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Research Progress in Pathogenesis and Therapeutic Strategies of Alzheimer's Disease: From Molecular Pathology to Clinical Application

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Abstract: *Alzheimer's disease (AD) is currently the most common cognitive impairment disorder and has become a major health concern as the global population ages. Focusing on this area, we systematically reviewed research progress in this field and conducted in-depth discussions from gene expression to clinical application. Studies have shown that significant breakthroughs have been made in molecular pathological changes, innovative diagnostic methods, and the development of treatment strategies. Given the complexity of the disease, its prevention and treatment require a comprehensive, multi-faceted approach. This article focuses on how basic research results can better serve the clinic and explores the principles for formulating individualized treatment plans. The latest research progress not only enriches the theoretical basis for clinical practice but also provides new ideas for future research.*

Keywords: *Alzheimer's Disease; Dementia; Neurodegenerative Disorder; Pathogenesis; Molecular Pathology; Therapeutic Strategies; Clinical Application*

1. Introduction

1.1 Research Background

Alzheimer's disease (AD) is the most common form of dementia. Currently, it is estimated that there are about 50 million people worldwide suffering from dementia, with AD accounting for 50% to 75% of all cases [1]. According to a report by the World Health Organization, dementia accounts for 11.2% of the disability-adjusted life years among people aged 60 and above, surpassing the impact of stroke, cardiovascular diseases and cancer [2]. With the acceleration of global population aging, predictions show that by 2050, the number of people suffering from dementia worldwide will reach 152 million, with the growth rate in developing countries being the most significant. Gender analysis shows that the incidence rate of women is 1.17 times that of men, and the standardized mortality rate is also higher. Specifically in the United States, it is projected that by 2050, the number of Alzheimer's disease (AD) patients aged 65 and above will increase from 5.8 million to 13.8 million. In addition, from 2000 to 2018, the mortality rate related to AD increased by 146.2%, making AD the fifth leading cause of death among the elderly in the United States [3]. AD patients lead to social isolation, deterioration of physical health, psychological disorders and economic difficulties among caregivers, thereby imposing a huge social burden and subsequently causing serious social consequences, including family conflicts, patient abuse and suicidal behavior [4-5].

1.2 Global Research Status

Research statistics on Alzheimer's disease show differences among various regions of the world. In North America, the National Institutes of Health (NIH) of the United States has invested 3.2 billion US dollars in Alzheimer's disease research. And nearly half (more than 45%) of the world's clinical trials take place in North America. The U.S. Food and Drug Administration (FDA) has taken the lead by approving new therapies such as Aducanumab. In Europe, researchers have achieved remarkable results in basic science and the search for new biomarkers. They have invested approximately 1.5 billion euros in brain disease research through the "Horizon Europe" program. They also established EPAD, which has developed into the largest research organization for Alzheimer's patients in Europe. In the Asia-Pacific region, Japan is demonstrating how to care for patients with Alzheimer's disease in new ways. China is also making rapid progress and has established the world's largest clinical information database

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for Alzheimer's disease at present. Australian scientists have made a real breakthrough in the early detection of the disease.

Our research achievements go far beyond the laboratory; they touch upon real-world medical practices and the broader society. In the laboratory, we have made some exciting progress in the field of brain science. By observing the development process of Alzheimer's disease and different treatment combinations, we have opened up new doors for personalized treatment. With the increase in the number of elderly people in the global community, doctors now have more advanced tools to select the appropriate treatment plan for each patient and have found ways to detect problems earlier and match treatment plans more precisely according to each patient's needs. This means that patients can usually maintain an independent life for a longer period of time, and it also makes the lives of their families easier. All of this also means lower medical expenses. When patients receive the right care at the right time, hospitals can make more effective use of resources and pharmaceutical companies can develop more effective drugs. Ultimately, this not only helps families control medical expenditures but also assists the government in managing medical budgets.

2. The Clinical Features and Pathological Changes of AD

2.1 Clinical Manifestations

The main manifestations of AD are progressive memory loss and cognitive decline, which have become the primary characteristics of neurodegenerative diseases. These symptoms usually develop progressively, among which memory dysfunction is the most prominent initial manifestation [6].

