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RECENT ADVANCES IN THE PATHOPHYSIOLOGICAL MECHANISMS OF ALZHEIMER'S DISEASE: A SYSTEMS-LEVEL PERSPECTIVE

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ABSTRACT

Alzheimer's disease (AD) is a progressive and complicated neurological illness that is the most common cause of dementia worldwide. Despite extensive research, the pathophysiological causes of Alzheimer's Disease (AD) remain inadequately understood, and no cures currently exist. This review summarizes recent advancements in our understanding of AD pathogenesis, concentrating on molecular, cellular, and systemic mechanisms. Significant findings indicate that emerging insights into amyloid-beta (Aβ) fibril polymorphisms, nanoplaques, and clearance deficiencies are altering the paradigm, despite the amyloid cascade hypothesis continuing to inform the initial stages of the disease.It is now known that tau pathology is a dynamic process that acts like a prion and is affected by glial contacts and changes after translation. Chronic neuroinflammation makes neural injuries worse. This is caused by glial senescence, astrocytic GABA signaling, and NLRP3 inflammasome activation.Oxidative stress, mitophagy impairment, and mitochondrial dysfunction are some of the things that can lead to dementia. Loss of synapses, which is closely linked to cognitive impairment, happens when neurotransmission is disrupted and microglial pruning is done incorrectly.Pathological cascades are exacerbated by vascular and metabolic dysfunctions, including insulin resistance, glymphatic failure, and pericyte depletion. Neurogranin, CSF MTBR-tau243, plasma p-tau217, and AI-based neuroimaging metrics exemplify novel diagnostic biomarkers that are improving early detection. Antioxidants, senolytics, epigenetic therapies, and gut-brain axis regulation represent therapeutic advancements that extend beyond the targeting of Aβ and tau. All of these results show how complicated AD is and support using more than one method to improve diagnosis, treatment, and long-term outcomes.

KEYWORDS: Alzheimer's disease, Pathophysiology, Amyloid-beta and Tau, Neuroinflammation, Biomarkers

INTRODUCTION

The most prevalent cause of dementia is Alzheimer's disease (AD), which is characterized by increasing memory loss, cognitive dysfunction, and loss of independence.[1] It is a major public health and socioeconomic concern, affecting approximately 57 million people worldwide and expected to reach 152 million by 2050.[2,3] While mutations in APP, PSEN1, and PSEN2 produce uncommon familial AD, over 99% of cases are sporadic and entail intricate interplay between genetic, environmental, and aging-related variables.[2] The strongest genetic risk factor is still the ApoE ε4 variant, although new GWAS data link genes related to immunology, lipid metabolism, and endocytosis (e.g., TREM2, BIN1, CLU).[2,5]Current research emphasizes how epigenetic dysregulation contributes to AD. Neuroplasticity and cognitive function are impacted by abnormal DNA methylation and impaired histone acetylation (e.g., Tip60-HAT imbalance). Aging exacerbates these processes through oxidative stress, immune dysregulation, and impaired clearance pathways.[6,7] AD is increasingly recognized as a multifactorial disease involving amyloid and tau pathologies, chronic neuroinflammation, glial senescence, mitochondrial dysfunction, and vascular injury.[2,5,8] Tools such as dCas9-DNMT3a have shown promise in modifying gene expression and reducing Aβ production in vivo. Senolytic treatments have been shown to lower tau load and rescue cognitive function in animals.[8.] Precision medicine and systems-level methods are becoming more popular to address the complexities of AD. Early diagnosis is made possible by frameworks like AT(N) (Amyloid, Tau, Neurodegeneration), and therapy stratification is guided by multimodal biomarkers.[2.9]Research such as the GHABS is essential for comprehending population-specific risk in various ethnic groups.[3.] All things considered, current research shows that AD is a dynamic condition caused by interrelated molecular and systemic components.[10] To create tailored, disease-modifying treatments and early diagnostic tools, a fuller comprehension of these pathways is essential.

LITERATURE REVIEW

Alzheimer's disease (AD) is the most common neurodegenerative disorder and the main cause of dementia worldwide. Alzheimer's disease is characterized by cognitive impairments, synaptic abnormalities, and neuronal loss. Advancements in the field of AD etiology have significantly expanded the scope of understanding the disease mechanisms beyond the traditional amyloid cascade theory. Current evidence indicates that Alzheimer's disease is a multifactorial and systems-based disease with complicated connections between the following pathological entities: Aβ deposition, tauopathy, neuroinflammation, mitochondrial abnormalities, vascular damage, synapse loss, and metabolism disturbance.[2 10 11] The amyloid cascade hypothesis has emerged as the leading model for

AD pathogenesis. The amyloid cascade hypothesis suggests that the accumulation of toxic Aβ peptides via a series of degenerative processes induces excessive phosphorylation of tau, oxidative damage, synapse dysfunction, neuronal death, and impaired cognition.[13] These Aβ peptides result from the proteolytic processing of the amyloid precursor protein (APP), which involves β- and γ-secretases and leads predominantly to the production of Aβ40 and the more aggregation-prone Aβ42 peptides.[14] Recent structural investigations based on cryo-electron microscopy and solid-state NMR revealed significant diversity in Aβ fibril structures indicating diverse pathological strains.[15 17] Furthermore, genetic findings support the hypothesis of the crucial importance of the amyloid hypothesis in AD pathogenesis. The APOE e4 allele still represents the most significant genetic risk factor in AD development and is related to higher Aβ protein deposition and reduced peptide elimination.[4 18 19] In addition, genetic association analysis has revealed susceptibility genes for AD linked to the immune response, lipoprotein metabolism, and endosomal transport mechanisms, such as TREM2, BIN1, and CLU.2 Overall, it appears that the onset of AD occurs due to complex associations among genetic susceptibility, aging, and cellular dysfunction. Tau proteinopathy also constitutes an important neuropathological hallmark of AD. While physiologically, tau protein binds to microtubules, thereby maintaining their stability and facilitating axonal transport, pathological processes such as hyperphosphorylation, truncation, and acetylation lower tau protein affinity to microtubules, resulting in NFTs formation.[17 27] In addition, several studies provide evidence that tau protein pathology is likely to spread in a prion-like fashion through neurons connected with each other in a circuit and is better correlated with cognitive deficits than amyloid plaques.[28] Furthermore, defective endosomal trafficking and gliosis-induced pathways play critical roles in tau transmission.[26 35] Various biomarkers including p-tau217 in plasma and MTBR-tau243 in CSF have shown high specificity toward tau pathology. [58 59] Neuroinflammation has recently been identified as a key mediator for AD development. The secretion of inflammatory mediators such as pro-inflammatory cytokines, reactive oxygen species, and neurotoxic factors by activated microglia and astrocytes results in neuronal damage and synapse loss.[12 14] The activation of the NLRP3 inflammasome is one of the major signaling events responsible for chronic inflammatory processes in AD.[39] In addition, the induction of senescence in glial cells plays a role in chronic inflammation by virtue of the SASP, thus affecting the clearance of proteins and promoting neurodegeneration.[45 38] It is now well established that mitochondrial dysfunction and oxidative stress represent early pathogenic events in AD onset. Changes in mitochondrial dynamics, decreased ATP production, compromised mitophagy, excessive production of ROS, and disturbances in calcium handling play an important role in neuronal and synaptic damage.[46 48] Tau-induced mitochondrial protein abnormalities including MFN1, MFN2, and DRP1 cause mitochondrial dysfunction and energy deficit.[47] This has prompted scientists to develop mitochondrial therapy for AD.[45 49] Degradation of synapses is regarded as the best-known neuropathological hallmark of cognitive decline in Alzheimer's disease. Aβ oligomers affect synaptic

