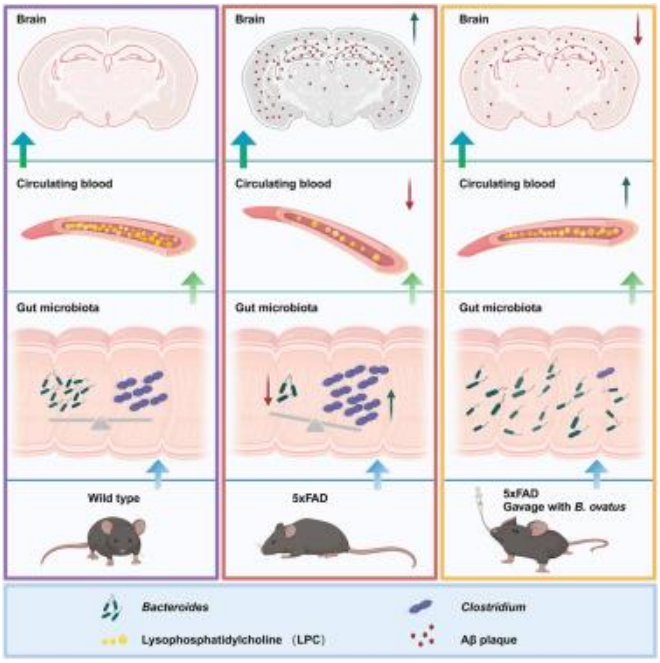

Figure 12: Graphical abstract demonstrating the experimental design of the study, showing how different mouse genotypes have connections between introduced or natural gut microbiota and amyloid plaque formation [10].

2.6 Mendelian Randomization for Genetic Targets and Potential Connections

Mandelian randomization, commonly referred to as MR, has become a popular way to reproduce currently licensed drugs and discover new targets for therapeutics [11]. It has also become a way to study the relationship between the genetic predisposition to AD and other diseases, such as epileptic diseases and cancer. MR uses genetic variants that are associated with exposure to variables to estimate the causal effect of a suspected outcome [12].

In a recent study, MR was used to find new genetic targets for AD and determine if they were druggable. The mechanisms, side effects, and efficacy were all tested as well. Through this process, three druggable genes were identified: *EPHX2, SERPINB1*, and *SIGLEC11*. These genes were picked out because they showed significant levels in blood and brain tissue when analyzed, making them reasonable targets [11].

For *EPHX2*, there was a significant association with hippocampal volume, which may provide some clues to the pathological mechanisms of Alzheimer's. This also makes it a promising target for treatment of AD, as the hippocampus is one portion of the brain that typically shows severe degradation. *SERPINB1* was shown to be upregulated in patients with AD, and expression of it in the prefrontal cortex is positively associated with increased amyloidosis. SIGLEC11 in higher levels may trigger an inflammatory response that is associated with onset of AD pathology and symptoms. Overall, targeting these genes showed no side effects [11].

