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Multifactorial Pathogenesis, Diagnosis, and Therapeutic Strategies in Alzheimer's Disease

Yongzhang Lin

School of Life Sciences, Shanghai University
Shanghai, China, 200444
ghtyui@shu.edu.cn

Abstract:

Alzheimer's disease (AD) has traditionally been explained by the amyloid cascade hypothesis as its core mechanism. However, the limitations of single-target therapies reflect that AD cannot be simply explained by a linear pathogenic mechanism. This review examines key mechanisms including the Aβ-tau axis, neuroinflammation, genetic factors, and mitochondrial metabolic abnormalities, proposing that AD pathogenesis should instead be modeled as a multifactorial pathological network. Different pathological nodes amplify disease severity collectively, with multiple factors synergistically driving neuronal network dysfunction and cognitive decline. The review also examines trends in blood biomarkers, imaging, and digital metrics, exploring stratified diagnostics and node-targeted therapies for multifactorial pathogenesis. This model integrates diverse mechanisms into a comprehensive disease network, providing a theoretical foundation for precision medicine.

Keywords: Alzheimer's disease; Multifactorial pathogenesis; Amyloid protein; Tau; Neuroinflammation; Biomarkers; Disease-modifying therapy

1. Introduction

Alzheimer's disease is one of the most common neurodegenerative disorders and the primary cause of dementia in the elderly [2,19]. Despite decades of research into its molecular and cellular mechanisms, and despite researchers accumulating substantial evidence of pathogenic processes—including Aβ deposition, tau pathology, neuroinflammation, and neuronal loss [1,38]—the disease mechanism remains incompletely explained by any single theoretical framework. Clinical treatment outcomes vary significantly among individuals, and single-target interventions yield limited effects. These findings suggest that disease progression may not be explained by a simple linear cascade model [6].

The amyloid cascade hypothesis laid a crucial foundation for AD research [38]. However, as studies deepen and patient data expand, growing evidence indicates that Aβ, tau, immune inflammation, and metabolic abnormalities all influence disease progression [27]. These pathological factors do not fol-

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low a linear cause-and-effect sequence but are more likely to mutually regulate and amplify each other under specific conditions.

Therefore, conceptualizing AD as a multifactorial, dynamically evolving pathological network facilitates the integration of disparate mechanisms. Moreover, thoroughly understanding and refining the pathogenic mechanisms lays the theoretical groundwork for stratified diagnosis and intervention [4]. Building upon the review of classical mechanisms, this paper further emphasizes the interrelationships among key pathological factors to propose a more integrated pathogenic framework.

2. A Multifactorial Pathogenic Network of Alzheimer's Disease

2.1 Linear Cascade and Synergistic Drive of the Aβ-Tau Axis

Aβ deposition and abnormal tau aggregation have long been regarded as core pathological hallmarks of AD [1,38]. Amyloid precursor protein (APP) is cleaved by β- and γ-secretases to produce Aβ proteins, with Aβ42 exhibiting greater hydrophobicity that facilitates oligomerization and deposition. Current clinical data and research indicate that abnormal Aβ alone is not a sufficient condition for AD onset. Some patients maintain relatively stable cognitive function despite significant amyloid deposition. Reduced amyloid deposits also often fail to correlate linearly with clinical improvement [37,39]. These phenomena suggest Aβ functions better as an early influence within a multifactorial pathogenic framework, rather than independently driving disease progression [6]. A sequential and synergistic relationship likely exists between Aβ and tau. As shown in Figure 1, tau plays a crucial role in Aβ-mediated neurotoxicity. Abnormal tau phosphorylation, its propagation across neurons, and subsequent synaptic dysfunction correlate positively with cognitive decline [8-12]. The Aβ-tau interaction can be viewed as a dynamic coupling mechanism involving triggering and amplification [41]. Aβ establishes the pathological environment early in the disease, while tau pathology spreads and amplifies neuronal dysfunction.