function, reduce dendritic spine formation, and block neuroplasticity.[50] In addition, tau oligomers cause circuit disorganization in the hippocampus and irregularities in neural oscillations due to cognitive impairment.[33 51] Neurogranin and synaptophysin are some of the promising synaptic markers in detecting synaptic damage and neurodegenerative processes.[46 60] Furthermore, recent investigations have pointed out the role of complement-dependent microglia in synaptic elimination in AD's early stages.[26] Vascular and metabolic disturbances have been identified as important features that contribute to the underlying mechanisms in Alzheimer's disease (AD). Vascular disturbances, blood brain barrier disruption, glymphatic disturbances and decreased cerebral perfusion cause pathological deposition of Aβ and tau. Moreover, metabolic disturbances such as insulin resistance and lipid dysregulation are also implicated in the development of neuronal dysfunction. Mediterranean-type diets have been shown to improve cerebral perfusion and biomarkers related to AD, whereas Western-type diets have been shown to increase tau levels and induce rapid neurodegeneration.[9] Recent advances in the field of biomarkers have greatly improved the early diagnosis and monitoring of AD. The diagnostic accuracy of plasma p-tau 217 has been similar to that of cerebrospinal fluid biomarkers and amyloid PET.[57 61] Other biomarkers like neurofilament light chain (NfL), glial fibrillary acidic protein (GFAP), and Aβ42/Aβ40 ratio provide important information on axonal injury, astrocytic activation, and amyloid deposition.[2 3] Structural MRI and deep learning algorithms in artificial intelligence-based neuroimaging approaches have also further improved the sensitivity and specificity of early disease detection.[62] Therapeutic strategies for AD are moving more and more towards multimodal and precision-based approaches. Anti-amyloid monoclonal antibodies, including aducanumab, lecanemab and donanemab, have demonstrated efficacy in reducing amyloid plaque burden, although clinical benefits remain limited.[64 65] At the same time, tau-targeting therapies such as antisense oligonucleotides, nanobodies and proteolysis-targeting chimeras (PROTACs) are being actively investigated.[32 44] In addition, novel therapeutic approaches targeting the broader pathological network underlying AD progression, such as senolytics, epigenetic modulators, antioxidants, mitochondrial enhancers, and gut-brain axis interventions are being explored.[45 65 68] .Together, the existing literature supports the notion that Alzheimer's disease is a multifactorial neurodegenerative disorder driven by interconnected molecular, immunological, vascular, metabolic, and neurodegenerative pathways, rather than a single pathogenic mechanism. A comprehensive understanding of these complex interactions is required for the development of sensitive diagnostic biomarkers and precision-based therapeutic strategies that can target the multifaceted nature of Alzheimer's disease.

PATHOPHYSIOLOGICAL MECHANISMS

Alzheimer's disease (AD) is a multifactorial neurodegenerative disorder that develops over decades through intricate and interconnected pathological processes.[11] These include the build-up of amyloid-

beta (Aβ), tau hyperphosphorylation, oxidative damage, synaptic and neuronal loss, chronic neuroinflammation, and cerebrovascular dysfunction.[12] An integrated and evidence-based summary of the main molecular and cellular pathways underlying AD pathogenesis is given in the ensuing subsections.

Amyloid-Beta (Aβ) Pathology

A key concept for comprehending the pathophysiology of Alzheimer's disease (AD) is still the amyloid cascade theory.[13] It suggests that aberrant amyloid-beta (Aβ) peptide buildup sets off a series of harmful events that eventually result in tau hyperphosphorylation, synaptic dysfunction, neuronal death, and cognitive decline.

β-secretase (BACE1) and γ-secretase sequentially cleave the transmembrane amyloid precursor protein (APP) to create Aβ. Aβ40 and Aβ42 isoforms are produced by this mechanism; the latter is more neurotoxic and prone to aggregation. Aβ is eliminated under healthy conditions through cellular absorption, glymphatic drainage, and enzymatic breakdown. Aβ gradually builds up in the brain parenchyma and cerebrovasculature as a result of these clearance processes being overburdened or compromised in AD.[14]Significant structural variability in Aβ fibrils extracted from postmortem human brains has been revealed by recent biophysical studies.[15]Advanced cryo-electron microscopy (cryo-EM) and solid-state nuclear magnetic resonance (NMR) have been used by researchers to identify different structural strains of Aβ42 fibrils in different individuals. It is believed that these polymorphic assemblies contribute to the variability seen in AD clinical symptoms, potentially affecting the rate of disease development, localized brain involvement, and response to treatment.[16, 17]One of the most impactful genetic risk factors for late-onset AD is the **APOE ε4** allele. Mechanistically, APOE ε4 promotes the aggregation and reduced clearance of Aβ peptides.[18] In vitro studies using human iPSC-derived neurons have shown that APOE ε4 enhances the expression of insulin-like growth factor-binding protein 3 (IGFBP3), which, in turn, increases the early nucleation and fibrillization of Aβ42. This axis—**APOE ε4 → IGFBP3 → Aβ42 aggregation**—establishes a clear genetic-to-molecular link underpinning early Aβ pathology.[19]Nanoplaques have become extremely important pathogenic intermediates for soluble Aβ species. These nanoplaques, which were found using Thioflavin-T fluorescence correlation spectroscopy (ThT-FCS)20, are large, soluble, fibrillar Aβ aggregates that have a high potential for seeding and immunogenicity. Clinical evidence indicates that pro-inflammatory cytokines like IL-8 and macrophage inflammatory proteins (MIP-1α/β) are correlated with elevated nanoplaque levels in cerebrospinal fluid (CSF), suggesting that nanoplaques may function as both active mediators and biomarkers of neuroinflammation.[21]In addition to harmful gain-of-function implications, changing APP expression regulation itself might be a useful target for treatment. The ability to transcriptionally inhibit APP without causing DNA breaks has been shown by recent advancements utilizing CRISPR/dCas9-based epigenetic regulation.

