Role of Amyloid Beta and Tau Protein in Alzheimer's disease

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***Abstract*—Alzheimer's disease is the leading cause of dementia and represents the most prevalent neurodegenerative condition worldwide. It is characterized by progressive deterioration in short-term memory and cognitive abilities, eventually interfering with everyday activities and behavior. Although the majority of cases occur sporadically, a smaller proportion is inherited, enabling the identification of specific genes that, along with neuropathological findings, provide valuable insight into the broader origins of the disease.**

A variety of environmental and metabolic influences, such as inflammation and vascular dysfunction, are also believed to contribute to the initiation and advancement of the disorder. Despite widespread neuronal shrinkage and synaptic loss across the cerebral cortex, the precise mechanisms responsible for these changes are still not fully understood. The primary pathological features associated with Alzheimer's disease are amyloid-β plaques and neurofibrillary tau tangles. Although these protein accumulations have been intensively studied for decades, their exact contribution to disease progression remains uncertain.

This review explores several proposed mechanisms involved in Alzheimer's disease, including inflammation, mitochondrial impairment, oxidative stress, and disruptions in protein clearance pathways.

***Index Terms*—amyloid-β plaques, Alzheimer's disease etiology, dementia, neurodegeneration, neurofibrillary tau tangles**

I. Introduction

1.1 Alzheimer's disease

Alzheimer's disease (AD) is a chronic and progressive neurodegenerative condition that is recognized as one of the leading causes of dementia across the globe. The prevalence of the disease continues to rise, particularly among older adults. Reports from the United States estimate that approximately 5.4 million individuals of different age groups have been affected, and the number is expected to increase considerably in the coming decades. [1-4]

AD is associated with a gradual deterioration of cognitive abilities, behavioral and personality alterations, neuronal degeneration, synaptic dysfunction, formation of senile plaques, and neurofibrillary tangles. The disease is considered multifactorial in nature, arising from both genetic and environmental influences. Genetic mutations account for fewer than 5% of cases and are mainly linked to early-onset or familial Alzheimer's disease (FAD). Mutations in genes such as amyloid precursor protein (APP), presenilin 1

(PSEN1), and presenilin 2 (PSEN2) are strongly implicated in the development of familial forms of the disorder. In contrast, sporadic cases are more commonly associated with non-genetic factors, including metabolic abnormalities and environmental influences.[4-6]

Alzheimer's disease late-onset or sporadic Alzheimer's disease (SAD) is strongly influenced by factors such as inflammation, oxidative stress, and metabolic dysfunction. In addition, alterations in the APOE gene have been widely associated with an increased risk of developing sporadic forms of the disease. Over the past several decades, extensive research has focused on understanding the underlying mechanisms and identifying effective therapeutic approaches for AD; however, its precise cause remains incompletely understood.[7-8]

To explain the onset and progression of AD, several hypotheses have been proposed, among which the amyloid hypothesis is one of the most prominent. Current evidence suggests that the excessive accumulation of amyloid-beta (Aβ) peptides, the formation of neurofibrillary tangles caused by hyperphosphorylated tau protein, cholinergic system impairment, neuroinflammation, oxidative stress, metabolic abnormalities, and disrupted cerebral energy metabolism all contribute to neuronal degeneration in AD.[9]

At present, the approved pharmacological treatments for AD mainly include acetylcholinesterase inhibitors such as donepezil and rivastigmine, along with N-methyl-D-aspartate receptor (NMDAR) antagonists. Although these medications can temporarily improve symptoms, they do not effectively halt or reverse disease progression.[10-12]

Despite considerable advances in understanding the biological and clinical features of AD and identifying numerous risk factors, therapies capable of slowing or preventing disease progression remain limited. This challenge has emphasized the importance of developing reliable experimental models that closely mimic the pathological and clinical characteristics of AD. Over the years, a wide variety of animal models have been established, ranging from short-lived organisms such as worms to long-living mammals, including transgenic models that successfully reproduce many AD-related features. [13-14] However, translating findings from preclinical animal studies into successful clinical treatments continues to be difficult. Moreover, animal-based research often requires substantial time, labor, and resources, creating additional barriers to efficient drug discovery.