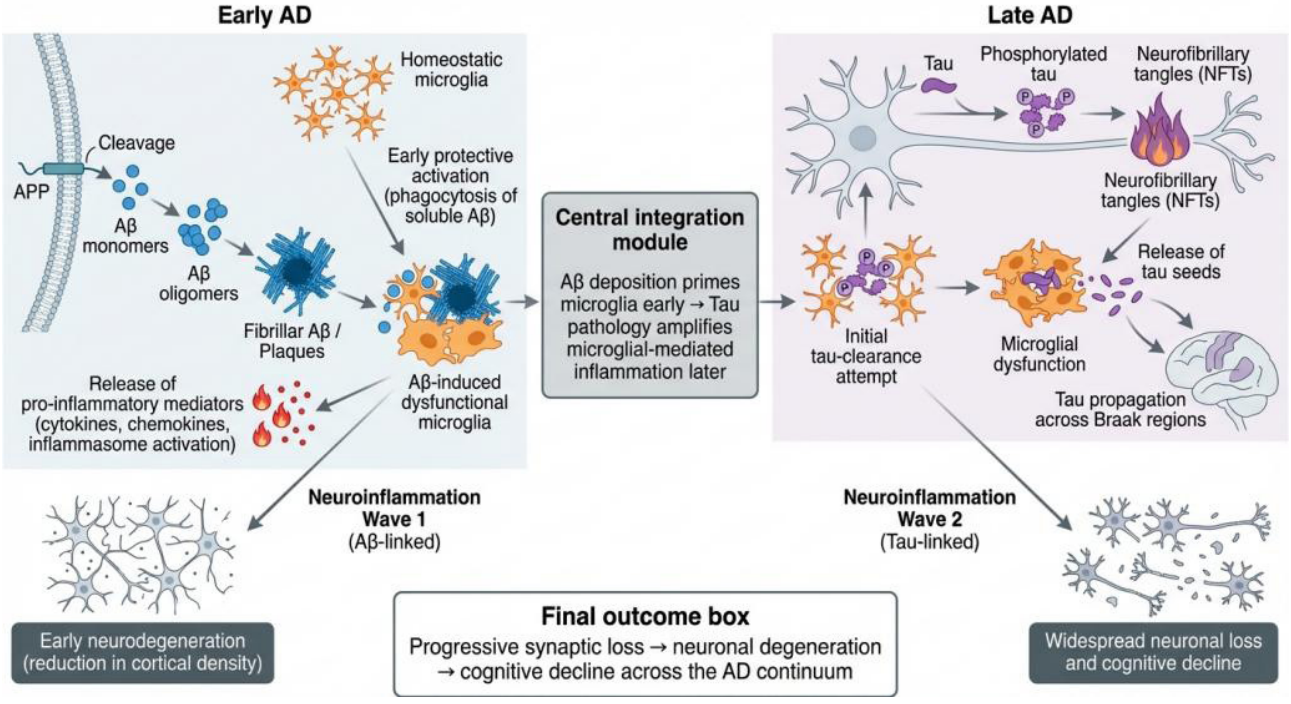

Figure 1. Stage-dependent coupling of amyloid-β, microglial activation, and tau pathology across the Alzheimer's disease continuum.

This schematic depicts a stage-dependent model linking amyloid-β (Aβ) accumulation, microglial activation, and tau-driven neurodegeneration across early and late phases of Alzheimer's disease (AD). In early AD, disrupted Aβ homeostasis leads to oligomer and plaque formation, triggering microglial activation. Initially protective responses may promote Aβ clearance, but sustained deposition drives microglial dysfunction and an Aβ-associated inflammatory response (Wave 1), contributing to early synaptic alterations.

A central integration module emphasizes temporal coupling between pathologies, whereby early Aβ deposition shapes microglial states that later amplify tau-associated inflammation. In late AD, tau hyperphosphorylation, aggregation, and propagation coincide with impaired microglial clearance and a second wave of neuroinflammation (Wave 2), facilitating neurofibrillary spread across Braak regions. These interacting processes culminate in progressive synaptic loss, neuronal degeneration, and cognitive decline, framing AD as a dynamic, stage-dependent network disorder rather than a linear cascade.

2.2 Mechanisms Amplifying Neuroinflammation

The functional state of microglia and astrocytes alters under different microenvironments, with specific pro-inflammatory states exacerbating neuroinflammation and thereby influencing pathological severity. Unlike neuroinflammation being viewed as a secondary reaction within traditional pathological frameworks, it more closely resembles an environment that accelerates disease progression [3,13]. Under controlled conditions of early Aβ accumulation, microglia enhance migration and phagocytose necrotic neurons to maintain local homeostasis. However, as pathological burden progressively increases, metabolic and signaling pathways undergo alterations. Inflammatory-primed microglia continuously release pro-inflammatory cytokines, which in turn exacerbate neuronal stress and synaptic damage [14]. Based on imaging and molecular studies, inflammatory signaling carries distinct biological significance in early versus late disease stages, with its effects dependent on the disease phase [7]. Within a multifactorial pathogenic framework, neuroinflammation should be viewed as a regulatory and amplifying factor—neither inherently pathogenic nor protective. Whether microglia maintain homeostasis or exacerbate neuroinflammation depends on the microenvironmental state.

2.3 Genetic and Mitochondrial Disorders

Based on current evidence, risk genes such as APOE ε4 not only affect Aβ clearance efficiency but also participate in regulating lipid metabolism and neuroinflammation, thereby altering system stability at multiple nodes [15,20,21]. In some familial AD cases, mutations in APP or PSEN also lead to increased Aβ production, making it more prone to oligomerization and deposition [17,38].