Delivery of dCas9 coupled to the methyltransferase Dnmt3a lowered Aβ42/40 ratios, attenuated plaque load, enhanced spatial memory, and successfully suppressed APP transcription in a knock-in mice model of AD. This method presents a viable pathway for gene-specific, transient epigenetic treatment.[22]Studies demonstrating that Aβ oligomers affect synaptic homeostasis, boost calcium influx via NMDA receptors, and decrease mitochondrial function further illustrate the dual nature of Aβ, involving both extracellular plaque development and interactions with intracellular signaling pathways.[23.]These consequences trigger apoptotic pathways and increase oxidative stress. Interestingly, it has also been suggested that Aβ functions as an antimicrobial peptide. According to certain research, its buildup may originally represent a defense against microbial invasion. But under long-term circumstances, this reaction turns maladaptive and feeds a vicious cycle of degeneration and inflammation.

When taken as a whole, these results highlight the complex function of Aβ in AD pathogenesis. The change from soluble oligomers to insoluble fibrils is a complicated, controlled process that affects the course of disease at the molecular, cellular, and systemic levels rather than being only a result of deposition.Recent research highlights the importance of peripheral and cerebrovascular pathways in regulating Aβ load, going beyond traditional models of Aβ synthesis and plaque deposition.Dysfunction of the choroid plexus lowers cerebrospinal fluid turnover, which hinders Aβ's glymphatic clearance and causes it to build up in the brain parenchyma and vascular.[24]Furthermore, systemic metabolic interactions show that apolipoproteins like APOB and APOE affect peripheral transport and brain influx of Aβ peptides, especially through the triglyceride-rich lipoprotein–Aβ route.[25] Microglial TREM2 signaling is essential for immune-level plaque confinement; its absence leads to a diffuse distribution of Aβ, which increases neurotoxicity and weakens the barrier that normally surrounds plaques.26. These findings imply that both inadequate peripheral clearance and immune modulation intrinsic neuronal dysregulation contribute to amyloid disease.

Tau Protein and Neurofibrillary Tangles (NFTs)

Axonal microtubules are often stabilized by tau, a microtubule-associated protein.The structural and functional variability of tau strains in AD has been highlighted by recent proteomic studies using Probe-dependent Proximity Profiling (ProPPr), which have demonstrated that various tau fibrils engage diverse protein partners, such as VPS35, LAMP2, and GSK3α.[27] Tau experiences acetylation, truncation, hyperphosphorylation, and other post-translational changes in AD that lessen its affinity for microtubules and encourage aggregation into NFTs. NFTs spread between synaptically linked neurons in a prion-like fashion. Compared to Aβ load, this spatial progression has a stronger correlation with cognitive deterioration and is consistent with Braak staging.[17] [28]Compared to conventional p-tau species, emerging biomarkers such as MTBR-tau243, which is generated from the microtubule-binding repeat region, have higher specificity for aggregated tau, making them valuable

for monitoring tangle pathology.[29]HDAC7 suppresses TFEB acetylation in astrocytes, which prevents autophagy and tau lysosomal breakdown. TFEB activity is restored, lysosomal function is improved, and tau buildup is decreased with pharmacological suppression of HDAC7.[30]Vascular deposition of tau, especially in cerebral arterioles and perivascular astrocytes, indicates a direct connection between tauopathy and vascular dysfunction and indicates poor glymphatic clearance.[31]In Calb1::P301S mice, novel therapeutic peptides such as DEPTAC lower insoluble tau levels and restore hippocampus synaptic plasticity by targeting tau for dephosphorylation via PP2A-Bα.[32]The toxicity of tau varies depending on the kind of neuron. Increased expression of tau kinases such as MARK4 makes calbindin-negative excitatory neurons in the ventral hippocampus selectively susceptible. Memory impairments and neuronal atrophy are reversed by inhibiting MARK4.[33]

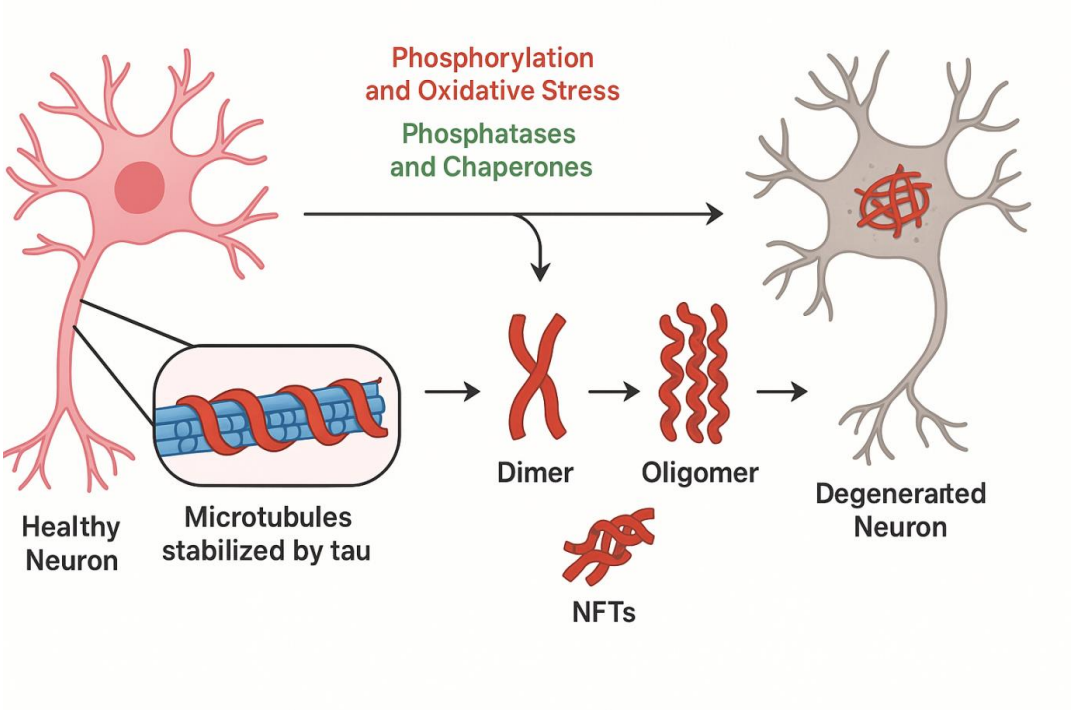

Figure-1 Pathophysiology of Tau in Alzheimer's Disease.

