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# Research Progress on the Pathogenesis of Alzheimer's Disease

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## Abstract

Alzheimer's disease (AD) is a progressive neurodegenerative disorder and the most common form of dementia in the elderly. Currently, its pathogenesis is no longer confined to traditional theories but instead exhibits the characteristics of a complex network involving multi-factorial and multi-level interactions. Traditional research has long focused on the classic pathological hypotheses of $\beta$-amyloid (A$\beta$) deposition and Tau protein hyperphosphorylation. However, the pathogenesis of Alzheimer's disease (AD) involves more extensive systemic imbalances, indicating that its pathology has transcended the classical pathways of A$\beta$ and Tau proteins. It manifests as a widespread and interconnected network of functional dysregulation at molecular, cellular, and systemic levels, encompassing multiple domains such as protein homeostasis disruption, metabolic pathway disturbances, neuroimmune inflammation, cerebrovascular dysfunction, and gut-brain axis dysregulation. Therefore, therapeutic strategies targeting a single target often yield suboptimal outcomes. Current studies have revealed that core molecular pathology does not exist independently from emerging mechanisms such as neuroinflammation, metabolic dysfunction, vascular impairment, and gut microbiota dysbiosis. Instead, these factors jointly drive the pathological progression of AD through complex interactions. This review aims to systematically integrate recent advances from molecular and cellular levels to the systemic level, elucidating the specific patterns by which these mechanisms intertwine and amplify each other. By doing so, it seeks to uncover the systemic nature of AD pathology and provide a solid theoretical basis for shifting towards multi-targeted, systemic intervention strategies in the future.

## Keywords

Alzheimer's Disease, $\beta$-Amyloid, Tau Protein, Neuroinflammation, Systemic Imbalance

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## 1. Introduction

Alzheimer's disease (AD) is a progressive neurodegenerative disorder and the most common form of dementia in the elderly, with main clinical manifestations including progressive memory impairment, cognitive decline, and neuropsychiatric symptoms [1] [2]. Its pathological features include extracellular A$\beta$ plaque deposition and intracellular neurofibrillary tangles (NFTs) [3]. Historically, the amyloid cascade hypothesis and the Tau protein hypothesis have been the primary directions in AD pathology research [4]. According to the amyloid cascade hypothesis, A$\beta$ accumulation triggers hyperphosphorylation and aggregation of Tau protein, leading to NFT formation, inflammation, synaptic damage, neuronal loss, and ultimately cognitive decline and behavioral abnormalities [5]. However, repeated failures of clinical trials targeting single agents have prompted the academic community to gradually explore and recognize AD as a systemic disease involving multiple factors and pathways [6]. In recent years, the research perspective has shifted from isolated molecular events to complex interaction networks. Increasing evidence suggests a synergistic interaction between A$\beta$ and Tau proteins that jointly suppresses gene transcription related to synaptic function [7]. Although the immune system is deeply involved in the pathological processes of A$\beta$ and Tau, combination therapies targeting both A$\beta$ and Tau remain the primary approach to halting AD progression in its early stages [5].

The complexity of AD is reflected not only within the central nervous system but also in its extensive interactions with peripheral systems. Metabolic abnormalities are prevalent in patients with AD [8]. As a major peripheral organ involved in A$\beta$ metabolism, the liver plays a critical role in the pathophysiology of AD, and its cholesterol metabolic dysregulation may accelerate the pathological progression of AD. Furthermore, the gut microbiota engages in bidirectional communication with the brain via the microbiota-gut-brain axis, and dysbiosis of this microbiota is closely linked to the pathogenesis of AD [9]. Neuroinflammation, one of the core features of AD, is closely associated with the activation of microglia and astrocytes [10]. This review will delve into multiple core interactive dimensions constituting the multidimensional pathogenic network of AD, including the interaction network of molecular pathological mechanisms, the interplay effects among neural, immune, and metabolic systems, and the bidirectional communication between the brain and peripheral systems, thereby comprehensively analyzing the process from molecular pathology to systemic imbalance [11]. It further emphasizes the importance of shifting focus from single molecular targets to understanding complex interaction networks, thus providing a theoretical foundation for developing more effective multi-target therapeutic strategies.