Consequently, current research increasingly focuses on alternative approaches, including advanced in vitro systems, in silico modeling, and pluripotent stem cell technologies, which may provide improved platforms for understanding disease mechanisms and developing future therapeutics for Alzheimer's disease.[15-16]

1.1.1 Pathophysiology of Alzheimer's disease

Alzheimer's disease (AD) is a chronic, progressive, and irreversible neurodegenerative disorder that primarily affects memory, cognition, behavior, and functional abilities. It is recognized as the most common cause of dementia among elderly individuals worldwide. The pathophysiology of Alzheimer's disease is highly complex and multifactorial, involving a combination of genetic, biochemical, molecular, and environmental factors that collectively contribute to neuronal dysfunction and progressive brain degeneration. Although extensive research has been conducted over the past several decades, the exact mechanisms responsible for the initiation and progression of AD are still not fully understood. Nevertheless, several characteristic pathological features and mechanistic hypotheses have been identified that explain the disease process to a significant extent.

The hallmark pathological changes observed in Alzheimer's disease include extracellular deposition of amyloid-beta (Aβ) plaques, intracellular formation of neurofibrillary tangles (NFTs) composed of hyper phosphorylated tau protein, synaptic dysfunction, progressive neuronal loss, mitochondrial abnormalities, oxidative stress, excitotoxicity, vascular impairment, and chronic neuroinflammation. These pathological alterations gradually impair neuronal communication and ultimately lead to widespread brain atrophy, especially in regions associated with learning and memory such as the hippocampus and cerebral cortex. The cumulative effect of these changes results in progressive cognitive decline and behavioral abnormalities characteristic of AD.

One of the earliest explanations proposed for the pathogenesis of Alzheimer's disease was the **cholinergic hypothesis**, which emerged during the 1970s. According to this theory, the primary cause of cognitive deterioration in AD patients is the deficiency of the neurotransmitter acetylcholine (ACh), which plays a crucial role in memory formation, attention, learning, and other higher cognitive processes. In AD, degeneration of cholinergic neurons occurs predominantly in the basal forebrain, particularly within the nucleus basalis of Meynert, leading to reduced cholinergic transmission in the cerebral cortex and hippocampus. This neurotransmitter deficit was believed to contribute significantly to memory impairment and cognitive dysfunction observed in affected individuals.[17-8]

The cholinergic hypothesis gained considerable attention because it provided the foundation for the development of therapeutic agents aimed at enhancing cholinergic neurotransmission. As a result, acetylcholinesterase inhibitors such as donepezil, rivastigmine, and galantamine were developed and remain widely used for symptomatic treatment of Alzheimer's disease. These drugs act by inhibiting the enzyme acetylcholinesterase responsible for the breakdown of acetylcholine, thereby increasing the availability of ACh at synaptic junctions. Although these medications can temporarily improve cognitive function and delay symptom progression in some patients, they do not halt neuronal degeneration or cure the disease.

Consequently, researchers recognized that additional pathological mechanisms must also be involved in AD progression.

Subsequently, the **amyloid cascade hypothesis** became one of the most influential and widely accepted theories explaining Alzheimer's disease pathogenesis. This hypothesis proposes that abnormal metabolism and processing of amyloid precursor protein (APP) initiate the pathological cascade leading to neurodegeneration. APP is a transmembrane protein normally present in neuronal cells and can undergo cleavage through different enzymatic pathways. In Alzheimer's disease, APP is abnormally cleaved by β-secretase and γ-secretase enzymes, resulting in the formation of amyloid-beta peptides, particularly the highly aggregation-prone Aβ42 isoform.[18]

These amyloid-beta peptides accumulate progressively in the extracellular spaces of the brain, where they aggregate into oligomers, fibrils, and eventually insoluble amyloid plaques. The accumulation of Aβ plaques interferes with synaptic communication, disrupts neuronal signaling, induces oxidative stress, alters calcium homeostasis, damages cell membranes, and activates microglial cells and inflammatory pathways. Soluble Aβ oligomers are considered especially neurotoxic because they impair synaptic plasticity and contribute directly to memory dysfunction. Over time, chronic amyloid toxicity leads to neuronal injury and cell death, thereby contributing to progressive cognitive decline.