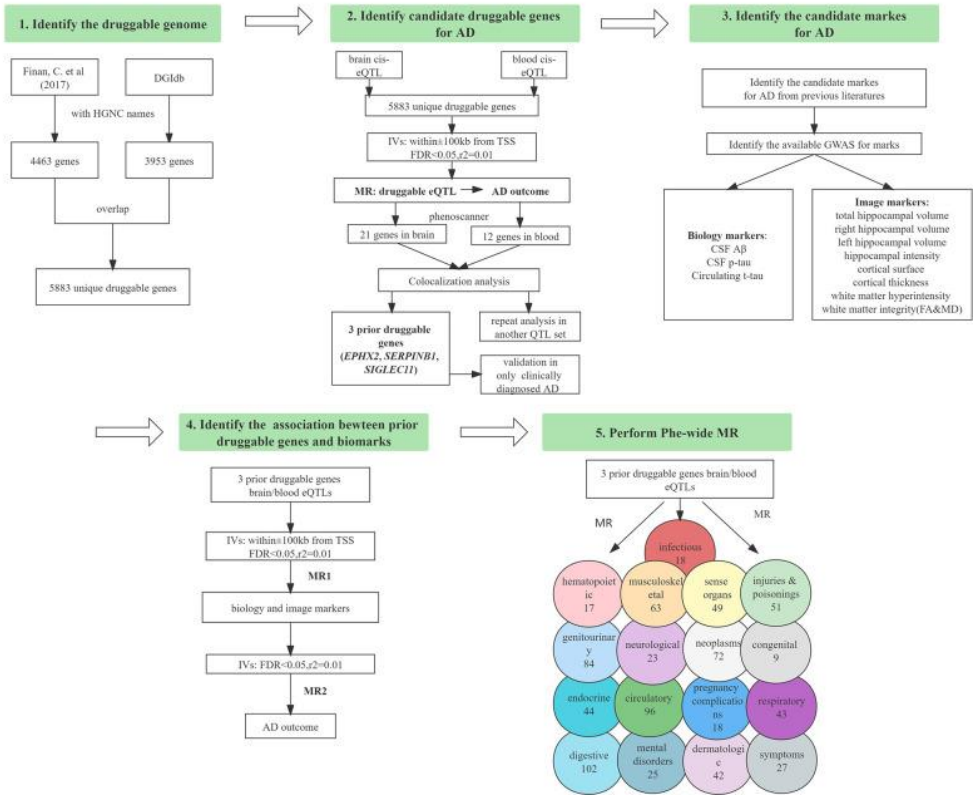

Figure 13: Overview of this study and the process of mendelian randomization [11]

2.7 Stem Cell Therapies for AD

Stem cells are undifferentiated cells that can mature into specialized cells. They show severe potential in the treatment of Alzheimer's, and an approach using stem cells creates a more favorable environment for neural recovery, which promotes regeneration in brain tissue and within neurons. There are four types of stem cells that have been investigated for their use in AD: neural stem cells, mesenchymal stem cells, embryonic stem cells, and induced pluripotent stem cells [1].

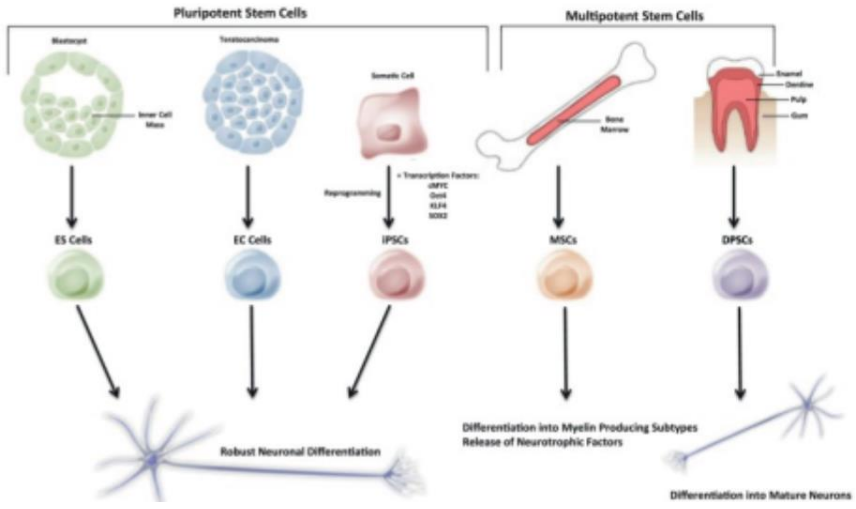

Figure 14: Types of stem cells commonly used to study and treat neurological deficits [1].

MSCs have been shown to reduce inflammation by fighting amyloid-beta plaques, untangling neurofibrillary tangles, and addressing abnormal protein degradation. Human mesenchymal stem cells, specifically, have active migration and multipotent potential, as well as neuroprotective, immunomodulatory, and paracrine effects [1]. NSCs, on the other hand, have been shown to reduce loss of spatial memory and learning, protect cerebral capillaries, reduce Aβ and tau pathologies, and enhance neurogenesis [1].

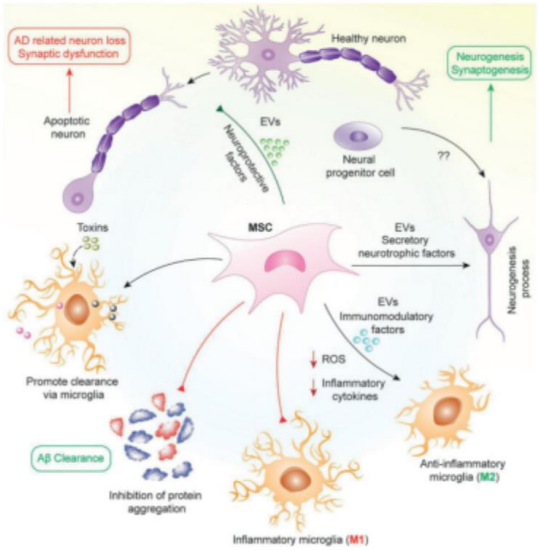

Figure 15: Mechanism of protective effects of MSCs in AD [1].