## 2. Interaction and Amplification Network of Core Molecular Pathology

### 2.1. Toxic Synergy and Positive Feedback Loop between Aβ and Tau Proteins

A$\beta$ and Tau proteins do not exist in isolation in the pathogenesis of AD but con-

stitute a mutually reinforcing, self-amplifying vicious cycle. The deposition of A$\beta$ oligomers and fibrils not only directly impairs synaptic function but also induces Tau hyperphosphorylation, leading to the formation of NFTs; their synergistic action exacerbates neuronal toxicity [12]. In this interaction, on one hand, A$\beta$ oligomers can activate specific kinases, such as glycogen synthase kinase-3 (GSK-3), to directly promote Tau hyperphosphorylation [13]. GSK-3 can modify multiple sites on the Tau protein within NFTs, and its overexpression is associated with Tau hyperphosphorylation, neuronal death, and cognitive decline. On the other hand, abnormal Tau protein can impair neuronal function by affecting the metabolism of amyloid precursor protein (APP), thereby promoting A$\beta$ production and aggregation [14]. This positive feedback loop promotes the close interplay of two pathological processes, which may collectively contribute to disease progression. Wha Jin Lee *et al.* found that A$\beta$ pathology can accelerate the spread of Tau pathology in the brain. Combining cross-sectional and longitudinal molecular imaging with network connectivity analysis, this study revealed that the lateral entorhinal cortex, as an early site of Tau NFT formation, is influenced by remote, connection-mediated A$\beta$/Tau interactions, identifying two types of A$\beta$/Tau interactions associated with the initiation and acceleration of Tau spread [15]. Beyond direct interactions, A$\beta$ and Tau can also synergistically damage neurons through shared downstream pathways [16]. For instance, Musa O Iliyasu *et al.* pointed out that A$\beta$ aggregation triggers oxidative stress, inflammatory cascades, and caspase activation, leading to Tau hyperphosphorylation into NFTs and ultimately resulting in neuronal injury [17]. Moreover, their combined toxicity far exceeds that of either pathology alone, jointly impairing synaptic function, inducing neuroinflammation, and causing cognitive decline [5]. Alejandro R Roda, in animal models and clinical trials of A$\beta$-targeted immunotherapy, found that treatment not only reduced A$\beta$ but also lowered Tau levels; similarly, Tau-targeted immunotherapy also reduced A$\beta$ levels [5]. This suggests that even in the early stages of the disease, the combined application of therapies targeting both A$\beta$ and Tau may become an effective strategy to delay AD progression. Therefore, a thorough understanding of this positive feedback loop not only provides a theoretical basis for developing combination therapies that can simultaneously target A$\beta$ and Tau pathology (particularly in the early stages of the disease), but also suggests that monitoring the progression of A$\beta$ pathology may hold significant biomarker value for predicting Tau diffusion and disease staging.

### 2.2. The Role of Microglia and Astrocytes in Pathological Propagation

Microglia and astrocytes, as the primary glial cells of the central nervous system, play pivotal roles in the propagation and amplification of AD pathology, forming a tight triangular interaction network with A$\beta$/Tau pathology. Microglia are the resident immune cells of the brain; they sense A$\beta$ via receptors such as TREM2 and subsequently exert clearance functions [18]. However, in late-stage AD, the clearance function of microglia often becomes impaired, further promoting the release of inflammatory factors such as interleukin-1$\beta$ (IL-1$\beta$) and tumor necrosis

