

Inflammatory Mechanisms and Treatments of Alzheimer's Disease: An Integrative Review of Neuroscience and Bioinformatics

Bangyu Li*

Department of Mathematics, Santa Monica College, Santa Monica, USA

* Corresponding Author: 18538105153@163.com

Abstract. The most common type of dementia, Alzheimer's disease (AD), is characterized by plaques of amyloid-beta ($A\beta$) and then tangles of tau protein aggregating in the brain, causing neurodegeneration and cognitive decline. The association between neuroinflammation and the pathogenesis of AD has come to be increasingly well acknowledged. This review discusses the inflammatory pathways involved in AD, focusing on microglia and astrocytes, as well as the involvement of various proinflammatory cytokines (i.e., $TNF-\alpha$ and $IL-1\beta$). The $NF-\kappa B$ signaling and the NLRP3 inflammasome are also reviewed for their effects on neuronal death and cognitive dysfunction. Additionally, the unifying function of bioinformatics in AD research, combining genomic and transcriptomic analyses with proteomics and metabolomics, is explored. These tools have uncovered crucial genetic and molecular pathways associated with inflammatory cross-talks in AD, revealing possible drug targets. An overview of treatments such as nonsteroidal anti-inflammatory drugs (NSAIDs), immunotherapies, and newer therapies like stem cell therapy and RNA interference is provided, along with their efficacy and drawbacks. The review concludes by highlighting the importance of multidisciplinary approaches and individualized therapies to enhance therapeutic outcomes in AD patients.

Keywords: Alzheimer's disease; Neuroinflammation; Microglia; Astrocytes; Cytokines.

1. Introduction

A person's memory, problem-solving, and other cognitive skills deteriorating to the point that they seriously interfere with day-to-day functioning is referred to as having dementia. The World Health Organization estimates that in 2022, there will be over 55 million people living with dementia globally; by 2050, that number is expected to rise to 139 million. The most prevalent kind of dementia, accounting for 60–70% of cases, is Alzheimer's disease (AD). Dementia is caused by a variety of brain traumas and illnesses. Neurons in the brain die as a result of AD-induced nerve inflammation and the buildup of proteins with the abnormal structures of tau and $A\beta$ [1]. The role of neuroinflammation in Alzheimer's disease (AD) has often been disregarded. The involvement of neuroinflammation in the pathogenesis of AD is being discussed in a growing number of scientific publications; nevertheless, a precise explanation of how neuroinflammation affects the illness is yet unknown. As advances in artificial intelligence and computer technology continue. In order to get fresh insights into the processes behind the pathogenesis of AD, it is essential to successfully combine these breakthroughs with classic neuroscience investigations.

2. Inflammation in AD

2.1. The role of inflammation in AD

It is crucial to comprehend the basic features of inflammation in order to clarify the connection between inflammation and AD. A vital part of the body's immunological response, inflammation may take two forms: acute and chronic. Inflammatory reactions are caused by a combination of immune cells, such as mast cells, dendritic cells, neutrophils, and lymphocytes, and non-immune cells, such as fibroblasts, epithelial cells, and endothelial cells. One may broadly categorize the chemicals that cause inflammation into two groups: transcription factors and cytokines. Inflammation in

neurodegenerative illnesses has a distinct mechanism that might manifest in two ways. Cytokines that cause peripheral inflammation include TNF- α , interleukin 6 (IL-6), and interleukin 1 β (IL-1 β). These cytokines have the ability to penetrate and alter the blood-brain barrier (BBB), causing it to produce proinflammatory mediators and increasing its permeability to cells, which permits leukocytes to enter the brain.

2.2. The function of microglia and astrocytes

As the immune system's resident cells in the brain, microglia are essential to the central nervous system's (CNS) immunological defense. They stay dormant under physiological settings, but their highly motile processes actively monitor the parenchyma and cerebral surroundings. When microglia detect a signal in the central nervous system, they will transition from a resting state to an activated state, which is characterized by morphological alterations and gene expression modifications, including those of pro- and anti-inflammatory chemicals and microglial surface receptors [2]. The most prevalent glial cells in the brain, astrocytes carry out a number of intricate and vital processes in the central nervous system (CNS), such as information processing via neural circuits, synaptic transmission, and preservation of brain homeostasis. Astrocytes become active and have particular immunological activities in AD. Numerous substances, including as pathogenic A β , tau species, and proinflammatory cytokines, may activate microglia and astrocytes.