Strong genetic evidence supports the amyloid hypothesis. Mutations in genes encoding amyloid precursor protein (APP), presenilin-1 (PSEN1), and presenilin-2 (PSEN2) have been identified in familial early-onset Alzheimer's disease. These mutations increase the production or aggregation tendency of amyloid-beta peptides, particularly Aβ42, thereby accelerating plaque formation and disease progression. Additionally, individuals with Down syndrome, who possess an extra copy of chromosome 21 containing the APP gene, frequently develop Alzheimer-like pathology at an earlier age, further supporting the role of amyloid accumulation in AD pathogenesis.

Despite substantial evidence supporting the amyloid hypothesis, several limitations and controversies remain. Some individuals exhibit significant amyloid plaque accumulation without severe cognitive impairment, whereas others demonstrate extensive neurodegeneration with relatively low plaque burden. Furthermore, many anti-amyloid therapeutic agents have shown limited clinical success in preventing or reversing cognitive decline. These observations suggest that amyloid deposition alone may not fully explain the complexity of Alzheimer's disease and that additional pathological processes such as tau pathology, neuroinflammation, mitochondrial dysfunction, vascular changes, and synaptic degeneration also play crucial roles in disease progression.[19]

Another major pathological feature of Alzheimer's disease involves the formation of **neurofibrillary tangles** composed of abnormally hyper phosphorylated tau protein. Under normal physiological conditions, tau protein stabilizes microtubules within neurons and maintains axonal transport. However, in AD, tau undergoes abnormal hyper phosphorylation, causing it to detach from microtubules and aggregate into paired helical filaments that form intracellular neurofibrillary tangles. These tangles disrupt neuronal transport systems, impair synaptic function, and ultimately lead to neuronal death. The severity of tau pathology has been found to correlate more closely with cognitive decline than amyloid plaque burden, highlighting its significant contribution to disease progression.

In addition to amyloid and tau pathology, oxidative stress and mitochondrial dysfunction are important contributors to neuronal degeneration in Alzheimer's disease. Increased production of reactive oxygen species (ROS) damages lipids, proteins, nucleic acids, and cellular organelles, thereby impairing neuronal survival. Mitochondrial dysfunction further reduces cellular energy production and enhances oxidative injury, promoting apoptosis and neurodegeneration. Chronic neuroinflammation mediated by activated microglia and astrocytes also contributes significantly to neuronal damage through the release of pro-inflammatory cytokines, chemokines, and neurotoxic substances.[20]

Overall, the pathophysiology of Alzheimer's disease involves a complex interplay among amyloid-beta accumulation, tau hyper phosphorylation, cholinergic dysfunction, oxidative stress, mitochondrial impairment, synaptic degeneration, and neuroinflammatory processes. These interconnected mechanisms progressively damage neuronal networks and ultimately result in the characteristic cognitive and behavioral impairments associated with the disease. Continued research into these pathological pathways is essential for the development of more effective disease-modifying therapies aimed at preventing or slowing the progression of Alzheimer's disease.[21]

1.1.1 Alzheimer's Hypothesis

i) Amyloid Hypothesis

The amyloid hypothesis is one of the most widely accepted and extensively studied theories explaining the pathogenesis of Alzheimer's disease (AD). This hypothesis proposes that abnormal production, accumulation, and aggregation of amyloid-beta (Aβ) peptides within the brain represent the primary pathological events that initiate a cascade of neurodegenerative processes leading to Alzheimer's disease. According to this concept, excessive deposition of Aβ peptides contributes to synaptic dysfunction, neuronal injury, tau pathology, neuroinflammation, and ultimately progressive cognitive decline.