2.2 Pathological Characteristics

The pathological feature of AD is complex neuropathological changes [7]. This includes the accumulation of extracellular amyloid plaques (mainly composed of β -amyloid protein peptide aggregates) and intracellular neurofibrillary tangles containing hyperphosphorylated tau protein. These pathological changes are accompanied by severe cerebral amyloid angiopathy, which is caused by the deposition of Aβ on the walls of cerebral blood vessels, leading to progressive neuronal degeneration and loss [8]. AD can only be determined through postnatal brain tissue examination, which is the gold standard for distinguishing AD from other types of dementia. However, this invasive procedure has certain limitations in the clinical setting and is usually diagnosed through cognitive assessment, biomarker analysis, and neuroimaging techniques, etc [9].

2.3 Diagnostic Criteria

According to the working group of the National Institute on Aging - Alzheimer's Association (NIA-AA) in the United States, the diagnostic criteria for AD adopt a dual-track system to adapt to the diagnostic capabilities of different medical institutions. This guideline retains the basic framework for "suspected AD dementia" established in 1984 and has undergone significant revisions based on 27 years of clinical experience. The diagnostic methods incorporated technical means such as magnetic resonance imaging (MRI), positron emission tomography (PET), and cerebrospinal fluid biomarker analysis [10].

3. Research Progress on The Pathogenesis of AD

3.1 Amyloid Cascade Hypothesis

This hypothesis holds that the abnormal accumulation of amyloid - β protein (AβP) in the brain is regarded as the key starting point for disease, and this change can cause abnormal nerve fibers, cell damage, vascular problems and cognitive decline. This type of protein originates from a precursor substance (APP) that has been processed in two different ways: one generates normal protein fragments, while the other produces complete proteins that may cause problems. This process mainly consists of two steps: first, the formation of problem proteins (through accumulation or APP fragment formation), followed by the triggering of nerve cell damage and the appearance of abnormal fibrous structures. At the microscopic level, this protein interferes with the calcium balance within cells, causing excessive phosphorylation of tau protein and ultimately forming a special helical structure [11].

Researchers have discovered a new mechanism by which Aβ disrupts brain function. Before the

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formation of amyloid plaques, tiny cluster-like structures will first form. They interfere with the information transmission points between nerve cells, disrupt normal brain communication, lead to a reduction in neural connections, and eventually cause cell death.

This kind of damage can also trigger a chain reaction. When proteins accumulate in large quantities in the brain, they will cause a series of inflammatory responses in the brain. Microglia in the brain clear these proteins but at the same time release some chemicals that may make the situation worse. At the same time, these harmful substances can also block the blood vessels in the brain and affect the supply of nutrients.

Meanwhile, researchers found that the substance is contagious and can spread from one area of the brain to others. Therefore, focusing on small protein clumps is more helpful for us to understand the progression of diseases than observing large plaques. These new understandings provide important ideas for the development of innovative therapies.

3.2 Tau Protein Pathology

The microtubule associated protein Tau plays a key role in the pathogenesis of Alzheimer's disease. The insoluble polymers formed in its specific area (microtubule binding zone) are significantly associated with the cognitive impairment symptoms of patients. This protein not only forms abnormal structures during the development of the disease but also has the characteristic of cross-regional transmission, spreading between different brain regions. From the perspective of molecular structure, this protein has many chemically modified sites, including multiple sites that can be phosphorylated and cleaved. Research has found that in the patient's brain, the microtubule binding region becomes the main component of abnormal protein masses and constitutes their core structure [12].

The latest research has clarified the mechanism by which specific proteins in the brain damage neurons. When tau molecules carry excessive phosphate ions, they lose their function of maintaining the cytoskeleton, leading to damage to the internal transport system of the cell. This process is regulated by two key enzymes, GSK-3β and PP2A. Once an anomaly occurs, tau will undergo a configurational change and aggregate. These tiny polymers are more destructive than large fibrous tangles and mainly affect intercellular connections and energy metabolism. Abnormal tau is transmitted between cells through neural networks and transported by tiny vesicles (exosomes). When abnormal proteins enter healthy cells, they will induce normal tau to misfold, forming a chain reaction. The emergence of inflammatory responses will exacerbate this spread, forming a cycle of cell damage.