Concurrently, mitochondrial dysfunction and energy metabolism imbalance are increasingly recognized as critical factors in neuronal vulnerability. Mitochondrial dysfunction induces oxidative stress, reduced ATP production, and abnormal mitochondrial dynamics. These factors amplify neural network instability in patients with Aβ and tau pathology [16,18]. Mitochondrial impairment reflects decreased system stability and heightened disease susceptibility.

2.4 Multifactorial Pathogenesis Framework

Considering the aforementioned mechanisms, the pathogenesis of AD should be understood as a multifactorial, multistage construct. Aβ deposition, tau diffusion, inflammatory regulation, genetic susceptibility, and metabolic imbalance collectively influence disease progression [27,41]. Different nodes exhibit relative dominance at distinct disease stages, ultimately converging at the level of synaptic dysfunction and neuronal network dysfunction to drive the emergence and progression of clinical symptoms.

The multifactorial pathogenic framework does not entirely negate the classical pathological framework. Rather, it supplements it by incorporating additional factors influencing disease progression, emphasizes the interactions between these factors, and integrates them into a comprehensive system. By clarifying the distinct pathological processes and multiple pathogenic factors, we can provide research directions for subsequent diagnosis and targeted therapies.

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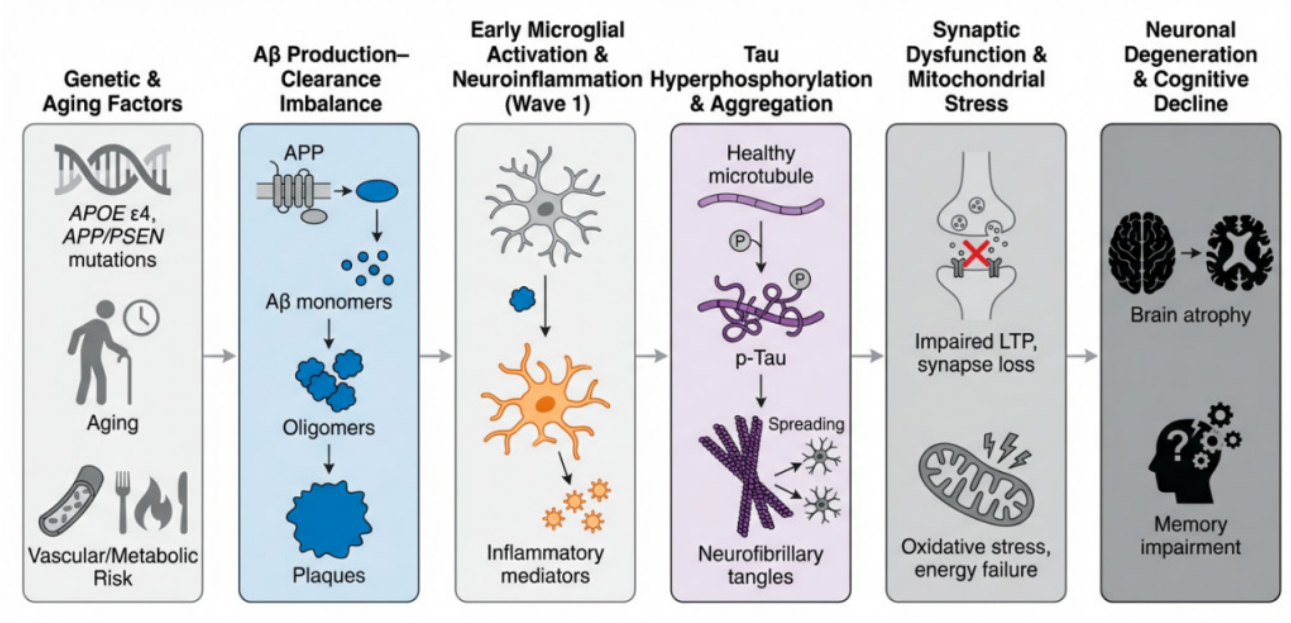

Figure 2. A multi-factorial, network-based model of Alzheimer's disease pathogenesis.

This schematic illustrates a network-based framework of Alzheimer's disease (AD) pathogenesis, in which interacting molecular, cellular, and circuit-level processes drive disease progression. Genetic susceptibility and aging-related factors disrupt amyloid-β (Aβ) homeostasis, promoting oligomer accumulation and plaque deposition. Early Aβ-associated pathology is linked to microglial activation and neuroinflammatory signaling, which shape the neural microenvironment. In this context, tau undergoes abnormal phosphorylation, aggregation, and propagation, contributing to synaptic dysfunction and mitochondrial stress. These converging processes ultimately lead to neuronal degeneration and cognitive decline. The model highlights stage-dependent interactions and feedback among pathogenic nodes, framing AD as a dynamic network disorder rather than a linear cascade.

