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CHEMICAL BASIS OF ALZHEIMER'S DISEASE: MOLECULAR PATHWAYS AND THERAPEUTIC TARGETS

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Abstract

Alzheimer's disease (AD) is a progressive, multifactorial neurodegenerative disorder and the leading cause of dementia worldwide. The disease is characterized by memory impairment, cognitive decline, and behavioral abnormalities. The major pathological hallmarks of AD include extracellular amyloid-beta (Aβ) plaque deposition and intracellular neurofibrillary tangles formed by hyperphosphorylated tau protein, which ultimately cause neuronal death and synaptic loss, oxidative stress, mitochondrial dysfunction, and chronic neuroinflammation. Multiple molecular pathways contribute to neuronal degeneration and cognitive impairment. Recent studies have highlighted the involvement of genetic factors such as amyloid precursor protein (APP), presenilin (PSEN1 and PSEN2), and apolipoprotein E (APOE). Unfortunately, patients with AD may suffer for many years with progressive dementia due to a lack of effective treatment options. With an aging population in many countries, AD is estimated to affect 78 million people worldwide by 2030. This review summarizes the molecular mechanisms underlying Alzheimer's disease and discusses recent advances in therapeutic targets and diagnostic biomarkers.

Keywords: Alzheimer's Disease, Amyloid-Beta Plaques, Dementia, Neurofibrillary Tangles, Neurodegeneration, Amyloid Precursor Protein, Presenilin, Apolipoprotein

1. Introduction

Alzheimer's disease is a chronic neurodegenerative disorder primarily affecting elderly individuals. It accounts for approximately 60–70% of dementia cases globally. The disease gradually impairs memory, language, decision-making ability, and cognitive functions. The pathological features of AD were first described by Alois Alzheimer, a German physician who identified the typical disease of the brain in a 51 years old woman patient in 1906. AD is considered the fifth leading cause of death among women compared to being the eighth among men. Globally, dementia is the fifth leading cause of death with a new case every three seconds. Currently, about 23 million in the Asia Pacific, 8.8 million in Europe, 5.8 million in the USA, 5.3 million in India, 50 million people worldwide are living with dementia and it would reach 152 million by 2050.

The exact etiology of Alzheimer's disease remains unclear; however, several molecular mechanisms are involved in disease progression. The amyloid cascade hypothesis, tau pathology, neuroinflammation, oxidative stress, and mitochondrial dysfunction are considered central contributors to neuronal degeneration.

2. Amyloid-Beta Plaque Formation

The amyloid cascade hypothesis is one of the most widely accepted theories explaining Alzheimer's disease pathogenesis.

Amyloid plaques and neurofibrillary tangles (NFTs) in the brain are the neuropathological hallmarks of Alzheimer's disease (AD). Amyloid plaques are composed of β-amyloid peptides (Aβ), while NFTs contain hyperphosphorylated tau proteins. Amyloid precursor protein (APP) is a transmembrane protein normally involved in neuronal growth and repair. In AD, APP undergoes abnormal cleavage by β-secretase and γ-secretase enzymes, producing amyloid-beta peptides, especially Aβ42, which aggregate to form extracellular plaques.

Accumulation of Aβ peptides causes:

- Synaptic dysfunction (memory loss)
- Neuronal toxicity

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- Calcium imbalance
- Oxidative stress
- Activation of inflammatory pathways

fibrils entangle with cellular debris to form the dense, insoluble senile (amyloid) plaques found in the spaces between neurons. Amyloid plaques interfere with neuronal communication and eventually trigger neuronal death.

3. Tau Protein Hyperphosphorylation

Tau is a microtubule-associated protein responsible for stabilizing neuronal microtubules. In Alzheimer's disease, tau becomes abnormally hyperphosphorylated, causing detachment from microtubules and formation of neurofibrillary tangles (NFTs). In AD, this balance is disrupted by overactive kinases (enzymes that add phosphate) and underactive phosphatases (enzymes that remove phosphate).

Consequences of tau pathology include:

- Disruption of axonal transport
- Cytoskeletal instability
- Synaptic failure
- Neuronal apoptosis
- Difficulty communicating, swallowing, or walking
- Cognitive decline

Tau tangles correlate strongly with cognitive decline severity in AD patients.

Flow diagram:

Tau protein

↓

Hyper phosphorylation

↓Kinase

Detached Tou

↓

Aggregation

↓

NFTs

↓

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Neurodegeneration

↓

Dementia

4. Neuroinflammation

Neuroinflammation plays a crucial role in Alzheimer's disease progression. Activated microglia and astrocytes release inflammatory cytokines such as:

- Tumor necrosis factor-alpha (TNF-α)
- Interleukin-1β (IL-1β)
- Interleukin-6 (IL-6)
- Inflammasome Activation
- Blood-Brain Barrier (BBB) Leakage

These inflammatory mediators enhance neuronal injury and accelerate Neurodegeneration. Extrinsic factors, such as brain trauma, diet, systemic and local infections, and the gut microbiota, have an impact on the inflammatory component of Alzheimer disease.

Recent studies have shown that excessive activation of microglia contributes to synaptic loss and neuronal toxicity. Chronic neuroinflammation also promotes amyloid deposition and tau pathology.