Amyloid-beta (Aβ) peptides are small hydrophobic peptide fragments consisting of approximately 39–43 amino acid residues. Among the various isoforms, Aβ40 and Aβ42 are the most predominant and

biologically significant forms. Aβ42, in particular, is considered highly pathogenic because of its greater hydrophobicity and tendency to aggregate rapidly into oligomers and fibrils. Numerous experimental, genetic, and clinical studies have demonstrated that both Aβ40 and Aβ42 play important roles in neuronal degeneration and impairment of cognitive functions. These peptides are capable of triggering a series of pathological events including oxidative stress, synaptic dysfunction, mitochondrial damage, neuroinflammation, and tau hyperphosphorylation, eventually resulting in neuronal death.[22]

The concept of amyloid involvement in Alzheimer's disease emerged following the identification and isolation of amyloid-like proteins from senile plaques and meningeal blood vessels of AD patients. Similar pathological deposits were also observed in individuals with Down syndrome, who commonly develop early-onset Alzheimer-like dementia. This observation suggested a possible association between amyloid deposition and neurodegeneration. Further support for the hypothesis came with the discovery of amyloid precursor protein (APP), a transmembrane glycoprotein responsible for generating amyloid-beta peptides. Identification of APP and its genetic association with familial Alzheimer's disease strongly reinforced the idea that abnormal amyloid metabolism plays a central role in AD pathogenesis.[23]

The amyloid hypothesis postulates that excessive production or impaired clearance of Aβ peptides leads to their abnormal accumulation either intracellularly or extracellularly in the brain. These peptides may exist in several forms including soluble monomers, soluble oligomers, insoluble fibrils, and extracellular amyloid plaques. Among these, soluble Aβ oligomers are considered particularly neurotoxic because they interfere with synaptic signaling and impair neuronal plasticity even before plaque formation becomes evident. Progressive accumulation of Aβ ultimately promotes the formation of neuritic plaques and cerebral amyloid angiopathy, both of which are characteristic pathological hallmarks of Alzheimer's disease.[24]

Amyloid-beta peptides are generated through the proteolytic processing of amyloid precursor protein (APP). APP can undergo two major metabolic pathways: the **non-amyloidogenic pathway** and the **amyloidogenic pathway**. Under normal physiological conditions, APP is predominantly processed through the non-amyloidogenic pathway, which prevents the formation of Aβ peptides. In this pathway, APP is initially cleaved by α-secretase, an enzyme belonging mainly to the ADAM (a disintegrin and metalloprotease) family, particularly ADAM10. α-secretase cleaves APP within the Aβ region, thereby preventing amyloid-beta formation and releasing a soluble extracellular fragment known as sAPPα, which possesses neuroprotective properties.

In contrast, the amyloid genic pathway leads to the production of amyloid-beta peptides and is considered central to Alzheimer's disease pathology. In this pathway, APP undergoes sequential proteolytic cleavage by two major enzymes: β-secretase and γ-secretase. Initially, β-secretase, also known as β-site APP cleaving enzyme-1 (BACE1), cleaves APP at the N-terminal region of the Aβ domain. This cleavage generates a

soluble extracellular fragment termed sAPPβ and a membrane-bound C-terminal fragment consisting of 99 amino acid residues, commonly referred to as CTF99 or C99.

Subsequently, the C99 fragment is further cleaved by the γ-secretase complex, a multi-subunit enzyme complex composed of presenilin-1 (PS1) or presenilin-2 (PS2), nicastrin, anterior pharynx-defective-1 (Aph-1), and presenilin enhancer-2 (PEN-2). Among these components, PS1 and PS2 form the catalytic core of the complex. γ-secretase-mediated cleavage results in the generation of different Aβ isoforms, predominantly Aβ40 and Aβ42. Although Aβ40 is produced in larger quantities, Aβ42 is more aggregation-prone and exhibits greater neurotoxicity, making it more strongly associated with Alzheimer's disease progression.[25]

Accumulated Aβ peptides aggregate to form oligomers, protofibrils, fibrils, and ultimately extracellular amyloid plaques within the brain parenchyma. These aggregates disrupt neuronal communication, impair synaptic transmission, alter calcium homeostasis, induce oxidative stress, and activate microglial-mediated inflammatory responses. Chronic amyloid accumulation also contributes to tau hyperphosphorylation and neurofibrillary tangle formation, thereby linking amyloid pathology with other major pathological features of Alzheimer's disease.

