# Alzheimer's Disease Pathogenesis: Classic Versus Novel Perspectives

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**Abstract.** Alzheimer's disease (AD) is a neurodegenerative disease of the central nervous system characterized by progressive cognitive impairment and behavioral deficits. Its pathogenesis is complex and has not been fully elucidated to date. This review aims to systematically elaborate on the multifactorial pathogenic mechanisms of AD. Traditionally, senile plaques formed by β-amyloid (Aβ) deposition and neurofibrillary tangles caused by hyperphosphorylation of the microtubule-associated protein Tau are regarded as the core pathological features of AD. In recent years, studies have found that microglial dysfunction, gut microbiota dysbiosis, mitochondrial dysfunction, and genetic risk factors all play key roles in the occurrence and progression of AD. These mechanisms are intertwined, forming a complex network that collectively drives neuronal loss and synaptic damage. This article reviews the latest research progress on the aforementioned major mechanisms, aiming to provide a theoretical basis for in-depth understanding of the pathophysiological processes of AD. Finally, based on the understanding of the multi-mechanism network, this article prospects the multimodal therapeutic strategies targeting Aβ, Tau, and neuroinflammation in combination, which may be an important direction for the development of new AD drugs in the future.

**Keywords:** Alzheimer's disease (AD), β-amyloid protein (Aβ), Tau, drug targets.

## 1. Introduction

Alzheimer's disease (AD) is a degenerative brain disease that commonly occurs in middle-aged and elderly individuals. Patients experience irreversible gradual decline in memory, along with a certain degree of deterioration in other cognitive abilities. AD is characterized by the destruction of nerve cells and neural connections in the cerebral cortex, as well as a significant decrease in brain mass [1].

Dr. Alois Alzheimer discovered the main characteristics of AD through autopsy on his patient, making significant contributions to dementia research. To honor his significant contributions, his colleagues named the disease after him [2].

Alzheimer's disease (AD) exerts a profound negative impact on humans. It is the most common form of dementia, accounting for approximately 60-80% of all dementia cases [3]. The World Health Organization (WHO) estimates that in 2021, the number of people living with dementia exceeded 55 million. This figure is projected to rise to 78 million by 2030 and 139 million by 2050 [4]. These figures indicate a growing number of people affected by dementia, suggesting that the prevalence of AD is highly likely to keep rising.

AD has an extremely complex pathogenesis. Currently, most research on AD focuses on its mainstream classical mechanisms, while there is a lack of comprehensive descriptions of the latest mechanisms. Although numerous newly identified mechanisms have been reported in recent studies, there is a scarcity of overall summaries integrating both traditional and emerging mechanisms. This article will introduce two mainstream core mechanisms and four newly identified research mechanisms of AD pathology, aiming to provide a relatively systematic summary and offer insights for the development of drugs for AD.

## 2. Traditional Pathogenic Mechanisms of Alzheimer's Disease

The traditional pathogenic mechanisms of Alzheimer's disease (AD) mainly include the β-amyloid hypothesis and the mechanism related to Tau protein and neurofibrillary tangles.

### 2.1. The β-Amyloid Hypothesis

Professor John Hardy played a pivotal role in the proposal and establishment of this hypothesis. In 1992, John Hardy and Gerald Higgins proposed that β-amyloid protein (AβP) is the main component of amyloid plaques, and its deposition is the pathogenic factor of pathological changes in AD. Neurofibrillary tangles, neuronal loss, vascular damage, and dementia symptoms are all direct consequences of this deposition [5]. Subsequent studies have further deepened and comprehensively developed this hypothesis.

Gene mutations can cause alterations in the structure and function of amyloid precursor protein (APP), which in turn leads to the deposition of β-amyloid protein in the cerebrospinal fluid (CSF), forming β-amyloid plaques [6]. β-amyloid plaque deposition can result in a reduction in the number of neuronal axons in the hippocampus. Additionally, high concentrations of β-amyloid protein can overactivate synaptic NMDA receptors, leading to synaptic loss [6]. Both of these pathways contribute to the pathology of AD.