A simplified pathway representation:

Aβ / Tau accumulation

↓

Microglial activation

↓

Cytokine release

↓

Oxidative stress

↓

Neurodegeneration

5. Oxidative Stress

Oxidative stress is a process referring to an imbalance between antioxidants and oxidants in favour of oxidants. It occurs due to an imbalance between reactive oxygen species (ROS) production and antioxidant defense mechanisms. Emerging evidence suggests that accumulated oxidative stress may be one of the key mechanisms causing cognitive aging and

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neurodegenerative diseases such as Alzheimer's disease (AD).Oxidative stress participates in the development of AD by promoting Aβ deposition, tau hyperphosphorylation, and the subsequent loss of synapses and neurons.

In AD brains:

- Increased lipid peroxidation occurs
- Protein oxidation damages neurons
- DNA damage accumulates
- Mitochondrial dysfunction
- Metal Dyshomeostasis

Amyloid-beta peptides enhance ROS generation, which further aggravates neuronal degeneration.

6. Mitochondrial Dysfunction

Mitochondria are essential for ATP production and cellular energy metabolism. In the brain, where neurons have exceptionally high energy demands to maintain synaptic activity and plasticity, dysfunction in mitochondrial processes compromises neuronal function and viability, contributing to early neuronal death and the onset of the AD symptoms. In Alzheimer's disease, mitochondrial dysfunction results in:

- Reduced ATP synthesis (Bioenergetic Failure)
- Increased oxidative stress
- Calcium dysregulation
- Neuronal apoptosis
- Impaired Dynamics & Mitophagy

Defective mitochondrial function impairs neuronal survival and contributes significantly to cognitive decline. Mitochondria dysfunction leads to altered electron transport chain function, free radical generation and oxidative stress.

7. Genetic Factors in Alzheimer's Disease

Several genes are associated with AD pathogenesis:

Gene	Function	Role in AD
APP	Amyloid precursor protein	Increased Aβ production
PSEN1	Presenilin-1	Alters γ-secretase activity
PSEN2	Presenilin-2	Promotes amyloid accumulation

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APOE ε4	Lipid transport protein	Major genetic risk factor

APOE ε4 allele significantly increases the risk of late-onset Alzheimer's disease by affecting amyloid clearance and lipid metabolism.

8. Synaptic Dysfunction and Neuronal Death

Synaptic dysfunction is an early feature of Alzheimer's disease. Aβ oligomers impair neurotransmitter signaling and reduce synaptic plasticity. Synaptic impairment is likely to be the basis of memory loss in AD

Neuronal death occurs through:

- Apoptosis
- Excitotoxicity
- Calcium overload
- Inflammatory signaling
- Synaptic Stripping
- Damage of nucleic acid

Loss of synapses directly correlates with memory impairment and cognitive decline.

Flow chart:

Aβ Plaques

↓

Synaptic Dysfunction

↓

Neurotransmission

↓

Memory & Learning Deficits

↓

Neuronal Degeneration (Microglial Activation)

↓

Neuronal Apoptosis

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9. Biomarkers and Diagnosis

Biomarkers are measurable indicators that reflect biological processes occurring within the body. They may be detected in blood, body fluids, organs, or tissues, and some can also be assessed through digital methods. Biomarkers assist doctors and researchers in monitoring normal physiological functions, identifying disease conditions, and evaluating health status.

Important biomarkers used in AD diagnosis include:

- Cerebrospinal fluid (CSF) Aβ42
- Total tau protein
- Phosphorylated tau
- PET imaging biomarkers
- Genetic biomarkers

Recent advances in molecular diagnostics and neuroimaging or Positron Emission Tomography (PET) ,structural MRI have improved early detection of Alzheimer's disease.

10. Therapeutic Approaches

Current therapeutic strategies for Alzheimer's Disease mainly focus on slowing disease progression and reducing neuronal damage. These approaches include:

- Amyloid-beta clearance
- Inhibition of tau protein aggregation
- Modulation of neuroinflammatory pathways
- Antioxidant-based therapies
- Neuroprotective strategies

Recently approved anti-amyloid therapies have shown moderate clinical benefits, although challenges remain regarding safety and long-term efficacy.

11. Future Perspectives

Future research should focus on:

- Early Diagnostics and Biomarkers
- Gene-targeted therapies
- Personalized medicine
- Stem cell therapy
- Neuroimmune modulation

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- Disease-Modifying Therapeutics
- Emerging Frontiers
- Precision and Preventive Medicine

The most popular techniques present for detecting local brain functional changes use nuclear medicine imaging devices: Positron Emission Tomography (PET) and Single Photon Emission Computed Tomography (SPECT). Understanding the complex interaction among amyloid deposition, tau pathology, neuroinflammation, and metabolic dysfunction may lead to more effective treatments. Continued multidisciplinary research is expected to pave the way for innovative treatments and improved management of Alzheimer's disease in the future.

12. Conclusion

Alzheimer's disease is a multifactorial neurodegenerative disorder involving complex molecular mechanisms. Amyloid-beta accumulation, tau hyperphosphorylation, oxidative stress, mitochondrial dysfunction, neuroinflammation, and genetic susceptibility collectively contribute to disease progression. Although significant progress has been made in understanding AD pathology, effective disease-modifying therapies are still limited. Ongoing research focused on elucidating molecular pathways, identifying reliable biomarkers, and developing targeted therapeutic interventions holds promise for improving early diagnosis, slowing disease progression, and enhancing the quality of life of affected individuals.

Continued research into molecular pathways and targeted therapeutic approaches may provide better strategies for prevention, diagnosis, and treatment of Alzheimer's disease.

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