factor-$\alpha$ (TNF-$\alpha$). These pro-inflammatory factors can exacerbate Tau phosphorylation and neuronal damage, creating a vicious cycle of neuroinflammation [19]. TREM2, a key immune receptor on microglia, is a significant genetic risk factor for late-onset AD; loss-of-function mutations (e.g., R47H) disrupt immune surveillance, aggravate amyloid pathology, and promote neuroinflammation. The TREM2-apolipoprotein E (APOE) pathway is the core mechanism driving the disease-associated microglia (DAM) phenotype. In AD, reactive astrocytes significantly influence A$\beta$ aggregation and clearance by releasing APOE, particularly the APOE4 isoform [20]. Meanwhile, various factors secreted by astrocytes also regulate microglial activity and synaptic function. The function and morphology of astrocytes are altered in the brains of AD patients, leading to dysregulation of their purinergic receptors (particularly the P2Y1 receptor); these receptors are not only crucial for maintaining normal astrocyte function but are also heavily involved in neuroinflammation in AD [21]. The neuroinflammatory environment constituted by these glial cells both triggers AD and exacerbates pathological spread and neuronal network disruption. In the preclinical stage of AD, levels of glial fibrillary acidic protein (GFAP) in plasma and soluble TREM2 (sTREM2) in CSF are already elevated. Marta Fernández-Matarrubia *et al.*, using methods such as enzyme-linked immunosorbent assay (ELISA) in populations with mild cognitive impairment, found that plasma GFAP was negatively correlated with the CSF A$\beta$42/40 ratio, suggesting that astrocytic reactivity may influence amyloid accumulation; whereas CSF sTREM2 was significantly correlated with CSF phosphorylated tau-181 (p-tau181) and neurogranin levels, indicating that microglial reactivity promotes Tau pathology [22]. Therefore, the tight interaction network formed by glial cells and A$\beta$/Tau collectively amplifies neurodegenerative processes by releasing inflammatory mediators, regulating pathological protein clearance, and influencing synaptic plasticity. This makes glial cell-associated molecules (such as TREM2, APOE, and GFAP) highly promising biomarkers for early diagnosis and intervention targets, providing a new direction for precision therapy based on neuroinflammatory stratification.

## 3. Systemic Driving Role of Metabolism and Energy Imbalance

### 3.1. Brain Insulin Resistance and Glucose-Lipid Metabolic Disorders

Impaired insulin signaling is prevalent in the brains of patients with AD, a phenomenon often referred to as "Type 3 diabetes" [23]. This impairment leads to reduced neuronal glucose utilization efficiency, exacerbates cerebral energy metabolism disorders, and further promotes A$\beta$ accumulation and Tau protein hyperphosphorylation. As a key kinase downstream of the insulin signaling pathway, abnormal activation of GSK-3 plays a central role in AD pathology. GSK-3 not only phosphorylates multiple sites on the Tau protein, promoting the formation of neurofibrillary tangles (NFTs), but also regulates A$\beta$ production, thereby establishing a close link between insulin resistance and the two core pathological fea-

tures of AD [24]. Furthermore, lipid metabolism abnormalities, particularly cholesterol metabolism disorders associated with the apolipoprotein E (APOE) genotype, serve as a critical metabolic hub linking genetic risk to pathological manifestations. The APOE ε4 allele is the strongest genetic risk factor for AD; by affecting cholesterol transport and metabolism, it directly alters cell membrane fluidity, A$\beta$ generation and clearance processes, and exacerbates neuroinflammatory responses [25]. Notably, the liver, as the primary organ for peripheral cholesterol metabolism and A$\beta$ clearance, contributes to AD progression through dysfunction that disrupts systemic lipid homeostasis. On the other hand, characteristic early changes in AD primarily involve oxidative stress responses resulting from mitochondrial dysfunction. While inducing A$\beta$/Tau toxicity, this response further damages biological macromolecules, disrupts intracellular calcium homeostasis, and ultimately becomes a driving force triggering apoptosis [6]. Mitochondrial dysfunction interacts with abnormal brain glucose and lipid metabolism to jointly drive the pathological process of AD.