### 2.2. Tau Protein and Neurofibrillary Tangles

Tau protein is a type of microtubule-associated protein. Under controlled phosphorylation modification, it can bind to microtubules and promote their assembly. However, hyperphosphorylation of Tau protein causes it to lose its ability to bind to microtubules and dissociate from them. The dissociated abnormal Tau protein then self-aggregates, first forming insoluble paired helical filaments and straight filaments, and eventually assembling into neurofibrillary tangles, which in turn impair neuronal function [3].

The accumulation of neurofibrillary tangles reduces acetylated α-tubulin, damaging the structure and function of neurons. It also activates microglia and astrocytes, which release inflammatory factors, exacerbating neuroinflammation and neuronal damage. Additionally, it can induce misfolding of normal Tau protein in adjacent neurons, leading to the spread of Tau pathological changes in the brain and aggravating cognitive decline [3].

## 3. Recent Research Mechanisms

Regarding the recent research mechanisms of Alzheimer's disease (AD), this article will mainly introduce AD induced by LDAM, correlation studies between the gut-brain axis theory and AD, mitochondrial dysfunction, as well as AD induced by genetic risk factors.

### 3.1. Alzheimer's Disease Induced by Lipid-Laden and Dysfunctional Microglia (LDAM)

Microglia are resident immune cells of the central nervous system. A subset of microglia that are lipid-laden and dysfunctional is termed lipid-laden and dysfunctional microglia (LDAM). They are found in the brains of the aged and Alzheimer's disease (AD) patients, and their abnormal lipid metabolism may induce AD by impairing microglial function and neurons.

A variety of genes can induce the formation of LDAM, including the APOE gene (especially APOE4), TREM2 gene, REV-ERBα gene, and the ABC gene family (ABCA1, ABCA7) [7].

LDAM can induce AD through multiple pathways. It produces large amounts of proinflammatory cytokines: microglia release IL-β, which induces astrocytes to adopt a proinflammatory phenotype, thereby reducing nutritional support, releasing neurotoxic factors, and damaging synapses and neurons. LDAM also generates substantial cytotoxic factors such as reactive oxygen species (ROS) [7]. The massive production of ROS inhibits the activity of NMDA receptors at neuronal synapses, thereby impeding neurotransmitter transmission and leading to cognitive impairment. LDAM has severe defects in phagocytic function: its uptake of lipids such as cholesterol from the extracellular

space is reduced, resulting in massive extracellular cholesterol accumulation, which in turn inhibits neuronal electrical activity and disrupts the homeostasis of neuronal networks. Additionally, its capacity for phagocytic clearance of Aβ is diminished, exacerbating Aβ plaque formation. It can also induce Tau phosphorylation in neurons with the APOE4/4 genotype, promoting AD pathology [7].

### 3.2. Correlation Studies between the Gut-Brain Axis Theory and Alzheimer's Disease

The gut-brain axis is a system that enables bidirectional communication between the gut and the brain through neural, endocrine, immune, and metabolic pathways [8].