Genetic studies provide strong evidence supporting the amyloid hypothesis. Mutations in APP, presenilin-1 (PSEN1), and presenilin-2 (PSEN2) genes are associated with familial early-onset Alzheimer's disease and lead to increased production or altered processing of Aβ42 peptides. Furthermore, individuals with trisomy 21 (Down syndrome), who possess an extra copy of the APP gene located on chromosome 21, frequently exhibit early amyloid deposition and Alzheimer-like neuropathology.

Despite extensive evidence supporting the amyloid hypothesis, certain limitations and controversies remain. Some patients exhibit significant amyloid plaque deposition without severe cognitive impairment, while others show cognitive decline with relatively low amyloid burden. In addition, several anti-amyloid therapies have demonstrated limited success in clinical trials. These findings suggest that although amyloid-beta accumulation is a critical factor in AD pathogenesis, it may act in conjunction with other mechanisms such as tau pathology, neuroinflammation, mitochondrial dysfunction, oxidative stress, and vascular abnormalities.

Overall, the amyloid hypothesis remains a fundamental framework for understanding Alzheimer's disease and has significantly influenced the development of diagnostic biomarkers and therapeutic strategies targeting amyloid-beta production, aggregation, and clearance.[26]

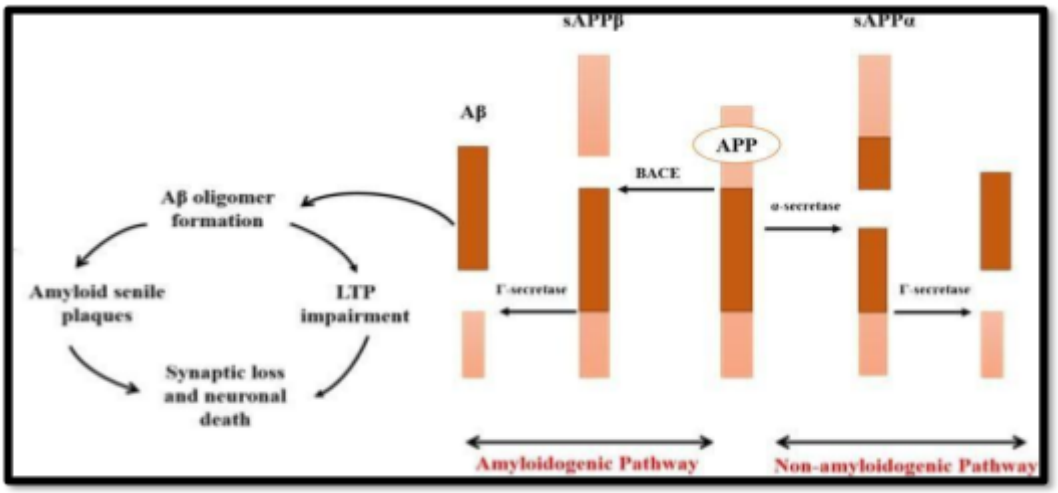

Figure 1.5: Amyloid cascade

The non-amyloidogenic pathway involves the enzymatic cleavage of amyloid precursor protein (APP) by α-secretase within the ectodomain region, thereby preventing the generation of amyloid-β (Aβ) peptides. This cleavage releases a large soluble N-terminal fragment known as soluble APP-α (sAPPα), which possesses significant neuroprotective and neurotrophic activities. Simultaneously, a membrane-bound C-terminal fragment termed C83 (CTFα) is produced. The C83 fragment subsequently undergoes proteolytic processing by γ-secretase, resulting in the formation of the p3 peptide (Aβ17–40/42), which exhibits considerably lower neurotoxicity compared to full-length Aβ peptides.[27]