3. Multimodal Diagnosis

The diagnosis of AD is increasingly centered on biomarker detection [5,19]. Aβ and tau-related markers enable disease identification prior to symptom onset [27]. Blood biomarkers, in particular, can accurately reflect a patient's disease status, type, and progression. For instance, plasma Aβ42/40 ratio and p-tau217, p-tau231 can differentiate AD from other neurodegenerative diseases [22,23]. Since blood sampling is required instead of invasive lumbar puncture for cerebrospinal fluid extraction, biomarker testing can be conducted in primary care settings, demonstrating significant application potential [24]. FDA-approved blood testing tools further advance the clinical translation of biomarker detection [25,26]. Blood biomarkers cannot serve as the sole diagnostic criterion; results must be interpreted holistically alongside imaging and clinical context [27]. Beyond bodily fluid markers, cutting-edge retinal imaging diagnostics and novel brain imaging techniques have emerged. Research using OCT technology to analyze changes in retinal microvascular structure can partially reflect neurodegenerative processes [28–30]. Integrating disease imaging data into large AI models to apply deep learning to MRI and PET data, and other imaging data, thereby constructing databases for predicting disease progression and automatically matching disease types, represents another key future direction in diagnostics [31,32]. Recent studies are also exploring the use of wearable device data to assess individual disease risk [33,34]. Early-stage AD diagnosis should progressively become simpler, more accessible, and earlier in the disease course. Concurrently, based on the multifactorial etiology framework, clinicians can validate test accuracy by examining multiple corresponding pathological factors. Establishing this multifactorial framework provides a roadmap for future diagnostics targeting individual contributing factors [5,27].

4. Therapeutic Strategies: From Single-Target to Multi-Point Regulation

Traditional approved drugs primarily alleviate symptoms by modulating neurotransmitter systems. For instance, donepezil, rivastigmine, and galantamine inhibit acetylcholinesterase, thereby increasing acetylcholine levels in the brain and improving cognitive function; memantine antagonizes glutamate-induced neurotoxicity, but traditional drugs cannot halt disease progression at a mechanistic level [5,43]. With deepening understanding of patholog-

ical mechanisms, disease modification has become the primary research focus. Anti-Aβ monoclonal antibodies can reduce cerebral amyloid burden through immunotherapeutic mechanisms [35,36], though their cognitive improvement remains relatively limited [35]. Debate persists regarding their efficacy and clinical significance [37-39]. Consequently, current drug development proceeds on multiple fronts simultaneously [40], as modifying a single pathogenic factor remains insufficient for effective disease treatment [50]. Alternatively, stem cell and gene therapies hold promising research potential. Animal studies indicate neural stem cells may improve synaptic function and inflammatory states through paracrine mechanisms [44–47]. The advent of gene delivery technologies provides feasible approaches for gene therapy [48,49]. Future AD treatments are more likely to focus on disease modification, utilizing biomarkers to assess therapeutic efficacy. Simultaneously targeting multiple pathogenic factors resembles the "cocktail therapy" approach used in HIV treatment [42,43].

5. Conclusions and Outlook

Based on accumulating evidence in recent years, the pathogenesis of Alzheimer's disease (AD) is better conceptualized as a multifactorial, multilevel dynamic framework rather than a linear process driven by a single pathogenic factor [6,38,41]. Key contributors, including neuroinflammation, synaptic dysfunction, mitochondrial metabolic imbalance, and genetic susceptibility, are highly interconnected and mutually regulated, collectively shaping disease progression across different stages [3,16,18,20,21].

A single hypothesis is no longer sufficient to explain the marked heterogeneity observed in AD in terms of clinical manifestations, pathological burden, and treatment responses [1,19,43]. Increasing evidence from the limited efficacy of Aβ-targeting therapies, along with advances in understanding immune and metabolic dysregulation, suggests that AD more closely reflects a state of systemic neuronal network dysfunction [35-39,3,16]. This multifactorial framework also provides important implications for diagnosis and treatment. Emerging approaches, such as blood-based biomarkers, enable clinicians to assess Aβ deposition and tau pathology more precisely [22-27], while therapeutic strategies should align with disease stage and dominant pathological drivers, favoring multi-target interventions over single-target approaches [40,42,43].

Looking forward, a central objective of future AD research is to further refine this multifactorial framework by integrating diverse lines of evidence and clarifying the interactions and synergistic effects among key pathological processes [27,41]. Such efforts will help establish a more structured, mechanism-based approach to diagnosis and treatment, moving beyond empirical symptom management toward precision intervention.

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