In a recent phase 1 clinical trial, the safety and dose-limiting toxicity of three repeated intracerebroventricular injections of human umbilical cord blood-derived MSCs was tested on nine patients. The most adverse side effects experienced by the patients was a mild fever, headache, nausea, and vomiting, all of which were mild and resolved within 36 hours, except for two patients who required an extra day of hospitalization to recover from their side effects [13].

The injections proved to be feasible, safe, and well-tolerated within the patients. Reduced levels of tau, phosphorylated tau, and Aβ42 levels were observed one day after administration. Despite this, the levels of these proteins increased again after four weeks, showing that the long-term effects of the MSCs were not effective. These results support that performing repeated administration of hUCB-MSCs may be necessary to preserve the therapeutic efficacy of the treatment [13].

Overall, this phase 1 clinical trial, along with other emerging trials, proves the potential of using mesenchymal stem cell-related therapies for the treatment of AD [13].

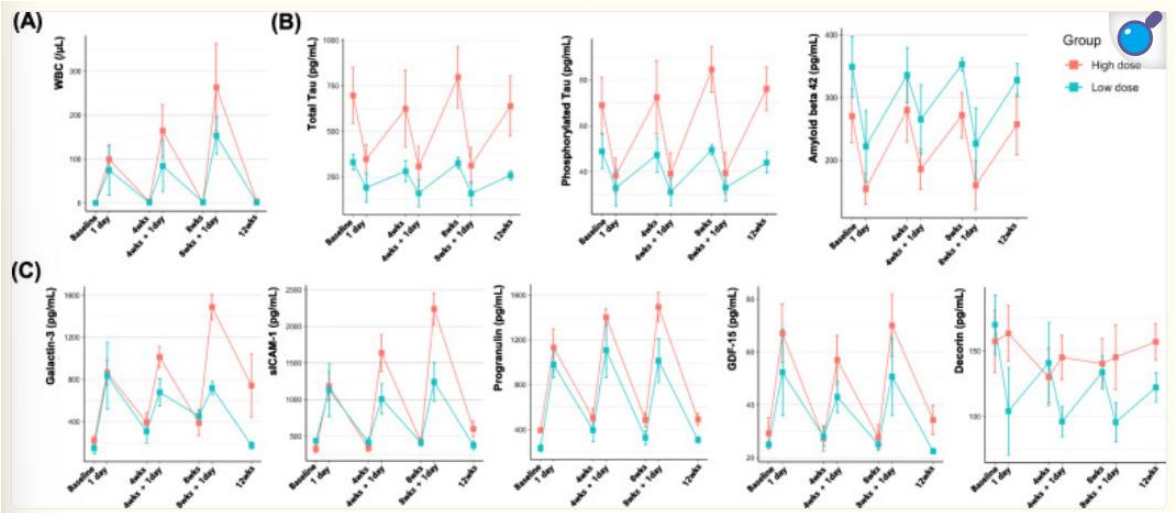

Figure 16: (**a**) White blood cell count, (**b**) Alzheimer's disease biomarkers, and (**c**) MSC-related biomarkers observed in the cerebrospinal fluid [13]

2.8 Inflammation and MSCs for AD

Inflamm-aging is a term used to describe how aging and chronic inflammation are associated with the onset of diseases like Alzheimer's, Parkinson's, heart disease, osteoporosis, and other chronic illnesses. Inflammation is a double-edged sword, since the activation of microglia and astrocytes can eliminate debris and pathogens, but can also cause harm to the neuronal system, especially if chronic [14].

Chronic, low-grade inflammation is associated with aging and disturbs the equilibrium of the nervous system, causing tissue atrophy and other harmful effects. An increase of serum proinflammatory cytokines, an effect of inflammation, can also lead to the development of some of these age-related diseases. MSCs have had promising results when used to control chronic inflammation in diseases like multiple sclerosis, leading scientists to investigate their potential with AD [14].