2.3. Inflammatory cytokines and signaling pathways

A factor that causes inflammation in neurodegeneration is nuclear factor- κ B, or NF- κ B. In AD animal models, NF- κ B has been shown to interact with astrocytes, tau protein, β -secretase, APOE, and other molecular components in several studies. In the future, NF- κ B inhibitors could possibly be a viable treatment option for AD. Nevertheless, the present pharmacological regulation faces difficulties due to an increased susceptibility to infections and poor specificity of the NF- κ B inhibitors utilized. A key player in this vicious cycle of neurodegeneration is NF- κ B, whose activation may contribute to neurodegeneration or neuroprotection. The nucleotide-binding oligomerization domain-like receptor pyrin domain-containing 3 (NLRP3) inflammasome is an important molecular component in the AD neuroinflammatory pathway when it comes to neuroinflammation. By decreasing A β phagocytosis, the NLRP3 inflammasome's activation promotes A β aggregation. When tau aggregates and A β oligomers are stimulated, microglia and astrocytes in the brain can assemble and activate the NLRP3 inflammasome, which in turn activates caspase-1 and secretes IL-1 β and IL-18. This, in turn, sets off the pathophysiological alterations and cognitive decline associated with AD [3].

The innate immune system's cells generate the powerful pro-inflammatory cytokine interleukin-1 beta, or IL-1 β . An higher risk of AD is linked to certain polymorphisms of IL-1 β that cause greater production. By activating protein kinase C and increasing γ -secretase activity, IL-1 β promotes amyloidogenic processing of APP and controls the production of amyloid precursor protein (APP) and increases APP secretion from glial cells [4]. TNF- α , also known as tumor necrosis factor-alpha, is a type 2 transmembrane protein that is nonglycosylated and monomeric, weighing 17 kDa. It is a member of the TNF/TNF receptor (TNF/TNFR) superfamily of ligand/receptor proteins [5]. TNF- α is essential for the regulation of chronic inflammation and may affect the production of A β plaques and neurofibrillary tangles, which furthers the development of AD pathology. TNF- α is a key pro-inflammatory cytokine that, if left unchecked by anti-inflammatory cytokines, promotes chronic inflammation by inducing the production of IL-1, IL-6, and IL-8. In addition, it activates γ -secretase in HEK cells, promotes the release of A β peptides, and increases the expression of APP and β -site APP cleaving enzyme 1 (BACE1) in mouse astrocytes.

2.4. Relationships between inflammation and neurodegeneration

Through the process of gliosis, which is accelerated by inflammation, brain immune cells like astrocytes and microglia become activated and may multiply, further encouraging neuronal damage and death. Age-related increases in baseline levels of inflammatory biomarkers have been shown to

have a deleterious effect on cognitive functions such as memory, processing speed, and cognitive function. According to earlier research, inflammatory cytokines might act as a stand-in for systemic inflammation, which has been linked to a reduction in neurological function [6].

3. Application of bioinformatics in the study of AD inflammation

3.1. Genomic and transcriptomic analysis

A vital role is played by single-cell RNA sequencing (scRNA-seq) and gene association studies (GWAS) in determining the susceptibility genes for AD and inflammation. By comparing the allele frequencies of genetic variations in people who are phenotypically dissimilar but ancestrally similar, GWAS seek to uncover relationships between genotypes and phenotypes [7]. Using GWAS, several sites with genetic variations impacting inflammatory pathways have been found in AD patients. The APOE ϵ 4 allele is the most prominent GWAS risk factor associated with inflammation and immunological response in the development of AD. Furthermore, an increasing number of GWAS risk genes linked to AD have been discovered, such as TREM2, INPP5D, MEF2C, and HLA-DRB5/DRB1 [8]. scRNA-seq has the ability to monitor the developmental paths of diverse cell lineages, discover unusual and complicated cell populations, and show regulatory links between genes. Organ dissociation, single-cell capture, cell lysis, mRNA reverse transcription, cDNA amplification, library creation, high-throughput sequencing, and data analysis are some of the stages that make up this technique [9]. Tang techniques, CEL-seq, SMART-seq, STRT-seq, and Drop-seq are some of the current scRNA-seq techniques [10]. The development of scRNA-seq has the potential to transform immunology research and solve current issues in the field.