(This figure shows how tau disease causes a neuron to deteriorate from a healthy neuron. A healthy neuron with tau protein-stabilized microtubules is seen on the left. Tau proteins start to separate from microtubules when under oxidative stress and phosphorylation (red text). As a result, dimers are created, which then combine to form oligomers and ultimately neurofibrillary tangles (NFTs). The injured neuron on the right illustrates how this cascade contributes to neuronal malfunction and degeneration. In order to prevent this process and preserve tau homeostasis, phosphatases and chaperones (green text) are mentioned.)

Extending our understanding of tau disease exposes the role of glial-mediated clearance pathways as well as intracellular trafficking systems. The aberrant uptake and aggregation of tau in recipient

neurons is facilitated by dysfunctional endosomal trafficking, particularly involving early endosomes identified by Rab5. This suggests vesicular dysfunction as a major factor in tau dissemination.[26] Further evidence supporting tau's key function in neurodegeneration comes from longitudinal neuroimaging studies that show a correlation between tau PET binding patterns and regional brain atrophy.[34] Furthermore, astrocytic engulfment of tau-laden synapses predominates in the brains of cognitively resilient individuals with high tau load, whereas microglial responses are shown in symptomatic patients. This implies that clinical outcomes could be influenced by the kind of glial cell interacting with tau clumps.[35]Furthermore, tau strain evolution has been demonstrated to be modulated by persistent low-grade inflammation, promoting the generation of more neurotoxic conformers, so connecting the development of tau pathology with the immunological milieu.[36]Even in the absence of overt neurofibrillary tangle formation, microglia and astrocytes excessively absorb synapses carrying tau oligomers in early-stage Alzheimer's disease (Braak stages III–IV), according to a recent cross-sectional study. Tau oligomers and glial activation play a crucial role in early synaptic dysfunction and cognitive decline, as demonstrated by the selective synaptic loss seen in postmortem brains from dementia patients but not in those with comparable disease but intact cognition.[37]

Neuroinflammation and Glial Activation

One of the main characteristics of AD is neuroinflammation, which begins early and frequently precedes overt plaque and tangle disease. In response to Aβ, microglia activate the NLRP3 inflammasome, which releases IL-1β and IL-18 and sustains chronic inflammation.[14]Furthermore, tau aggregates and inflammatory mediators have been shown to interact reciprocally. Cytokine-induced tau hyperphosphorylation further activates glial cells, resulting in a vicious feedback loop that exacerbates neurodegeneration. [38]A dietary molecule called betaine lowers oxidative stress and cytokine production in microglia by inhibiting NLRP3 and NF-κB activation.[39] In silico, neem-derived phytochemicals have demonstrated potential as NLRP3 inhibitors, exceeding common substances like oridonin in terms of binding and pharmacokinetics. [40]In tau models, the ApoE Christchurch variation suppresses neuroinflammatory signaling, whereas in amyloid models, it improves Aβ clearance. [41] By reducing downstream p38 MAPK activity and disease-associated microglial (DAM) markers, CD2AP-deficient microglia are less reactive and maintain synapses.[42,43]By releasing GABA and other inhibitory signals, astrocytes—traditionally thought of as support cells—contribute to AD. Memory is hampered by this astrocytic GABA, which is controlled by SIRT2 and ALDH1A1. This inhibitory tone is reversed and cognitive function is enhanced by inhibiting SIRT2.[44]An further level of intricacy is introduced by glial senescence. Tau propagation and synaptic injury are made worse by senescent microglia and astrocytes' SASP profile, which is defined by cytokine secretion, chemokine expression, and matrix remodeling enzymes.[45]Beyond microglial activation, neuroinflammation in AD involves a range of geographically and temporally

regulated glial cell responses.Microglial cytokines including IL-1α, TNF, and C1q cause A1-type reactive astrocytes to lose their neuroprotective qualities and release toxic mediators that aid in neuronal death and synaptic elimination.[34] This proinflammatory state is made worse by aging, as senescent microglia exhibit elevated SASP expression and downregulated homeostatic genes (such as TMEM119 and P2RY12). Senolytic therapies that eradicate these cells enhance memory in AD models.[45] Additionally, in late-stage AD, perivascular macrophages—which are different from microglia—accumulate surrounding damaged capillaries and aid in the disruption of the blood–brain barrier as well as local tau accumulation.[35] These results demonstrate that glial dysfunction and aging are active causes of neurodegeneration rather than just its byproducts.

Mitochondrial Dysfunction and Oxidative Stress

Neuronal bioenergetics, calcium buffering, and apoptosis regulation all depend on mitochondria. Mitochondrial dysfunction is one of the first observable cellular abnormalities in AD. Both human postmortem tissue and patient-derived exosomes show reductions in the mitochondrial fusion protein MFN-2, which are correlated with decreased mitochondrial mass and elevated LAMP-2 and golgin A4, indicators of organellar stress.[46] Tau directly interferes with the function of mitochondrial proteins such DRP1, MFN1, and MFN2. In the end, this promotes neuronal death by causing mitochondrial fragmentation, decreased ATP synthesis, calcium dysregulation, and increased ROS formation.[47] Oxidative damage has been linked to the failure of mitophagy, which is the process by which damaged mitochondria are broken down by autophagy. Tau phosphorylation and synaptic dysfunction are sustained by this vicious cycle of ROS buildup and mitochondrial damage.[48]It is now understood that oxidative stress and mitochondrial dysfunction are upstream factors in AD development rather than merely effects of proteinopathy. Increased amounts of malondialdehyde and 4-hydroxynonenal, which are signs of iron-catalyzed oxidative damage to lipids, are indicative of higher lipid peroxidation in the mitochondrial membranes of AD brains.[34] Variations in the TOMM40 gene, which is located next to APOE, may worsen abnormalities in energy metabolism and reactive oxygen species (ROS) regulation by further impairing mitochondrial protein import.[25] By directly interacting to mitochondrial proteins like MFN2 and DRP1, tau aggregates worsen these deficiencies by upsetting calcium homeostasis and fission-fusion dynamics.[47] These discoveries make mitochondrial stability a crucial therapeutic target, especially in the early phases of disease development.[49]

Synaptic Loss and Cognitive Decline

The biggest neuropathological indicator of cognitive impairment in AD is synaptic loss. Receptor trafficking, dendritic spine density, and synaptic vesicle cycling are all disrupted by soluble Aβ oligomers and hyperphosphorylated tau.[50]Tau reduces synaptic input and interferes with network oscillations that are essential for memory storage in Calbindin-negative vCA1 neurons. Optogenetic

activation of particular hippocampus circuits or MARK4 inhibition can reverse these abnormalities.[33, 51]Synaptic dysfunction is exacerbated by cholinergic deficiencies. Even in the context of tau disease, activation of the medial septum–CA1 (MS–CA1) circuit enhances memory function and restores theta-gamma coupling.[52]ZDHHC21 mutations diminish synaptic plasticity, impair long-term potentiation (LTP), and cause memory loss via interfering with NMDA receptor clustering and FYN kinase activity.[29]Neuronal exosomes from AD patients contain lower levels of synaptic biomarkers including neurogranin and synaptophysin, which supports their use as early markers of synaptic breakdown.[46]