When MSCs were used in a recent study, the large ratio normally seen between proinflammatory and anti-inflammatory cytokines in AD patients was found to decrease. It was seen that the number of inflammatory cytokines decreased and there was little change in anti-inflammatory cytokines, therefore reducing the risk of some of the detrimental effects of inflammation. This study showed that successful MSC transplantation improves issues related to chronic inflammation, which decreased the risk of onset of AD symptoms without showing adverse effects [14].

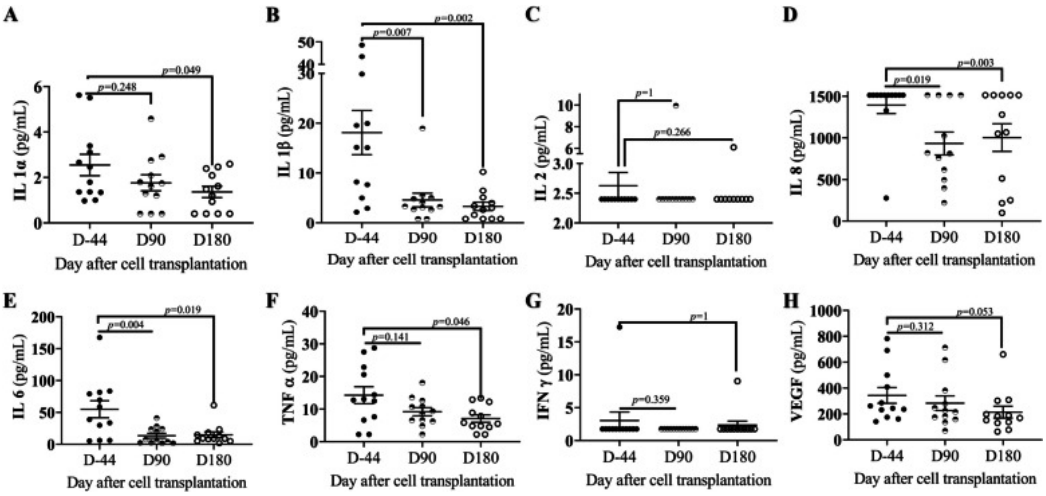

Figure 17: The effect of adipose stem cell transplantation on inflammatory cytokines in patients in a phase 1 clinical trial. (**a**) Interleukin 1**α**. (**b**) Interleukin 1**β**. (**c**) Interleukin 2. (**d**) Interleukin 8. (**e**) Interleukin 6. (**f**) Tumor necrosis factor **α**. (**g**) Interferon **γ**. (**h**) Vascular endothelial growth factor. [14].

2.9 Use of hMSC-EVs for AD Treatment

EVs, also known as extracellular vesicles, have been growing in popularity as a biological tool, as they have the capability to deliver DNA, RNA, proteins, and lipids to designated targets. EVs are heterogenous populations of membrane-based sacs that can be created *in vitro* and function in cell communication. They are effective in delivery as they can cross the blood-brain barrier and maintain a similar potency to their parent cells [4].

EVs that are derived from human mesenchymal stem cells, referred to as hMSC-EVs, have shown promise as a therapeutic agent for AD, as they exhibit immunoprotective and immunomodulatory abilities. The regenerative potentials of using hMSCs have been seen in other neurodegenerative diseases, so a recent study tested the use of hMSC-EVs on AD. When IV administration was used, the EVs were shown to aggregate in the liver and pancreas, so the team tried using IN, or intranasal administration, and that showed positive effects and aggregation in the brain [4].

hMSCs were harvested from bone marrow in this study and, when tested for their feasibility, the mice that received the treatment had a decrease in maze escape time and error, a decrease in A**β** density in the brain, lower levels of inflammation and astrocyte activation, and behaved better in cognitive tests. This study showed that hMSC-EVs can slow down AD pathogenesis when administered intranasally [4].