3.3 Neuroinflammatory Response

In the inflammatory response of AD, microglia exhibit A bidirectional regulatory effect. They can not only release inflammatory factors to damage neurons but also secrete nutrients and eliminate harmful substances (such as Aβ and tau) to maintain the balance of the neural environment. When inflammation occurs, activated microglia promote astrocytes to transform into type A1 through the NF-κB pathway, and then produce substances such as TNF, C1q and IL-1, which can damage neurons and oligodendrocytes. M2-type microglia, on the other hand, guide astrocytes to release anti-inflammatory substances through the STAT6 signaling pathway, thereby protecting the nerves [13]. The latest focus has been on two mutually cooperating proteins, TREM2 and APOE, which guide microglia in the brain to perform the cleaning function. Under normal conditions, it can not only eliminate damaged neurons but also control the level of inflammation.

3.4 Oxidative Stress and Mitochondrial Dysfunction

Oxidative stress and mitochondrial abnormalities are important links in the onset of Alzheimer's disease. When the oxidative and antioxidant systems within cells are out of balance, the excessive reactive oxygen species produced can damage macromolecules such as lipids, proteins and nucleic acids within the cells. Glutathione eliminates reactive oxygen species and enhances the antioxidant capacity of cells by converting into an oxidized state. In the brain regions affected by the lesion, not only does metabolic activity slow down, but the morphology of mitochondria also changes, and the function of energy metabolism enzymes declines accordingly. These mitochondrial functional disorders are manifested as decreased membrane potential, increased permeability and excessive generation of reactive oxygen species [14].

Oxidative stress and inflammation are jointly involved in the process of brain cell damage. When

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mitochondrial dysfunction occurs, harmful substances are released, triggering an inflammatory response. This change interferes with the process of mitochondrial division and fusion, thereby affecting energy generation. After proteins suffer oxidative damage, they are more likely to aggregate, form clumps and produce more harmful substances, creating a vicious cycle and continuously exacerbating cell damage. Cells have quality control mechanisms to clear damaged mitochondria and maintain the correct folding of proteins, but they are unable to resist continuous damage.

4. Progress in Research on Treatment Strategies

4.1 Analysis of Marketed Drugs

Over the past two decades, the FDA has approved two types of Alzheimer's drugs: cholinesterase inhibitors targeting cholinergic transfer and memantine acting on glutamatergic transfer. These drugs can delay cognitive decline [15]. And aducanumab has been approved as the first anti-amyloid treatment regimen, ushering in a new era of treatment. The results of its subsequent trials have shown a promising future.

4.2 Therapeutic Strategies Targeting Aβ

Aβ-targeted therapy mainly adopts three approaches in the research of Alzheimer's disease. BACE1 inhibitors reduce Aβ production by inhibiting β -secretase. BACE1 has significant neurological functions, and complete inhibition can cause adverse reactions. The γ-secretase inhibitor (semecastasta) is involved in the processing of multiple proteins, which leads to side effects and has not been clinically verified.

Breakthrough progress has been made in anti-A β monoclonal antibodies. Aducanumab has been approved by the FDA for the treatment of early cases. Donanemab outperformed Aducanumab in clearing brain amyloid plaques in the TRAILBLAZER-ALZ 4 study, confirming the therapeutic potential of antibody therapy [16].

4.3 Therapeutic Strategies Targeting Tau Protein

The tau protein treatment strategy in Alzheimer's disease research mainly includes three directions. One type is to regulate key kinases such as GSK-3β and CDK5 through the PI3K/AKT/GSK-3β pathway and p35/p39 protein, thereby inhibiting tau phosphorylation. The second category focuses on the catalytic effect of truncated fragments by blocking the transformation process of tau protein to the aggregated state. The third category is anti-tau antibody immunotherapy, which has shown good effects in improving the pathological changes of tau [17].