And in animal model studies, Juhyun Song *et al.* established an Alzheimer's disease (AD) model by injecting streptozotocin (STZ) into the rat ventricles and found that guanidine butyramide may alleviate neuronal apoptosis and cognitive decline by reducing A$\beta$ accumulation, improving insulin signaling transduction, inhibiting apoptosis, and activating Nrf2-mediated antioxidant pathways, thereby serving as a potential therapeutic agent for Alzheimer's disease [26]. This suggests that interventions targeting cerebral insulin resistance and dysregulated glucose-lipid metabolism (e.g., lifestyle modifications or relevant pharmacotherapy) may serve as adjunctive therapeutic strategies to delay the progression of AD.

### 3.2. Sleep Disorders and Impaired Glymphatic System Function

The brain primarily clears metabolic waste such as A$\beta$ via the glymphatic system [27]. In patients with AD, sleep architecture is often disrupted, characterized mainly by reduced non-rapid eye movement (NREM) sleep time and weakened slow-wave activity (SWA). This disruption directly impairs the clearance capacity of the glymphatic system, accelerating the accumulation of pathological proteins. The function of the glymphatic system relies on the coordinated action of arterial pulsation and aquaporin-4 (AQP4) water channels located on astrocytic endfeet, among other factors. Under AD pathological conditions, these components may all be compromised. Astrocytes undergo morphological and functional changes, and their purinergic receptors (such as P2Y1 receptors) become dysregulated. This not only affects normal astrocyte function but also deeply participates in the neuroinflammatory processes of AD, potentially leading to a systemic decline in whole-brain metabolic waste clearance efficiency [21]. Furthermore, neuroinflammation itself is a significant factor disrupting sleep-wake regulation. For instance, abnormal activation of microglia and the release of pro-inflammatory cytokines may interfere with sleep by impairing the function of brain regions such as the hypothalamus [19]. Therefore, sleep disturbances, impaired glymphatic system function, and core AD pathology constitute a complex interactive network,

wherein neuroinflammation serves as a key hub and amplifier. In intervention studies targeting slow-wave sleep, Yee Fun Lee *et al.* used optogenetic methods to restore SWA in animal models, demonstrating that this strategy can prevent A$\beta$ accumulation and restore neuronal calcium homeostasis, thereby providing a promising therapeutic target for AD [28]. Therefore, improving sleep quality and enhancing lymphoid system function may serve as effective non-pharmacological approaches for AD prevention and early intervention.

## 4. Bidirectional Communication between the Brain and Peripheral Systems and Systemic Imbalance

### 4.1. Mechanisms of the Gut Microbiota-Gut-Brain Axis

Gut microbiota dysbiosis often affects immune homeostasis, systemic metabolism, and the production of neuroactive metabolites, thereby deeply participating in the pathological process of AD [29]. The gut microbiota, through producing metabolites such as short-chain fatty acids and regulating the host's immune system, constitutes a bidirectional communication network known as the gut-brain axis [30]. This communication involves not only neural pathways but also blood circulation and immune signaling molecules, continuously influencing the homeostasis of the central nervous system. On one hand, neuroactive substances produced by microbial metabolism can enter the circulatory system, subsequently affecting brain function. Furthermore, their products can regulate neuroimmune responses, directly or indirectly modulating the pathological processes of A$\beta$ and Tau proteins, and thus directly affect the integrity of the blood-brain barrier as well as the maturation and function of microglia via blood circulation and vagal nerve pathways [31]. On the other hand, persistent disruption of the gut microbiota can lead to increased intestinal permeability, triggering systemic chronic low-grade inflammation [32]. Such a sustained, low-level systemic inflammatory state disrupts immune balance, making it easier for peripheral inflammatory factors to enter the brain or influence the center through signal transduction. There exists a tight bidirectional link between systemic inflammation and neuroinflammation; abnormal activation of the peripheral immune system can affect the brain's immune microenvironment [33]. In AD, this association is particularly significant, where peripheral metabolic abnormalities (such as insulin resistance and lipid metabolism disorders) often coexist with gut microbiota dysbiosis, jointly exacerbating systemic inflammation. Systemic inflammation, in turn, aggravates central neuroinflammation through pathways such as disrupting the blood-brain barrier and activating microglia, providing a favorable microenvironment for A$\beta$ deposition and Tau protein hyperphosphorylation. In animal studies, Xueshen Qian *et al.* induced experimental periodontitis in APP/PS1 transgenic AD mice to alter gut microbiota composition, induce colonic inflammation, and disrupt the intestinal epithelial barrier. They found that this disruption of gut ecology led to elevated systemic inflammatory levels, which subsequently impaired the blood-brain barrier, triggered neuroinflammation and synaptic damage, ultimately exacerbat-