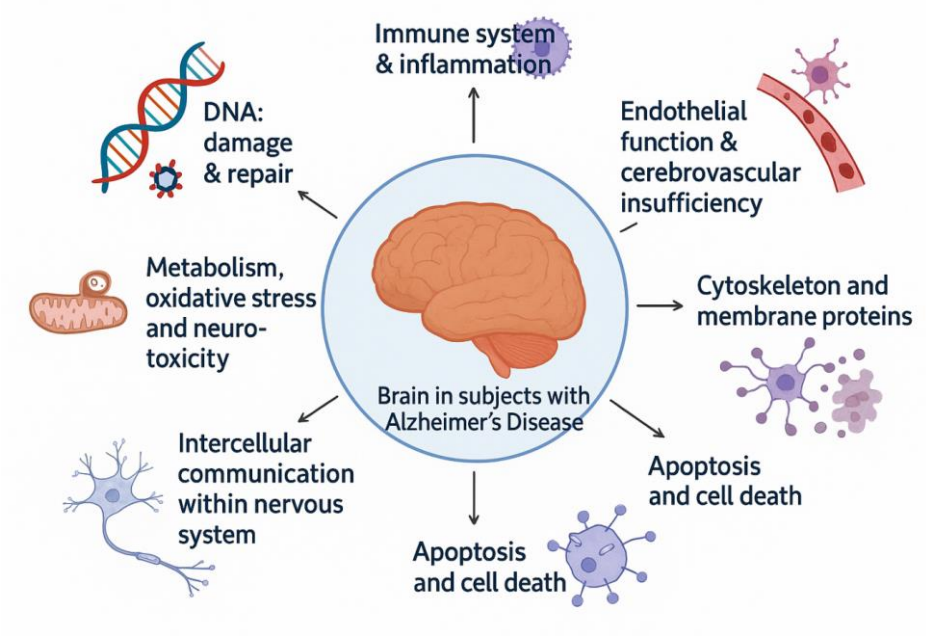

Figure-2 Overview of interconnected pathological mechanisms contributing to neurodegeneration in Alzheimer's disease.

(This image provides an overview of the several pathways that contribute to the pathogenesis of Alzheimer's disease. Immune system activation and chronic inflammation, endothelial dysfunction resulting in cerebrovascular insufficiency, and anomalies in cytoskeletal and membrane proteins are among the mechanisms that are disturbed in the affected brain. Neuronal apoptosis and cell death are influenced by these alterations. Impaired intercellular communication, mitochondrial dysfunction resulting in oxidative stress and neurotoxicity, DNA damage, and weakened repair mechanisms are further contributing factors. These interrelated mechanisms work together to cause neurodegeneration and cognitive deterioration in Alzheimer's patients.)

The most reliable indicator of cognitive impairment in AD is synaptic disruption, and there is growing evidence that both glial and neuronal components are involved. In AD, astrocytic expression of the glutamate transporter EAAT2 is reduced, resulting in increased extracellular glutamate and

excitotoxic dendritic spine loss.[34] Phase-amplitude coupling (PAC) anomalies, particularly theta-gamma rhythm desynchronization, interfere with information encoding and retrieval at the systems level, as demonstrated by MEG research in mice models.[53] Furthermore, in early AD, synapses are flagged for microglial-mediated pruning by the complement cascade (e.g., C1q and C3 tagging); preventing this interaction stops synapse loss and maintains memory function.[26] These findings demonstrate how excitotoxicity, network desynchrony, and defective immune surveillance all contribute to synaptic degeneration.

Metabolic and Vascular Alterations

Impaired brain clearance pathways and cerebrovascular abnormalities have been identified as important aspects of AD etiology. Regardless of amyloid burden, white matter hyperintensities (WMH) in periventricular and deep white matter regions are linked to decreased perfusion and predict faster cognitive deterioration.[54]In longitudinal cohorts, amyloid buildup, brain atrophy, and clinical conversion are correlated with the ALPS index, a diffusion MRI-based indicator of lymphatic system efficiency. Notably, increases in CSF Aβ42 are preceded by reduced ALPS readings, indicating that it may be an ultra-early marker.[55]Additionally, tau has been observed to build up along vascular walls, particularly in perivascular astrocytes, indicating that its retention and dissemination may be facilitated by poor clearance via glymphatic and perivascular pathways.[31]AD progression is also influenced by metabolic alterations. Increased brain perfusion and greater CSF Aβ42/40 ratios have been linked to dietary interventions such a Mediterranean-style diet. A Western diet, on the other hand, is associated with increased tau buildup and decreased brain blood flow.[9]

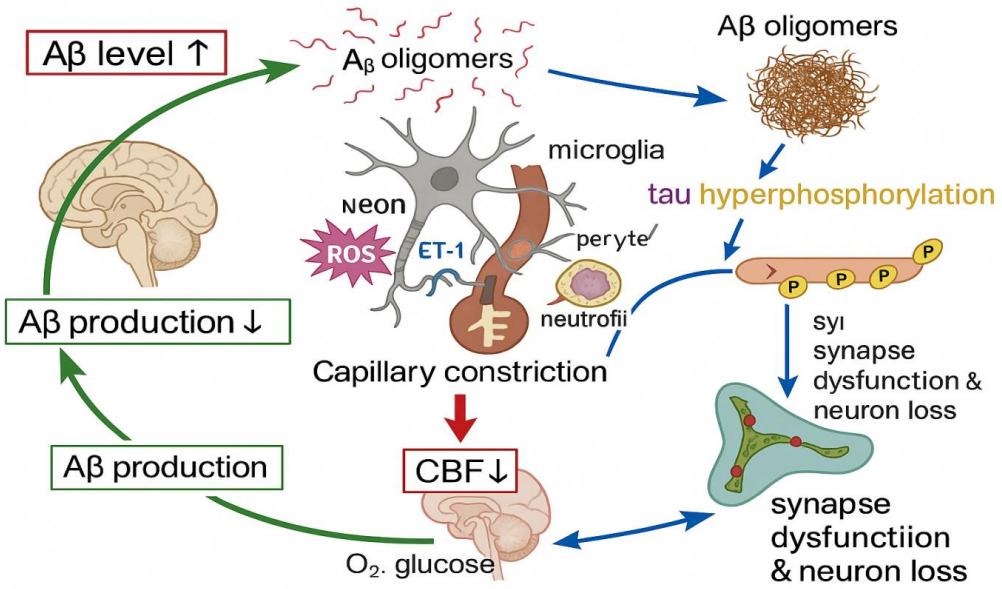

Figure-3 Aβ-induced capillary constriction and its role in tau pathology and neurodegeneration in Alzheimer's disease.