4.4 Other Treatment Strategies

In addition to conventional treatments, AD research also involves several new directions. Anti-inflammatory treatment protects neurons by controlling neuroinflammation and inhibiting microglial activation. A variety of non-steroidal anti-inflammatory drugs are currently in the clinical evaluation stage. Antioxidant therapy eliminates free radicals, reduces lipid peroxidation and alleviates oxidative stress in the patient's brain through vitamin E and curcumin, etc. Neural stem cell and mesenchymal stem cell transplantation can replace damaged neurons, promoting the secretion of neurotrophic factors and the repair of neural tissue. Gene therapy employs gene editing and viral vector technologies to regulate the expression of genes such as APP and PSEN1/2 [18-19].

4.5 Comparative Analysis of Treatment Strategies

The new therapy for AD has a dual nature. Antibody preparations such as ricanizumab and donanizumab can clear brain plaques and delay cognitive decline, but their efficacy is limited to early-stage patients and there is a risk of causing cerebral edema. Although laboratory research on tau protein has made progress, clinical translation still faces challenges. Traditional drugs that promote the secretion of neurotransmitters and neuroprotection in the brain can only alleviate the symptoms but cannot stop the progression of the disease. Although cutting-edge technologies such as stem cell transplantation and gene therapy have potential, their safety and efficacy still need to be deeply evaluated. Therefore, the combination of multiple treatment plans may have more advantages. Formulating personalized combined treatment plans based on the disease course stage and individual differences will be the key to future

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development.

Table 1 Summarizes the current therapeutic strategies for AD, including their mechanisms, clinical effects, and limitations.

Treatment Type	Representative Drugs	Mechanism of Action	Clinical Effects	Limitations
Aβ-Targeting Strategies	Anti-Aβ antibodies; BACE1 inhibitors; γ-secretase inhibitors	Clearance of brain Aβ aggregates; Inhibition of Aβ production; Promotion of microglial phagocytosis	Significant reduction in amyloid plaques; Antibodies show good efficacy in early-stage AD; Donanemab superior to Aducanumab in plaque clearance	ARIA risk; Limited to early-stage patients; BACE1/γ-secretase inhibition affects other vital functions; High treatment costs
Tau-Targeting Strategies	Tau phosphorylation inhibitors; Tau aggregation inhibitors; Anti-tau antibodies	Inhibition of tau hyperphosphorylation; Prevention of tau misfolding and aggregation; Clearance of pathological tau	Reduction in neurofibrillary tangles; Cognitive improvement in some patients; Promising preclinical results	Challenges in clinical translation; Limited long-term safety data; Mechanism requires further clarification
Anti-inflammatory	NSAIDs; Vitamin E; Curcumin;	Suppression of neuroinflammation; Free radical scavenging; Reduction of lipid peroxidation	Potential disease progression delay; Good safety profile; Beneficial for secondary symptoms	High individual variability; Mainly addresses secondary pathology; Better for prevention than treatment
Innovative Therapies	Stem cell therapy; Gene therapy	Replacement of damaged neurons; Neurotrophic factor secretion; Modulation of AD-related gene expression	Potential for neurodegeneration; Possible fundamental disease modification	Still in research phase; Safety and efficacy need validation; High technical requirements
Symptomatic Treatment	Cholinesterase inhibitors; Memantine	Regulation of neurotransmitter levels; Enhancement of synaptic function	Improvement in cognitive symptoms; Widely used in clinical practice	Cannot halt disease progression; Only symptomatic relief

5. Future Research Outlook

5.1 Limitations of Existing Research

At present, there are still many bottlenecks in the research of AD, and the pathological mechanism has not been clarified yet. The current diagnostic system overly relies on the manifestations of advanced cognitive impairment, and biological indicators are difficult to accurately identify early cases. At present, the approved drugs can only alleviate symptoms but fail to fundamentally intervene in the disease process or correct potential pathological changes [18].