In contrast, Aβ peptides generated through the amyloidogenic pathway tend to aggregate into oligomers and protofibrils characterized by β-sheet-rich secondary structures and reverse-turn conformations. These protofibrils are highly neurotoxic and progressively develop into mature fibrils and insoluble linear filaments that accumulate as amyloid plaques within specific brain regions. The deposition of amyloid plaques is considered a hallmark pathological feature of Alzheimer's disease (AD) and can be histologically identified using Congo red staining.[28]

ii. Defensive-Clearance Hypothesis: Aβ Degradation

According to the amyloid cascade hypothesis, Aβ peptides are continuously produced through proteolytic processing of APP and subsequently accumulate in various regions of the brain. Under physiological conditions, however, Aβ levels are tightly regulated through degradation by a group of enzymes collectively known as Aβ-degrading proteases (AβDPs). These enzymes maintain a dynamic balance between Aβ production and clearance. Therefore, elevated Aβ accumulation in AD may result not only from increased peptide production but also from impaired degradation and clearance mechanisms. This concept is supported by findings in sporadic Alzheimer's disease (SAD), where reduced clearance of Aβ from cerebrospinal fluid (CSF) has been observed.[29]

Aβ-degrading proteases, including various proteinases and peptidases, are localized within distinct subcellular compartments and brain regions. Depending on their localization and enzymatic specificity, these proteases generate different peptide fragments with varying degrees of pathogenic potential. Based on their functions under normal and disease conditions, AβDPs are broadly classified into endogenous regulators, which contribute to physiological Aβ homeostasis, and pathogenic regulators, which are associated with altered Aβ metabolism during disease progression.[30]

iii. Based on cholinergic hypothesis

According to the cholinergic hypothesis, impairment of cholinergic neurotransmission is considered one of the principal causes of cognitive decline and dementia in Alzheimer's disease (AD). Early therapeutic strategies for AD primarily targeted the cholinergic system, leading to the development of cholinesterase inhibitors such as Tacrine, Donepezil, Rivastigmine, and Galantamine, all of which received approval from the U.S. Food and Drug Administration for the management of AD symptoms. Subsequent advancements introduced Memogain, an inactive prodrug of galantamine that demonstrated approximately 3–5 times greater potency and nearly 15-fold enhanced bioavailability compared with its parent compound.[31]

In recent years, α7 nicotinic acetylcholine receptor (α7 nAChR) agonists have emerged as promising therapeutic candidates for symptomatic management of AD. Activation of these receptors enhances calcium influx and stimulates intracellular signaling pathways, thereby promoting the release of neurotransmitters including glutamate and gamma-aminobutyric acid (GABA). Investigational agents such as Encenicline and ABT-126 have shown fewer adverse effects compared with conventional acetylcholinesterase inhibitors and are being evaluated in clinical trials for their therapeutic potential in AD.[32]

Apart from cholinergic dysfunction, glutamatergic signaling has also been strongly implicated in AD pathogenesis, particularly through N-methyl-D-aspartate receptors (NMDARs), which are ligand-gated cation channels involved in excitatory neurotransmission, synaptic plasticity, and cognition. Binding of glutamate to NMDARs contributes to learning and memory processes; however, amyloid-β (Aβ) peptides can excessively activate these receptors, leading to glutamatergic dysregulation, neuronal toxicity, and abnormal intracellular calcium accumulation. [33]Aβ-mediated alterations may also disrupt endocytosis and modify the function of AMPA and kainate receptors, thereby exacerbating neuronal damage. These findings encouraged the development of NMDAR antagonists aimed at reducing Aβ-induced neurotoxicity. Memantine, a non-competitive NMDAR antagonist, is currently used in patients with moderate to severe AD, while several newer NMDAR antagonists continue to be explored in clinical studies.[34][35]

iv. Based on Aβ hypothesis

The amyloid-β (Aβ) hypothesis emerged after the discovery of mutations in the amyloid precursor protein (APP) gene and presenilin genes, which encode important subunits of the γ-secretase complex involved in APP cleavage. These findings suggested that excessive production and aggregation of Aβ peptides through the amyloidogenic pathway represent a central mechanism in the pathogenesis of Alzheimer's disease (AD). Consequently, β-secretase and γ-secretase became important therapeutic targets because inhibition of these enzymes could potentially decrease Aβ generation.[36]