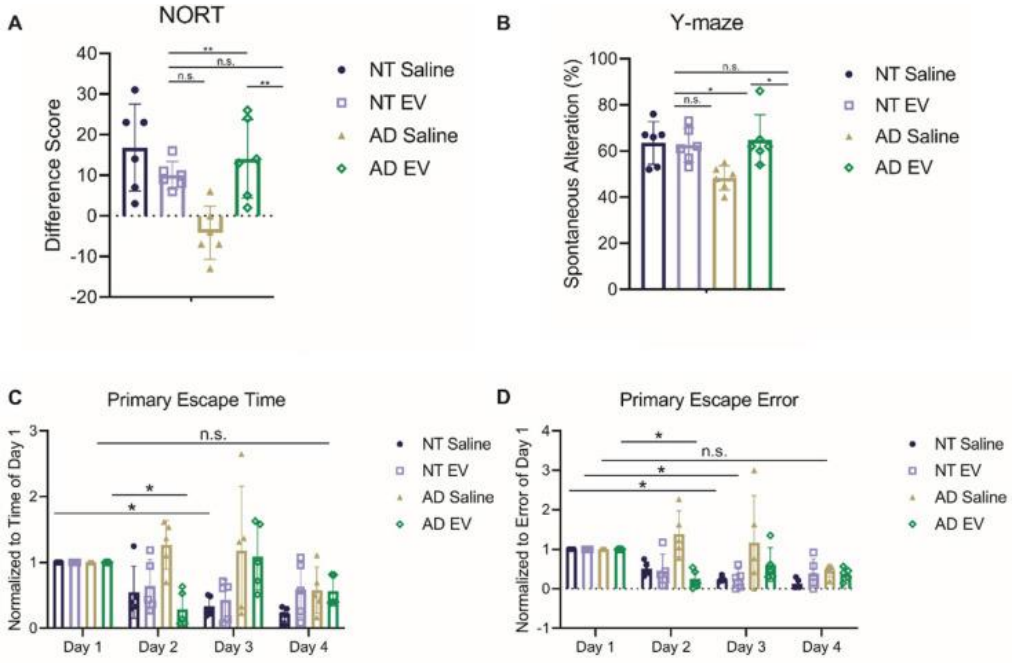

Figure 18: Testing done on 5XFAD mice to see how treatment with hMSC-derived EVs ameliorate cognitive decline. (**a**) Mice were tested for memory using novel object recognition test (NORT). (**b**) Y-maze test used to determine spatial working memory. (**c**) Primary escape time. (**d**) primary escape error [4].

2.10 Plasma Biomarkers for Screening

It has been shown in various studies that there are neuropathological changes in AD patients up to two decades before the onset of clinical symptoms. These changes could allow for much earlier screening and detection, allowing for intervention to occur before symptoms arise. Early intervention could postpone the clinical presentation or development of Alzheimer's [15].

In recent years, biomarker results from cerebrospinal fluid have improved our understanding of AD, but this method is invasive, high cost, and is not readily available. A new study used the ATN classification to measure a new screening technique for AD, which includes amyloid-mediated pathology, tau-mediated pathology, and neurodegeneration. The team came up with a new development involving blood-based plasma biomarkers, which are readily available, cost effective, and minimally invasive, all while showing association with later onset of AD [15].

This study aimed to find plasma biomarkers that correlate with CSF biomarkers, and the team found that A**β**42, A**β**40, t-tau, p-tau81, and NfL levels are significantly correlated with their CSF counterparts. This proves that changes in these plasma biomarkers may accurately reflect changes in CSF biomarkers and would therefore allow for detection without the negatives of CSF screening. This study specifically tested this method of screening with Chinese patients and found that AD could be detected up to 8 years before clinical onset [15].

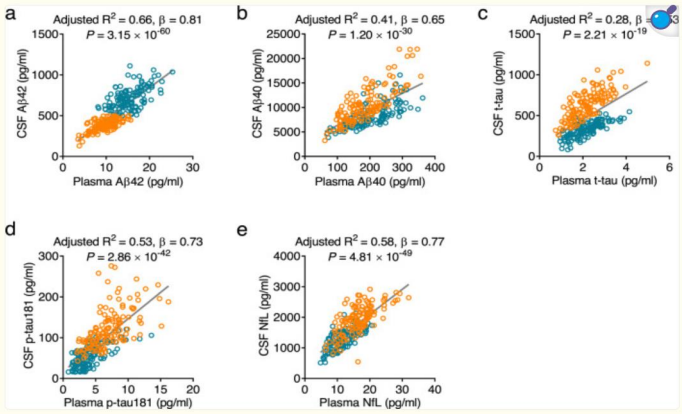

Figure 19: The concentrations of (a) A**β**42, (b) A**β**40, (c) t-tau, (d) p-tau181, and (e) NfL in plasma are correlated with their counterparts in CSF in this cohort [15].