5.2 Future Research Directions and Outlook

Alzheimer's research is making exciting leaps forward, with scientists exploring several promising

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new directions. Let's look at what's happening in four key areas:

Precision Medicine Advancement:

New advancements in precision medicine are revolutionizing our diagnostic and therapeutic models. Researchers deepen their understanding of disease characteristics by integrating multi-dimensional data such as genomics, proteomics and metabolomics. The application of computing technology can parse complex information in brain images and biomarkers, improving the accuracy of disease prediction. These in-depth understandings help the medical team to formulate personalized treatment plans based on the individual biological characteristics and disease features of the patients.

Technological Innovation:

Emerging cutting-edge technologies are reshaping research and clinical fields. Brain-computer interfaces have opened up new avenues and shown great potential for early screening and cognitive function improvement. Nano-drug delivery systems are expected to break through the limitations of the blood-brain barrier. Optogenetic technology enables precise regulation of neural circuits, providing a new direction for therapeutic intervention.

Preventive Medicine:

The research focus has shifted from simple treatment to prevention. The long-term impact of lifestyle habits and cognitive activities on brain health is currently being explored. Clinical trials focus on testing early intervention drugs for neurological diseases. Meanwhile, the health department assesses the input-output ratio of the prevention programs in each community, providing a basis for the medical system to optimize the allocation of prevention resources.

Translational Research:

Researchers are adopting innovative methods such as organoid culture, single-cell sequencing and high-throughput screening to deeply study the molecular mechanisms and signaling pathways at the cellular level. These methods can not only simulate the human microenvironment but also monitor drug responses in real time. By integrating multi-dimensional data analysis, effectiveness and safety can be accurately evaluated. This approach accelerates the development and validation process of new therapies and also provides more reliable scientific basis for individualized treatment plans.

5.3 Implementation Recommendations

The successful translation of research advances into practical applications requires systematic implementation strategies across multiple domains:

Clinical Practice Enhancement:

Standardized diagnosis and treatment standards are the key to improving the quality of AD care. Clinicians formulate treatment plans based on the latest research guidelines to ensure uniform diagnosis and treatment norms across medical institutions and provide patients with standardized and high-quality medical services. The advanced digital tracking system monitors the changes in patients' conditions in real time, assisting the medical team in adjusting treatment strategies promptly and optimizing intervention effects. The neurology, psychology, rehabilitation and social work teams, through close collaboration, provide patients with comprehensive care support from multiple dimensions such as cognitive function, mental health and daily living ability, ultimately achieving the best treatment effect.

Research Infrastructure Development:

A well-developed research system is the foundation for promoting AD research. In-depth collaboration among research institutions can not only expand the scale of clinical trials but also promote the sharing of data resources and accelerate scientific research breakthroughs. The establishment of a standardized sample bank provides reliable biological materials for researchers, which is conducive to in-depth studies of disease markers and development patterns. Through a rigorous clinical validation process, the innovative discoveries in the laboratory are transformed into practical treatment plans, ultimately benefiting the patient population.

Social Support Framework:

AD patients and their families need a complete support system to deal with the multiple challenges brought by the disease. A reasonable medical insurance plan can not only alleviate the economic burden on families but also ensure that patients receive continuous high-quality medical services. Professional

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support groups and systematic training provide caregivers with necessary skills guidance and psychological assistance, while creating space to help them balance caregiving stress. The application of intelligent technology-assisted tools can not only simplify the daily care process but also effectively ensure patient safety, allowing them to maintain their dignity while extending the time of independent living.

6. Discussion

6.1 Theoretical Contributions of Research Findings

This study has achieved significant theoretical breakthroughs through a systematic analysis of the pathological mechanism and treatment strategies of AD. The research has deepened the understanding of molecular pathology and integrated the research progress of multi-target therapy. By integrating the existing data, the interactive relationship between the amyloid protein cascade and the pathological process of tau protein was clarified, and at the same time, the importance of neuroinflammation in disease development was revealed, providing new ideas for the study of AD mechanisms. These findings have enriched the understanding of the pathogenic mechanism and laid the foundation for the optimization of treatment plans. The research also analyzed the current status of global AD research, revealed regional differences, and provided a basis for international collaboration and resource allocation.