(This picture depicts a pathogenic feedback loop in Alzheimer's disease that includes neuronal loss, capillary malfunction, and amyloid-β (Aβ) accumulation. High amounts of Aβ cause toxic Aβ oligomers to develop, which in turn cause tau hyperphosphorylation, synapse dysfunction, and neuronal death. Additionally, Aβ oligomers cause oxidative stress (ROS), activate neutrophils, microglia, and pericytes, and promote capillary constriction via endothelin-1 (ET-1) signaling. The supply of glucose and oxygen is hampered by this constriction, which lowers cerebral blood flow (CBF). Aβ synthesis is further stimulated by the decrease in CBF, resulting in a vicious cycle that worsens neurodegeneration.)

It is becoming more widely recognized that a key component of AD is the convergence of vascular disease and metabolic dysfunction.Hippocampal atrophy is accelerated by pericyte degeneration because it causes microvascular instability, increased capillary permeability, and reduced Aβ and tau clearance.[36] In terms of metabolism, AD brains show insulin resistance, which is typified by decreased expression of the glucose transporters (GLUT1 and GLUT3) and insulin receptor signaling. This promotes synaptic dysfunction, worsens tau pathology, and reduces neuronal glucose uptake [34].Disease is also exacerbated by dysregulated lipid metabolism, especially in the cholesterol and sphingolipid pathways. Neuronal membrane lipid composition is greatly impacted by APOE genotype, which also modifies membrane fluidity and Aβ aggregation propensity.[25] These results highlight the necessity of an integrated treatment approach that takes into account lipid balance, glucose metabolism, and vascular health.

EMERGING DIAGNOSTIC BIOMARKERS

One of the key challenges in clinical neurology and medication development is the accurate and timely identification of Alzheimer's disease (AD).[56] The sensitivity and specificity of early detection have been enhanced by recent developments in biomarker discovery, particularly in preclinical and prodromal stages. Together, these biomarkers—which include cerebrospinal fluid (CSF), plasma, neuroimaging modalities, and multimodal AI-based evaluations—contribute to a more sophisticated and comprehensive diagnostic paradigm. Phosphorylated tau (p-tau) isoforms in CSF and plasma have demonstrated remarkable promise as fluid biomarkers.[57] Notably, with performance comparable to FDA-approved CSF biomarkers, plasma p-tau217 has become the most accurate single plasma biomarker for predicting both tau and amyloid PET positivity.[2,58]In multiple cohorts, p-tau217 levels surpass p-tau181 and p-tau231 in longitudinal investigations, rising even before cognitive symptoms appear and tracking well with illness progression.[2] Furthermore, these phosphorylated tau markers serve as early-stage reporters of amyloid-triggered tauopathy rather than direct indicators of fibrillar tau since they are more indicative of amyloid pathology than of tau aggregates.[58]Apart from p-tau217, tau PET imaging signals and insoluble tau load have been strongly correlated with MTBR-tau243, a fragment of tau's microtubule-binding repeat domain. It predicts disease progression and postmortem

tangle pathology more accurately than previous phosphorylated tau indicators such as p-tau181. Plasma p-tau205 has also been connected to the degree of neurofibrillary tangles and amyloid plaque, which supports its potential as a biomarker in the diagnosis of AD.[59] The discovery of MTBR-tau243, a tau species produced from the microtubule-binding region of the tau protein, is a very novel development. In contrast to traditional phosphorylated tau biomarkers, CSF MTBR-tau243 is a direct biomarker of neurofibrillary tangles since it is selectively enhanced in connection to insoluble tau aggregates. MTBR-tau243 showed a higher connection with tau PET signals and cognitive decline than p-tau217 or p-tau205 in two large-scale investigations (BioFINDER-2 and Knight ADRC), indicating its superior specificity for tangle pathology and usefulness for disease staging and prognosis.[58] It has been established that neurogranin (Ng), a postsynaptic protein involved in memory consolidation and synaptic plasticity, is a hallmark of synaptic degeneration. Both familial and sporadic AD are linked to decreased Ng levels in the brain and CSF, and these levels are highly correlated with cortical atrophy and memory impairments.[46] Ng is considerably decreased in the CSF and neuronal exosomes of AD patients, according to Western blot and ELISA studies of neuronal exosomes, further demonstrating its diagnostic use for tracking synaptic integrity.[60]Another increasingly identified indicator of axonal degeneration is neurofilament light chain (NfL). Exosomal NfL levels offer a more accurate depiction of neurodegeneration at the neuronal origin, although CSF and plasma NfL levels are markedly increased in AD. NfL is a trustworthy biomarker for disease progression rather than early diagnosis since high levels of the protein are correlated with brain shrinkage, cognitive loss, and clinical staging.[2 46]By displaying microglial activity, PET tracers like [18F]DPA-714 and [11C]PK11195 provide high-resolution insights into neuroinflammation in terms of neuroimaging biomarkers. By focusing on the translocator protein (TSPO), which is elevated in reactive microglia, these tracers make it possible to identify neuroinflammatory cascades early on, frequently before obvious neuronal death.[3 21] TSPO binding affinity variability brought on by genetic variations, however, continues to be a technical drawback.

Table 1- Key AD Biomarkers and Their Pathophysiological Relevance.

Biomarker	Biological Source	Pathophysiological Relevance
p-tau217	Plasma, CSF	Highly accurate marker of tau pathology; correlates with tau PET and tracks disease progression. [3,59,61]
MTBR-tau243	CSF	Fragment from tau's microtubule-binding repeat domain; strongly linked to insoluble tau burden and PET signals.[59]
Neurogranin (Ng)	CSF, Plasma	Reflects synaptic integrity; elevated levels indicate synaptic loss and early neurodegeneration.[3,62]
Neurofilament light (NfL)	CSF, Plasma	Marker of axonal damage; rises early and tracks neuronal degeneration across AD stages.[62]
GFAP	Plasma, CSF	Astrocytic activation marker; elevated in preclinical and symptomatic AD stages.[3]
Aβ42/Aβ40 ratio	CSF, Plasma	Decreased ratio indicates amyloid deposition; widely used in

		early and differential diagnosis.[14]
Aβ Nanoplaques	CSF	Soluble, ThT-positive Aβ aggregates; linked to cytokines (IL-8, MIP-1α/β); may be both markers and drivers of inflammation.[21]
AS / ADS Scores	Structural MRI	Deep learning-derived scores quantify aging-related (AS) and AD-specific (ADS) atrophy patterns for early diagnosis.[62]