ing cognitive impairment and intracerebral A$\beta$ deposition in mice [34]. Therefore, intervention and modulation of gut microbiota may represent a novel adjunctive therapeutic approach for preventing or delaying AD progression.

### 4.2. Vascular Dysfunction and Blood-Brain Barrier Disruption

Cerebrovascular pathology is a common co-pathological feature of AD and is closely associated with cognitive decline. Common vascular pathologies include cerebral amyloid angiopathy and endothelial dysfunction, which lead to abnormal regulation of cerebral blood flow and compromised integrity of the blood-brain barrier (BBB) [35]. BBB disruption not only causes chronic cerebral hypoperfusion, resulting in neuronal energy crisis and dysfunction, but also permits inflammatory factors, neurotoxic substances, and other harmful molecules from the peripheral circulation to enter the brain parenchyma [33]. This loss of barrier function causes the brain to lose its critical immune privilege, exposing it to systemic pathophysiological changes. In normal aging and neurodegenerative diseases such as AD, the physiological properties of the BBB undergo pathological alterations or suffer damage; the extent of this disruption correlates with cognitive impairment and may even serve as a biomarker for disease diagnosis [35]. Therefore, cerebrovascular dysfunction and BBB leakage are crucial components of the systemic imbalance in AD. Furthermore, the clearance capacity of the damaged BBB is significantly reduced, representing a key peripheral-related factor contributing to the abnormal accumulation of A$\beta$ within the brain. Under physiological conditions, transporters on the BBB, particularly low-density lipoprotein receptor-related protein 1 (LRP1), are responsible for actively exporting A$\beta$ from the brain to the peripheral circulation for clearance [8]. However, in the pathological state of AD, cerebrovascular lesions and BBB dysfunction lead to reduced LRP1-mediated A$\beta$ efflux. Concurrently, the expression of the receptor for advanced glycation end products (RAGE), which mediates the transport of peripheral A$\beta$ into the brain, may increase, further exacerbating the net accumulation of A$\beta$ in the brain. Beyond the brain, the liver, as a major peripheral organ, plays a vital role in A$\beta$ metabolism and clearance; moreover, impaired hepatic cholesterol metabolism may aggravate the progression of AD [36]. Consequently, the decline in BBB clearance function, combined with dysfunction of peripheral clearance organs, collectively constitutes the systemic imbalance underlying A$\beta$ pathology.

Vascular factors and neurodegenerative lesions do not exist independently; rather, they interact to form a vicious cycle that ultimately leads to the overall failure of the "neurovascular unit." Vascular-originated injuries, such as the appearance of extracellular amyloid plaques and intracellular neurofibrillary tangles (NFTs) following cerebral ischemia, cause hyperphosphorylation of Tau protein, thereby exacerbating Alzheimer's disease-like pathological changes [37]. Conversely, neurodegenerative lesions further impair vascular regulatory functions, affecting the regulation of vascular tone and angiogenesis, which intensifies cerebrovascular dysfunction. Rebecca L. Winfree *et al.* employed immunoassays and mass spec-