6.2 Research Limitations

This study has several limitations. Due to the complex structure of the brain, the interactional relationships among various regions have not yet been fully clarified. The evaluation of therapeutic effects mainly relies on literature data and lacks long-term clinical observation. The regional adaptability of the treatment plan also needs to be verified. Future research should expand the sample size, extend the follow-up period, pay attention to the demographic characteristics of patients, and ensure the therapeutic effect through rigorous verification.

7. Conclusion

This review examines the current research status of Alzheimer's disease, including molecular pathology and treatment strategies. This disease involves multiple pathogenic mechanisms, mainly including amyloid protein cascade, tau protein pathology, neuroinflammation and mitochondrial dysfunction caused by oxidative stress. Recently, antibody treatments targeting Aβ and tau proteins have shown potential, but disease improvement and early intervention still face challenges. The limitations of the research indicate the need to integrate multi-target therapy and personalized medicine. In the future, multi-target combined therapies should be developed, individualized treatment should be promoted, and preventive intervention should be strengthened. A deeper understanding of the pathogenesis and treatment strategies will help control this neurodegenerative disease.

References

[1] Eratne D, Loi SM, Farrand S, Kelso W, Velakoulis D, Looi JC. Alzheimer's disease paper 1: Clinical update on epidemiology, pathophysiology and diagnosis. Australas Psychiatry. 2018 Aug;26(4):347-57.
[2] Ballard C, Gauthier S, Corbett A, Brayne C, Aarsland D, Jones E. Alzheimer's disease. Lancet [Internet]. 2011 Mar [cited 2025 Jul 30];377(9770):1019–31. Available from: https://linkinghub. elsevier.com/retrieve/pii/S0140673610613499
[3] Zhang XX, Tian Y, Wang ZT, Ma YH, Tan L, Yu JT. The epidemiology of alzheimer's disease modifiable risk factors and prevention. J Prev Alzheimers Dis [Internet]. 2021 Jul [cited 2025 Jul 30];8(3):313–21. Available from: https://linkinghub.elsevier.com/retrieve/pii/S2274580724005235
[4] Pudelewicz A, Talarska D, Bączyk G. Burden of caregivers of patients with alzheimer's disease. Scand J Caring Sci [Internet]. 2019 Jun [cited 2025 Jul 30];33(2):336–41. Available from: https: //onlinelibrary.wiley.com/doi/10.1111/scs.12626
[5] Kim B, Noh GO, Kim K. Behavioural and psychological symptoms of dementia in patients with alzheimer's disease and family caregiver burden: a path analysis. BMC Geriatr [Internet]. 2021 Dec [cited 2025 Jul 30];21(1):160. Available from: https://bmcgeriatr.biomedcentral. com/articles/10. 1186/s12877-021-02109-w

ISSN 2616-5791 Vol. 6, Issue 8: 98-105, DOI: 10.25236/AJMHS.2025.060813

[6] Sun BL, Li WW, Zhu C, Jin WS, Zeng F, Liu YH, et al. Clinical research on alzheimer's disease: progress and perspectives. Neurosci Bull [Internet]. 2018 Dec [cited 2025 Aug 2];34(6):1111–8. Available from: http://link.springer.com/10.1007/s12264-018-0249-z

[7] Šerý O, Povová J, Míšek I, Pešák L, Janout V. Molecular mechanisms of neuropathological changes in alzheimer's disease: a review. Folia Neuropathol [Internet]. 2013 [cited 2025 Aug 2];1:1–9. Available from: http://www.termedia.pl/doi/10.5114/fn.2013.34190

[8] Rostagno AA. Pathogenesis of alzheimer's disease. Int J Mol Sci [Internet]. 2022 Dec 21 [cited 2025 Aug 2];24(1):107. Available from: https://www.mdpi.com/1422-0067/24/1/107