Deformation-based morphometry (DBM) was used to create morphometric brain ratings, such as the Aging Score (AS) and AD-Specific Score (ADS), in a deep learning-based neuroimaging investigation. These scores measure structural brain shrinkage patterns at the individual level and are highly accurate at differentiating between Alzheimer's disease and normal aging. Interestingly, the ADS was high even in preclinical stages and showed a substantial correlation with memory impairment, indicating its potential as a non-invasive, early diagnostic biomarker for AD.[62]

Deep learning models used to MRI have also proven beneficial for quantitative imaging biomarkers. Structural brain atrophy can be measured with sensitivity and interpretability using tools like the Aging Score (AS) and AD-Specific Score (ADS), which are generated from deformation-based morphometry (DBM) and convolutional neural networks (CNNs). These models are adaptable to a wide range of ethnic cultures and capture disease-relevant neuroanatomical alterations, particularly in the hippocampus and parietal areas.[26]Lastly, multimodal strategies that include imaging biomarkers, plasma, and CSF are becoming more popular. In order to better disease staging and forecast the transition from moderate cognitive impairment (MCI) to AD, recent frameworks use machine learning techniques to synthesize signals from Aβ42/Aβ40, p-tau217, GFAP, and NfL with structural and functional imaging data.2,55 For instance, by integrating tau-PET with plasma p-tau217 and CSF MTBR-tau243, the A/T/N categorization approach based on amyloid (A), tau (T), and neurodegeneration (N) has been further developed, improving diagnostic accuracy and supporting trial stratification.[58] A highly reliable, non-invasive biomarker for identifying the pathophysiology of Alzheimer's disease is plasma p-tau217.[63] The study showed that p-tau217 levels in plasma closely match findings from CSF biomarkers and amyloid PET imaging using a fully automated immunoassay. Its viability for wider clinical usage is further demonstrated by its potential to replace more invasive and expensive diagnostic procedures like lumbar punctures and PET scans.[61]

THERAPEUTIC STRATEGIES AND TARGETS

Disease-modifying techniques are becoming more prevalent in Alzheimer's disease (AD) treatment. Many aspects of AD pathophysiology, such as amyloid-beta (Aβ), tau protein, oxidative stress, glial senescence, microbiome effect, and multi-targeted precision medicine, have been the focus of recent therapeutic advancements.

Anti-Aβ Therapies

Anti-amyloid treatments continue to be essential for treating AD.For AD in its early stages, monoclonal antibodies including aducanumab, lecanemab, and donanemab have been approved. Gantenerumab, another antibody in late-stage trials, targets fibrillar Aβ and has demonstrated a reduction in plaque levels but failed to achieve clinical efficacy in some cohorts.[64] These agents bind aggregated Aβ and promote clearance, showing success in reducing plaque load but with limited cognitive benefit and increased risks of ARIA (amyloid-related imaging abnormalities) [65] Furthermore, an active immunization strategy against Aβ is represented by the recently expedited ACI-24 vaccine, which is presently being studied clinically for prodromal and early AD[64].

Tau-Targeting Agents

Since tau pathology has a stronger correlation with cognitive decline than Aβ, several medicines that target tau are being researched. Antisense oligonucleotides, vaccinations, nanobodies, and PROTACs are a few of these. In preclinical studies, nanobodies like H3-2 and Z70mut1 reduce tau seeding and dissemination by blocking the LRP1-mediated pathway, hence preventing tau internalization.[32] By attracting the phosphatase PP2A-Bα, the new chemical DEPTAC (Dephosphorylation Targeting Chimaera) helps selectively dephosphorylate tau, lowering tau burden and saving cognitive impairments. [66]Additionally in the preclinical phases are kinase inhibitors that target GSK3β and CDK5, which mediate tau hyperphosphorylation. However, problems with selectivity and systemic toxicity continue to be major obstacles.[32]

Antioxidants and Mitochondrial Enhancers

Treatments that try to lessen oxidative stress and improve mitochondrial health are becoming more popular.Coenzyme Q10, MitoQ, and SS-31 peptides are mitochondrial enhancers that have demonstrated effectiveness in preclinical AD models by reducing reactive oxygen species (ROS) and restoring ATP generation.[45] Furthermore, GSK3β inhibition may work in concert with tau modification to improve mitochondrial stability and lower neuronal death. [65]

Senolytic Drugs

Protein clearance is hampered and persistent neuroinflammation is fueled by the senescence of astrocytes and microglia. Senolytics like quercetin and dasatinib have been demonstrated to improve cognitive outcomes in AD mouse models, lower tau and Aβ levels, and specifically eradicate senescent cells.[45] [67] The safety and viability of giving senolytics to individuals with mild AD have been established by early clinical studies such as SToMP-AD.[67] Combining these medicines with immunotherapies or metabolic treatments may make them very successful.[45]

Gut-Brain Axis Modulation

The impact of gut microbiota modulation on brain inflammation and amyloid processing is being studied, however this is still in its early phases.[68] Blood-brain barrier (BBB) permeability and systemic inflammation have been associated with altered microbiota composition.The ability of probiotics, rifaximin, and fecal microbiota transplantation (FMT) to alter neuroinflammatory tone in AD is being investigated.[65] Robust clinical evidence is still scarce, though.

Precision-Based Multimodal Strategies

Monotherapy techniques have proved mainly inadequate due to the intricacy of AD. The utilization of unique biomarker profiles to customize anti-inflammatory, anti-tau, anti-amyloid, and metabolic modulator combinations is a key component of precision medicine. For instance, targeted epigenetic regulation is provided by activation of Tip60 histone acetyltransferase (HAT), which restores gene expression relevant in synaptic plasticity without the extensive damage brought on by HDAC inhibitors.[65] NLRP3 inflammasome inhibitors, such as oridonin and chemicals derived from neem, are another promising field that targets neuroinflammation and microglial activation with great specificity.[40] These techniques provide a more individualized, pathophysiology-based approach to AD treatment when paired with imaging or fluid biomarker-guided classification.

ANIMAL MODELS AND EXPERIMENTAL APPROACHES

Animal models are crucial tools for understanding the mechanisms underlying Alzheimer's disease (AD) and assessing treatment approaches. Many transgenic and non-transgenic models have been created to simulate different elements of the illness, despite the fact that no single model can adequately depict the complexity of sporadic AD[69].