Databases are also essential to AD bioinformatics research. A group of academic institutions and healthcare facilities in the US and Canada called the Alzheimer's Disease Neuroimaging Initiative (ADNI) was founded in order to create standardized imaging methods and biomarker protocols for healthy individuals, people with mild cognitive impairment (MCI), and people with mild AD [11]. Therefore, the main objective of ADNI was to further our knowledge of the pathobiology of AD while simultaneously developing and validating biomarkers that may be used as surrogate outcome measures with higher statistical power than clinical or cognitive measures alone. High-throughput gene expression and other functional genomics datasets are archived and made publicly available via the Gene Expression Omnibus (GEO) database, a worldwide public repository [12]. You may use this database to research risk factors and genes associated with AD.

3.2. Proteomics and metabolomics analysis

It's crucial to first understand the notion of proteome and the main area of study in order to fully appreciate large-scale proteomics. Comprehensive analysis of proteins, other secondary metabolites, and their physiological roles is known as proteomics. Proteins are important cellular constituents or biomolecules. It is the goal of this discipline to identify proteins in bacteria as well as assess their location, amount, isoforms, molecular interactions, and post-translational modifications [13]. Thousands of proteins from a wide range of biological samples may be quantified by high throughput automation in large-scale proteomics. Earlier research on AD used co-expression network analysis and quantitative mass spectrometry (MS). According to research, this module may have a protective effect against AD since it was shown to be enriched with genetic risk factors for the disease as well as protein markers from anti-inflammatory microglia and astrocytes [14].

The study of the many and varied metabolic processes that occur inside biological systems is known as metabolomics. Finding and measuring every molecule in a biological environment is the main goal of metabolome analysis. Metabolomics has the potential to make preclinical research in animal models of AD more easily applicable to humans, as metabolic pathways are substantially similar across species. Moreover, the high lipid content of the brain implies that lipidomics might be a useful omics method that offers fresh perspectives on the etiology of AD.

3.3. Molecular networks and systems biology

The intricacy of AD's etiology is becoming more and more apparent to researchers as they continue to examine the disease's pathological features. On the one hand, via data analysis across numerous unique datasets and massive data volumes, researchers have shown that integrated bioinformatics may make it easier to explore complex biological networks. Using text mining, Gene Ontology, protein-protein interaction analysis, drug-protein interaction analysis, non-coding RNA-target interaction analysis, and Reactome functional enrichment analysis, they were able to determine which eleven proteins have the greatest potential to influence neuroinflammatory processes in AD [15]. Conversely, systems biology is being used by AD researchers to investigate how different cell signaling pathways affect the course of the illness and to better comprehend them [16]. The study of systems biology unifies many subfields that are accountable for complex behaviors and results, such as determining the connections between genes and behavior via the interactions of their constituent parts.

3.4. Applications of bioinformatics in target identification and drug discovery

Bioinformatics technology is advancing continuously, and as a result, its accuracy and breadth are becoming better. A growing number of research projects are aiming to use bioinformatics methods to find possible AD treatment targets. Drug development is using bioinformatics more and more, and this relationship will only grow. Possible therapeutic targets for AD have been identified in recent years using a variety of bioinformatics approaches, including protein signaling pathways, changes in molecular signatures across medication classes, drug interaction profiles, and their possible therapeutic mechanisms.

Furthermore, a number of research have used screening methods to find novel anti-inflammatory medications, such as non-steroidal anti-inflammatory medications (NSAIDs) [17]. A cost-effective and highly efficient method for finding and developing potential novel drugs is virtual screening (VS) [18]. A recent work established a server named DrugRep that carries out completely automated molecular 3D structure creation, docking, similarity comparison, binding affinity screening, and binding pocket prediction [19].

4. Neuroinflammation as a potential therapeutic target in AD

4.1. Anti-inflammatory drugs for AD treatment

The FDA has authorized a family of pharmaceuticals known as nonsteroidal anti-inflammatory drugs (NSAIDs) for use as analgesics, antipyretics, and anti-inflammatory agents [20]. Because NSAIDs are used so widely, they are a prime option for epidemiological studies looking at the possible benefits of anti-inflammatories for AD patients. Patients treated with NSAIDs had a lower chance of getting AD, according to some epidemiological research; however, this link has not been shown in other investigations. Moreover, there aren't many clinical studies that provide conclusive proof of how NSAIDs affect AD risk.