[9] Khan S, Barve KH, Kumar MS. Recent advancements in pathogenesis, diagnostics and treatment of alzheimer's disease. Curr Neuropharmacol [Internet]. 2020 Nov 9 [cited 2025 Aug 2];18(11):1106–25. Available from: https://www.eurekaselect.com/182327/article

[10] McKhann GM, Knopman DS, Chertkow H, Hyman BT, Jack CR, Kawas CH, et al. The diagnosis of dementia due to alzheimer's disease: recommendations from the national institute on aging-alzheimer's association workgroups on diagnostic guidelines for alzheimer's disease. Alzheimers Dement [Internet]. 2011 May [cited 2025 Aug 2];7(3):263–9. Available from: https://alz-journals.onlinelibrary. wiley. com/doi/10.1016/j.jalz.2011.03.005

[11] Hardy JA, Higgins GA. Alzheimer's disease: the amyloid cascade hypothesis. Science [Internet]. 1992 Apr 10 [cited 2025 Aug 3];256(5054):184–5. Available from: https://www.science.org/doi/10. 1126/science.1566067

[12] Horie K, Barthélemy NR, Sato C, Bateman RJ. CSF tau microtubule binding region identifies tau tangle and clinical stages of alzheimer's disease. Brain [Internet]. 2021 Mar 3 [cited 2025 Aug 3];144(2):515–27. Available from: https://academic.oup.com/brain/article/144/2/515/6024973

[13] Cai Y, Liu J, Wang B, Sun M, Yang H. Microglia in the neuroinflammatory pathogenesis of alzheimer's disease and related therapeutic targets. Front Immunol [Internet]. 2022 Apr 26 [cited 2025 Aug 3]; 13: 856376. Available from: https: //www. frontiersin. org/articles/10. 3389/fimmu. 2022. 856376/full

[14] Song T, Song X, Zhu C, Patrick R, Skurla M, Santangelo I, et al. Mitochondrial dysfunction, oxidative stress, neuroinflammation, and metabolic alterations in the progression of alzheimer's disease: a meta-analysis of in vivo magnetic resonance spectroscopy studies. Ageing Res Rev [Internet]. 2021 Dec [cited 2025 Aug 3];72:101503. Available from: https: //linkinghub. elsevier. com/retrieve/pii/S1568163721002506

[15] Khachaturian AS, Hayden KM, Mielke MM, Tang Y, Lutz MW, Gustafson DR, et al. Future prospects and challenges for alzheimer's disease drug development in the era of the NIA-AA research framework. Alzheimers Dement [Internet]. 2018 Apr [cited 2025 Aug 3];14(4):532–4. Available from: https://alz-journals.onlinelibrary.wiley.com/doi/10.1016/j.jalz.2018.03.003

[16] Zhang Y, Chen H, Li R, Sterling K, Song W. Amyloid β-based therapy for alzheimer's disease: Challenges, successes and future. Signal Transduct Target Ther [Internet]. 2023 Jun 30 [cited 2025 Aug 3];8(1):248. Available from: https://www.nature.com/articles/s41392-023-01484-7

[17] Gao Y, Tan L, Yu JT, Tan L. Tau in alzheimer's disease: Mechanisms and therapeutic strategies. Curr Alzheimer Res [Internet]. 2018 Jan 23 [cited 2025 Aug 3];15(3):283–300. Available from: https: //www.eurekaselect.com/151650/article

[18] Long JM, Holtzman DM. Alzheimer disease: an update on pathobiology and treatment strategies. Cell [Internet]. 2019 Oct [cited 2025 Aug 3];179(2):312–39. Available from: https://linkinghub.elsevier. com/retrieve/pii/S0092867419310074

[19] Cummings J, Lee G, Zhong K, Fonseca J, Taghva K. Alzheimer's disease drug development pipeline: 2021. Alzheimers Dement Transl Res Clin Interv [Internet]. 2021 Jan [cited 2025 Aug 3]; 7(1): e12179. Available from: https://alz-journals.onlinelibrary.wiley.com/doi/10.1002/trc2.12179