Transgenic Models of Mice

The 3xTg-AD mouse model has mutations in tau (P301L), PS1 (M146V), and APP (Swedish KM670/671NL), which cause age-dependent tau and amyloid diseases. It takes four months to discover intracellular Aβ, six months to detect extracellular plaques, and twelve months to detect neurofibrillary tangles. Additionally, these mice exhibit neuropsychiatric-like characteristics, such as decreased mobility and elevated anxiety, as well as cognitive impairments.[70] The APP/PS1 mouse does not normally create tau tangles, but it does acquire early amyloid plaques starting at six months of age due to human mutations in APP and presenilin-1. [41] Anti-Aβ treatments and amyloidosis are commonly evaluated using this paradigm. Tau-targeted therapies can be tested in P301S and P301L tau mice, which express human mutant tau and produce a strong tauopathy without amyloid accumulation.No. [36] Rapid drug screening pipelines employ the 5xFAD mouse, which expresses five familial AD variants in APP and PS1 and exhibits amyloid deposition as early as two months.[41]

Non-Transgenic and Humanized Models

In the absence of genetic alterations, the ICV-STZ model, which is produced by intracerebroventricular injection of streptozotocin, replicates characteristics of sporadic AD, such as insulin resistance, oxidative stress, and cognitive impairment.[70]

For researching isoform-specific effects on tau and amyloid disease, humanized APOE knock-in mice expressing APOE3 or APOE4 alleles are extremely useful. For instance, depending on the background model (e.g., PS19 vs. APP/PS1), animals with the ApoE Christchurch mutant (R136S) exhibit altered tau propagation and decreased microglial responsiveness as compared to controls.[41]

AD Models' Behavioral Testing

Verifying the translational relevance of AD models requires behavioral phenotyping. The Morris Water Maze (MWM) tests memory and spatial learning. As they age, 3xTg-AD mice exhibit reduced quadrant choice and increased escape latency.[70]

The Novel Object Recognition (NOR) test assesses recognition memory; models subjected to metabolic stress and older mice have markedly lower performance. [33]

Tests like the raised plus maze and fear conditioning are used to evaluate emotional and anxiety-related responses, which are frequently changed in AD models.[70]

Significantly, sex-based disparities have been noted. Compared to male 3xTg-AD mice, female mice experience more severe tau pathology and behavioral deficits, especially in the latter stages of the disease.[70]

Imaging and Molecular Techniques

In AD models, synaptic and pathogenic structures are seen using sophisticated imaging techniques as expansion and confocal microscopy.[70]

In vivo tracking of disease development is made possible by PET imaging using Aβ and tau tracers.New knock-in models and targeted gene regulation have been made possible by genetic editing with CRISPR/Cas9, including current work with CD2AP, APP, and Tip60.[43]

Statistical Methods and Experimental Design

In order to examine intricate relationships between age, sex, and genotype in behavioral datasets, sophisticated statistical techniques like multivariate regression and factorial ANOVA are being employed more frequently. Methodologically, longitudinal studies show that there are significant age-related differences in the time of phenotypic manifestation. The significance of longitudinal study designs is highlighted by the fact that both Aβ and tau accumulation—as well as the associated behavioral decline—develop over time in the same model.[70]

FUTURE DIRECTIONS AND RESEARCH CHALLENGES

The absence of reliable, scalable biomarkers continues to hinder early detection. Although GFAP and plasma p-tau217 seem promising, there is still a lack of uniformity across many groups.[6,55] Despite having strong predictive potential, MRI-based machine learning methods like the Aging Score (AS) and AD-Specific Score (ADS) remain underutilized in clinical settings.[2] Vascular comorbidities, lifestyle variables, sex, and APOE genotype all contribute to interindividual variability in clinical progression and treatment response.[54]Personalized medicine frameworks based on genetics, imaging, and fluid biomarkers are required because genetic variation leads to phenotypic variability.[2] Current clinical trials are examining precision medicine strategies that use p-tau217 and MTBR-tau243 to stratify patients.[2,58] Anti-Aβ, anti-tau, senolytics, and metabolic medicines are anticipated to work better in multimodal therapy than in monotherapies.[2 68]

Preclinical benefits are shown by non-pharmacological therapies such 40 Hz gamma stimulation, but standardized human studies are required.[2] Understanding prodromal dynamics and biomarker evolution requires longitudinal, ethnically diverse cohort studies such as GHABS and CLoCODE. [3 54]High-pathology people' cognitive resilience is linked to both effective immune control and maintained synaptic integrity. [47] Aβ and tau pathology are made worse by blood-brain barrier failure; treatments that restore endothelial function and glymphatic clearance are being developed. [64]Future drug development will depend on adaptive trial designs and the incorporation of real-world data from wearables, biobanks, and electronic health records. [2]

CONCLUSION

Alzheimer’s disease is a multifactorial neurodegenerative disease driven by interconnected molecular, cellular, metabolic, vascular and immunological mechanisms.Recent discoveries in relation to research on AD have resulted in advanced knowledge about the pathogenesis of the disorder, exceeding classical notions related to amyloid and tau. Although deposition of Aβ protein and its phosphorylated partner – tau – are the major pathogenic factors of AD, there is accumulating evidence pointing to the involvement of additional elements of the same complex pathogenetic process, such as inflammation, mitochondria dysfunction, synaptic damage, altered vasculature, and metabolic abnormalities.According to the latest studies, involving the cryo-electron microscopy and proteomics, structural variability of different strains of Aβ and tau fibrils has been shown to exist, which signifies the existence of multiple pathogenic variants of the disease-causing agents.The pathogenesis of tau protein spread through the brain, analogous to prion protein spread, is more understood to be a process influenced by the activation of glial cells and transmission along neuronal circuits. Activated microglia and astrocytes exhibit persistent inflammatory signaling that aggravates neurodegeneration.The role played by mitochondria dysfunction in the initiation of the pathological events that lead to AD development is becoming better understood due to the characteristics of

mitochondria dysfunction, including the impaired mitophagy, excessive generation of ROS, disrupted calcium signaling, and changes in metabolic functions.Synergistic effects of blood brain barrier (BBB) dysfunction, impaired glymphatics and insufficient cerebrovasculature make it difficult for the removal of Aβ and tau aggregates, hence resulting in pathological accumulation, especially characteristic of sporadic AD. Glial cell senescence and age-related immune dysfunction are further suggested to contribute to persistent neuro inflammation and inadequate clearance of pathogenic proteins in a number of recent studies. This information indicates that there is more likely an involvement of systems approach where multiple interrelated immunological, metabolic, vascular, and neurodegenerative factors act simultaneously, rather than single sequential pathway leading to AD development. Therefore, a thorough comprehension of these interconnected mechanisms is essential for the development of sensitive biomarkers and precision-based therapeutic strategies for Alzheimer's disease.

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