New advancements have occurred since 2020, when clinical studies concentrating on medicines for AD were recorded. Notably, the US FDA authorized Lecanemab and Aducanumab, two antibodies that target amyloid, ending almost two decades without new treatments for AD [21]. One of the proteinopathies linked to AD, aducanumab is a high-affinity, completely human IgG1 monoclonal antibody that targets a conformational epitope present on aggregated soluble oligomers and insoluble fibrils of β -amyloid. Targeting protofibrils, a kind of soluble aggregated $A\beta$, is lecanemab, a humanized IgG1 monoclonal antibody [22]. The primary distinction between Lecanemab and Aducanumab is found in their modes of action: Lecanemab prevents the development of amyloid plaques, whereas Aducanumab eliminates beta-amyloid from the brain.

4.2. Immunotherapies

Alzheimer's disease is fought using immunotherapy, which activates the immune system. Immunotherapy falls into two categories: active and passive. These methods lower the amount of A β in the brain and impede the course of the illness by inducing the immune system to break down and remove abnormal proteins via the use of synthetic peptides or monoclonal antibodies (mAbs) [23]. Passive immunotherapy does, however, have significant drawbacks; the uneven and variable results linked to this strategy imply that certain molecular targets and clinical trial procedures should be reevaluated.

The management of many immune-related disorders has been transformed by immunomodulatory medications. These substances alter the immune response via stimulating (immunostimulatory) or inhibiting (immunosuppressives) the generation of serum antibodies. Copaxone (glatiramer acetate) and Rapamycin are two prominent examples. Multiple sclerosis (MS) is an autoimmune disease of the central nervous system (CNS) that is treated with glatiramer acetate [24]. According to recent research, both *in vitro* and *in vivo*, GA-stimulated macrophages (M Φ) preserve synapses and aid in the removal of A β 42 oligomers, therefore shielding neurons from A β -mediated nanotoxicity [25]. Rapamycin is one of the most potent pharmaceutical approaches for directly addressing the signs of aging to increase longevity in a variety of animal models. It was first created to prevent organ transplant rejection [26]. There are several medications in testing right now, but before they are used in clinical settings, substantial advancements must still be made.

4.3. Other potential treatment strategies

Various treatment medication methods have not shown sufficient results in improving cognitive function in AD. On the other hand, stem cell therapy offers novel approaches to treating AD. This treatment may lessen neuroinflammation, which is important for patients who develop AD after aneurysmal subarachnoid hemorrhage (SAH) because neuroinflammation plays a major role in the progression of injuries and brain damage, which in turn causes cognitive decline [27]. Furthermore, RNA interference (RNAi) may make it easier to pinpoint the causes of AD and understand how those factors work. Through a post-transcriptional gene-silencing process, RNAi controls protein synthesis, hence regulating gene expression. Since different genes and proteins may have an impact on AD research, RNA interference (RNAi) has been widely used in fundamental biosciences to date. Future research into the creation of innovative treatments seems to be encouraged by this application.

4.4. Integration of treatment strategies and personalized treatment

The complex nature of AD has created a pressing need to design multi-target ligands (DMLs) to address the complementary pathways involved in this condition [28]. DMLs are conceptualized to enhance single-target therapies by potentially modifying multiple aspects of AD pathophysiology concurrently, reflecting our evolving understanding of the disease [29]. While DMLs are a promising therapy option for AD, researchers are still looking for more targeted approaches. In AD, precision medicine entails using biomarkers—genetic and imaging indicators, for example—to precisely diagnose and categorize patients according to their unique disease subtype. This technology allows for the creation of targeted medicines and more individualized treatment plans.

5. Discussion and future plan

5.1. Limitations of the existing study

Current research on inflammation in AD encounters several limitations and challenges. These include a lack of clarity regarding the precise role of inflammation in AD pathogenesis, difficulties in isolating specific inflammatory pathways, and the complexities involved in studying the dynamic interplay among various inflammatory mediators. Researchers are attempting to utilize bioinformatics in conjunction with other methodologies to further investigate AD. However,

achieving high data quality remains a significant challenge when applying bioinformatics to this field of study.

5.2. The direction of future study

For future studies, researchers should consider exploring the following points. First, it is important to strengthen multidisciplinary collaboration to enhance the understanding of the mechanisms underlying inflammation in AD. Second, the development of new technologies is essential for better identification and validation of therapeutic targets. Third, large-scale, long-term follow-up clinical studies are recommended to evaluate the effectiveness of new therapies.

6. Conclusion

At present, numerous studies investigate the mechanisms and treatments of inflammation in AD. However, the drugs developed targeting these mechanisms appear to achieve only modest therapeutic effects in clinical trials. In future research, researchers should aim to enhance the application of bioinformatics in the search for AD treatments, thereby facilitating the more efficient discovery of new therapies.

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