Gut microbiota dysbiosis is considered an important predisposing factor for the pathogenesis of Alzheimer's disease (AD), contributing to its occurrence and progression through four interconnected pathways. First, in the immune activation pathway, dysbiotic microbiota release proinflammatory substances such as lipopolysaccharides (LPS) and peptidoglycans, which activate intestinal mucosal immune cells and induce the release of proinflammatory cytokines. These cytokines penetrate the intestinal barrier, enter the systemic circulation, and then activate microglia in the brain via the damaged blood-brain barrier (BBB). The activated microglia subsequently release more proinflammatory factors and reactive oxygen species through the Toll-like receptor 2/4/TREM2 (TLR2/4/TREM2) pathway, which collectively induce β-amyloid (Aβ) deposition and Tau hyperphosphorylation, ultimately leading to neuronal death [8]. Second, in the metabolic disorder pathway, dysbiosis reduces the production of short-chain fatty acids (SCFAs) by normal microbiota, thereby losing their protective effects—including maintaining the intestinal barrier, inhibiting the overactivation of the hypothalamic-pituitary-adrenal (HPA) axis, and promoting the expression of brain-derived neurotrophic factor (BDNF) in the brain. Meanwhile, abnormal amino acid metabolism by the gut microbiota of AD patients produces harmful metabolites that enter the brain, further exacerbating neuroinflammation [8]. Third, in the neurotransmitter abnormality pathway, decreased abundance of microbiota that produce neurotransmitters such as γ-aminobutyric acid (GABA) and serotonin leads to insufficient peripheral neurotransmitters. This weakens the regulation of intracerebral pathways via the bloodstream or vagus nerve, triggering dysregulation of the cerebral cholinergic system and reduced synaptic transmission efficiency [8]. Fourth, in the barrier disruption pathway, dysbiosis first impairs intestinal epithelial tight junctions and increases intestinal barrier permeability, allowing microbiota and toxins to enter the bloodstream. LPS and proinflammatory factors in the blood then reduce the expression of tight junction proteins in the BBB. This, combined with the BBB damage caused by Aβ deposition in the brains of AD patients, ultimately enables peripheral toxins and proinflammatory factors to enter the brain, accelerating the pathological progression of AD [8].

### 3.3. Alzheimer's Disease Induced by Mitochondrial Dysfunction

Mitochondrial dysfunction is a core driver of the pathogenesis of Alzheimer's disease (AD). It induces the occurrence and progression of the disease through multidimensional pathological pathways and forms a vicious cycle with core pathological markers such as β-amyloid (Aβ) plaques and Tau neurofibrillary tangles (NFTs) [9].

From the perspective of interactions with pathological markers, abnormal function of the mitochondrial respiratory chain leads to excessive production of reactive oxygen species (ROS), which inhibits tau dephosphorylases (e.g., PP2A) and activates tau kinases (e.g., GSK-3β), thereby promoting Tau hyperphosphorylation and the formation of NFTs. Meanwhile, reduced ATP synthesis affects the activity of β- and γ-secretases, accelerating the cleavage of amyloid precursor protein (APP) into Aβ peptides. Aβ can directly bind to mitochondrial membrane proteins (e.g., TOMM40), and Tau can interact with voltage-dependent anion channel 1 (VDAC1), which in turn exacerbates mitochondrial damage [9]. In addition, Aβ can bind to the mitochondrial enzyme HSD10/ABAD to disrupt its function, and Tau oligomers can damage mitochondrial membrane potential by binding to cardiolipin, further amplifying the injury [10].

At the level of energy metabolism and stress damage, decreased efficiency of mitochondrial oxidative phosphorylation (OXPHOS) leads to abnormal glucose metabolism (downregulation of GLUT1/3 transporters) and lipid metabolism imbalance (toxic lipid accumulation due to impaired β-oxidation), triggering the interruption of neuronal energy supply. ROS can also oxidatively damage mtDNA and cardiolipin, activate the cGAS-STING pathway and NLRP3 inflammasome, and induce neuroinflammation and blood-brain barrier (BBB) disruption [9]. Moreover, mtDNA point mutations (e.g., genes encoding cytochrome c oxidase), nuclear gene (APP, PSEN1/2) mutations, and abnormal regulation of the APOEε4 allele can damage mitochondrial function either congenitally or acquiredly, exacerbating energy metabolism defects and oxidative stress [10].

In terms of mitochondrial quality control and calcium homeostasis, decreased expression of mitochondrial fusion proteins (MFN1/2, OPA1) and overactivation of fission protein (DRP1) lead to mitochondrial fragmentation, impairing axonal transport. Defects in the PINK1/Parkin pathway and lysosomal dysfunction block mitophagy, resulting in the accumulation of damaged mitochondria [9]. Meanwhile, abnormal function of the mitochondrial calcium uniporter (MCU) and excessive connection of mitochondria-associated ER membranes (MAMs) trigger calcium overload, inducing the opening of the mitochondrial permeability transition pore (mPTP) and activating the caspase cascade to trigger neuronal apoptosis [10].