2.11 Neuroimmune Screening

The term neuroimmune describes the intricate interplay between the nervous and immune systems and explains the coordinated regulation of many cell types, such as neurons, glial, and immune cells. Since recent studies have shown that abnormal activation of neuroimmune cells and their inflammatory response play a significant role in AD, a new study from 2023 aimed to identify immune cell-related genes in blood samples [16]. In the end, they identified 10 of these genes that could be diagnostic biomarkers for AD and provide guidance for treatment. By screening for these genes, the team could see if certain immune cell alterations and dysregulation may indicate disease status and progression. It was also discovered that gamma T cells and M2 macrophages, both immune response cells, are correlated in AD and could also potentially be used in diagnostics [16].

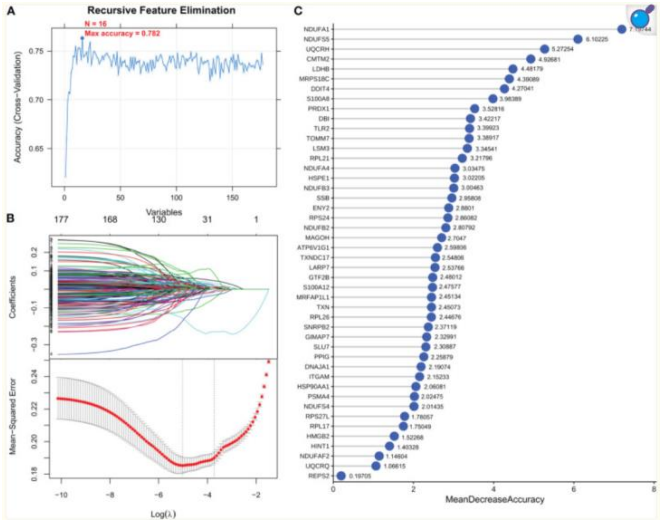

Figure 20: Optimization algorithm for screening important immune-related markers. DEGs parameter diagram of (**a**) RFE, (**b**) LASSO algorithm, and (**c**) RF filtering features [16].

3. Summary and Conclusions

3.1 Recent Discoveries

What we can take away from these recent developments is that there is likely a connection between chronic lithium use and prevention of neurodegenerative disorders [1]. There is also a likelihood that defective neuroprotective factors secreted by the pancreas due to diabetes may impact brain function and make a patient more susceptible to AD [2]. Also, there is a growing understanding of the connection between AD and the gut-brain axis, and delivery of Bacteroides ovatus and LPC to AD models were found to reduce amyloid plaque load in the brain [10]. Mendelian Randomization has also come to light as an effective way to identify novel druggable genes for AD and find potential genetic connections between Alzheimer's and other diseases [11, 12].

As the use of stem cells becomes better understood, so does their use in clinical applications for the treatment of AD. It has been seen that stem cell transplantation improves AD patients' inflammatory balance [14], and IN administration of MSC-derived EVs can slow down AD pathogenesis [4]. It is also seen that MSCs, when combined with low doses of lithium, can have effective proliferation within AD patients and cause volumetric expansion in the brain [1].

The development of more efficient screening is crucial for the early detection of AD, as this could lead to better treatment of the disease and prevention of clinical onset. Plasma ATN biomarkers have shown promise as a cost-effective and minimally invasive way to predict AD 8-10 years before the onset of symptoms [15]. Neuroimmune infiltration-related biomarkers may also be helpful in the diagnosis of AD and the detection of abnormal alterations associated with Alzheimer's pathology [16].

3.2 Future Directions

For the future, there are many goals in the realm of Alzheimer's treatment since there is still no real, effective means of curing or reversing the clinical effects of AD. If further developed, injections of MSCs or NSCS could prove to be beneficial in neural regeneration and neuroprotection [1, 4]. There is also a promising new treatment using lithium, but more research is needed on the use of a combination of stem cells and lithium to combat AD. Overall, the efficacy of stem cells as a therapy for AD is dependent on a better understanding of MSC characteristics in vivo and potential side effects [1]. Earlier identification of AD neuropathological changes could detect AD before the onset of symptoms, but more testing needs to be done to improve the efficacy of the newer screening techniques [13, 14].

Lastly, more research needs to be done on the correlation between AD and diabetes, bipolar disorder, and the gut-brain axis to better understand the pathophysiology of Alzheimer's Disease and to be able to fully understand how it connects with other chronic illnesses [1, 2, 8].

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