trometry to measure FLT1 protein levels in the CSF, plasma, and brain tissue of hundreds of AD patients, while also assessing A$\beta$ and Tau pathological biomarkers and cognitive function. The results indicated that higher FLT1 levels in CSF were associated with Tau-positive status. Furthermore, among amyloid-positive individuals, elevated FLT1 levels correlated not only with increased phosphorylated Tau levels but also with poorer baseline memory performance; this interaction was also validated in brain tissue analyses [38]. These findings suggest that the upregulation of FLT1 is a response to amyloid pathology, and its interaction with amyloid may drive a cascade involving the vascular and immune systems, thereby exacerbating Tau pathology and cognitive decline. This underscores the importance of maintaining cerebrovascular health and blood-brain barrier integrity in the prevention and treatment of AD. Relevant imaging or humoral biomarkers (such as vascular-related proteins in CSF/plasma) may aid in assessing disease risk and progression.

The complex pathological networks currently under investigation largely rely on preclinical animal models and cross-sectional or retrospective human studies for evidence support, which introduces certain limitations. Firstly, existing animal models fall short in simulating the complete and slowly progressive pathological spectrum of human Alzheimer's disease (AD), thereby limiting the directness and reliability of translating research findings into clinical applications. Secondly, the AD patient population exhibits significant heterogeneity in genetic background, comorbidities, lifestyle factors, and extent of pathological involvement, which may obscure core driving mechanisms and lead to individual variations in treatment responses. Lastly, substantial uncertainties remain regarding the causal relationships and precise temporal sequences among key pathological elements—including A$\beta$ deposition, Tau protein pathology, neuroinflammation, and vascular dysfunction. Whether a single factor initiates cascade reactions first or multiple factors dysregulate and amplify each other simultaneously requires further longitudinal studies to elucidate. These limitations suggest that future research should focus on developing models more closely aligned with human disease characteristics, advancing biomarker-based patient stratification, and utilizing longitudinal cohort data to understand the temporal dynamics of pathological events better.

## 5. Summary and Outlook

In summary, viewing AD from the holistic perspective of systems biology reveals that it can no longer be encapsulated by the relatively linear amyloid-beta cascade hypothesis. Instead, it manifests as a dynamic network intricately woven from multiple core pathological mechanisms. These include classic A$\beta$ deposition and Tau hyperphosphorylation, but also encompass persistently activated neuroinflammation, cerebral energy metabolism failure, dysfunction of clearance systems such as the glymphatic system, and disrupted signaling interactions between the brain and peripheral systems. These mechanisms do not exist in isolation nor simply accumulate; rather, they are deeply interconnected and continuously self-

reinforcing, driving the disease from an early, subtle state toward overt dementia symptoms. It is precisely this network-like pathological characteristic that fundamentally explains the remarkable diversity in clinical manifestations and disease progression among different patients. It also profoundly elucidates why many drugs targeting single endpoints (particularly A$\beta$) over the past few decades have shown suboptimal efficacy in late-stage clinical trials: within such a complex disease network, targeting merely one node often fails to block the transmission and amplification across the entire network. Therefore, AD should essentially be regarded as a systemic and whole-body disorder, with its roots potentially lying in overall metabolic disturbances, immune imbalance, and vascular dysfunction. In light of this, future research must move beyond localized or single-dimensional approaches toward more comprehensive and integrative exploratory pathways. Therapeutic strategies are shifting from single-target pharmacotherapy for late-stage patients to multi-target, systemic, comprehensive interventions implemented at early disease stages. These include modulating microglial function to transition them from a pro-inflammatory state to a protective, reparative state; improving the energy metabolism efficiency of neurons and glial cells to restore damaged mitochondrial function; enhancing the capacity of the glymphatic system and blood-brain barrier to clear and transport metabolic waste and abnormal proteins; and regulating system-level interactions such as the gut-brain axis and peripheral immune responses to maintain balance between the brain and the systemic environment. Research and clinical management of AD are in a stage of continuous progress and optimization. By integrating basic and clinical research findings to develop systemic therapeutic strategies targeting multiple pathogenic mechanisms, there is hope for more effectively controlling this complex disease in the future, thereby improving patient prognosis and quality of life.

## Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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