### 3.4. Alzheimer's Disease Induced by Genetic Risk Factors

The pathogenesis of Alzheimer's disease (AD) is closely associated with genetic risk factors, which induce the disease primarily by regulating key processes such as synaptic function, Aβ metabolism, and neuroinflammation.

SORL1 is a critical risk gene, and its dysfunction can exacerbate pathological progression: loss-of-function variants or specific mutations reduce the lysosomal degradation efficiency of Aβ, and also impair the trafficking and signaling of synaptic receptors (such as TrkB and EphA4), leading to inhibited synaptic formation and exacerbated Aβ-induced synaptic loss [11]; its rare variants can also promote the amyloidogenic processing of APP and Aβ secretion [11]. APOEε4 is the strongest risk factor for late-onset Alzheimer's disease (LOAD). It reduces Aβ binding and clearance efficiency, inhibits postsynaptic NMDA receptor membrane expression and calcium influx to impair long-term potentiation (LTP), and also decreases the expression of synapse-related genes through transcriptional or epigenetic regulation [11]. Additionally, it synergizes with gut microbiota metabolites to enhance β-secretase activity and exacerbate Aβ aggregation [12].

TREM2 variants have a significant impact on microglial function. Loss-of-function variants (e.g., R47H) inhibit the transition of microglia to disease-associated phenotypes, reduce Aβ clearance, cause abnormal synaptic pruning during development, and exacerbate synaptic loss with pathological progression in adulthood [11]. Moreover, the gut microbiota metabolite LPS can further inhibit TREM2 expression and weaken anti-inflammatory signaling [12].

In addition, LILRB2 acts as a high-affinity receptor for Aβ oligomers. Upon activation, it disrupts actin cytoskeleton stability through downstream signaling, resulting in an imbalance in synaptic plasticity [11]. CD33 variants enhance its expression, which inhibits microglial Aβ phagocytosis and promotes inflammation [12]. MicroRNAs (miRNAs) are also involved in regulation: for example, miR-33 targets ABCA1 to inhibit APOE lipidation, and miR-34a inhibits TREM2 expression, both of which reduce Aβ clearance efficiency [12]. These genetic factors interact through multi-level mechanisms, collectively mediating synaptic damage and pathological progression in AD.

## 4. Conclusion

In summary, research on the pathogenesis of Alzheimer's disease (AD) has transitioned from a classical single-factor understanding to a multi-dimensional, network-based systematic understanding. Among the traditional core mechanisms, β-amyloid (Aβ) deposition and hyperphosphorylation of the microtubule-associated protein Tau remain the initiating and core

driving links in the pathological process, laying the foundation for understanding the essence of the disease. However, newly identified mechanisms in recent years—such as neuroinflammation mediated by lipid-laden and dysfunctional microglia (LDAM), gut-brain axis dysfunction, mitochondrial energy metabolism disorders, and regulation by genetic risk factors—have further revealed the complexity of the disease's occurrence and progression. These mechanisms do not exist in isolation; instead, they are intertwined through pathways such as inflammatory signal transmission, metabolite exchange, and protein function interaction, forming a vicious cycle with Aβ and Tau pathology, and collectively exacerbating synaptic damage and neuronal loss.

The systematic collation of the aforementioned multi-mechanism network not only deepens the understanding of the pathophysiological processes of AD but also provides key insights for the development of clinical therapeutic strategies. Given that intervention targeting a single mechanism is often insufficient to block disease progression, multimodal therapeutic strategies with combined targets based on Aβ clearance, Tau disaggregation, and neuroinflammation regulation are expected to break through existing therapeutic bottlenecks and become an important direction for the development of new AD drugs in the future.

Future research needs to continue exploring new mechanisms while strengthening the analysis of associations between traditional and emerging mechanisms to identify key regulatory nodes and interactive pathways. With the deepening of understanding of disease mechanisms, targeted multi-target intervention strategies will be gradually improved, providing more effective theoretical and practical support for reducing the prevalence of AD and improving patient prognosis.

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