Amyloid hypothesis proposes that γ-secretase, a multi-subunit aspartyl protease complex, is responsible for the final cleavage of APP that leads to Aβ formation. Experimental studies in transgenic mouse models such as PDAPP and Tg2576 demonstrated that γ-secretase inhibitors significantly lowered Aβ levels, encouraging the development of several γ-secretase inhibitors (GSIs). However, the structural complexity and heterogeneity of γ-secretase complicated the identification of selective inhibitors. In addition to APP, γ-secretase also processes nearly 50 other type-I transmembrane proteins, making selective targeting extremely difficult.[37][38]

One of the most important substrates of γ-secretase is the Notch signaling pathway receptor, which regulates cellular differentiation, synaptic plasticity, neuronal survival, and tumor suppression. Inhibition of Notch processing by non-selective GSIs caused severe adverse effects, including gastrointestinal toxicity and immunosuppression.[39] Due to these target-related toxicities, the clinical development of several GSIs, including Semagacestat and Avagacestat, was discontinued despite their ability to reduce Aβ levels. To overcome these limitations, researchers developed Notch-sparing γ-secretase inhibitors such as BMS-708163, which demonstrated promising reductions of Aβ concentrations in cerebrospinal fluid and plasma with reduced toxicity.[40]

Following the limited success of GSIs, attention shifted toward β-secretase, also known as β-site APP cleaving enzyme-1 (BACE-1). BACE-1 is a type-I transmembrane aspartyl protease belonging to the pepsin family and plays a crucial role in the initial proteolytic cleavage of APP during the amyloidogenic pathway. The enzyme contains two catalytic aspartate motifs that form its active site. Another related enzyme, BACE-2, shares approximately 64% amino acid similarity with BACE-1; however, it has not been shown to significantly contribute to Aβ production. Multiple generations of peptide and non-peptide BACE-1 inhibitors have therefore been designed and evaluated in both preclinical and clinical studies as potential anti-Alzheimer agents.[41]

APP processing is considered a critical event in AD progression because the mode of APP cleavage determines whether toxic or non-toxic products are formed. In the non-amyloidogenic pathway, APP is

cleaved by α-secretase, resulting in the release of soluble APPα (sAPPα), a non-toxic fragment with neuroprotective properties. Since α-secretase cleavage prevents Aβ formation, enhancement of α-secretase activity has been explored as an alternative therapeutic strategy for AD. Members of the a disintegrin and metalloprotease (ADAM) family are primarily responsible for α-secretase activity. Although selective α-secretase activators are still under investigation, stimulation of α-secretase-associated signaling pathways has shown beneficial effects, including neuroprotection and reduced Aβ accumulation.

In addition, impaired clearance of Aβ has been observed in sporadic Alzheimer's disease (SAD), indicating that defective degradation and removal of Aβ peptides may also contribute significantly to disease progression.[42]

Aβ Degradation and Immunotherapeutic Approaches in Alzheimer's Disease. Enhancement of amyloid-β degradation pathways (AβDPs) is considered equally important as reducing Aβ production in the treatment of Alzheimer's disease (AD). Aβ-degrading proteases act on both soluble Aβ monomers and, to some extent, fibrillar Aβ aggregates, thereby reducing amyloid burden in the brain. These observations have encouraged the development of pharmacological strategies aimed at increasing the expression or activity of Aβ-degrading proteases while simultaneously inhibiting endogenous molecules that suppress their function.[43]

Several experimental studies have demonstrated the therapeutic significance of Aβ degradation pathways. Increased expression of Cathepsin B in animal models showed beneficial effects through enhanced degradation and clearance of Aβ peptides. Similarly, inhibition of Cystatin C, an endogenous inhibitor of Aβ-degrading enzymes, was associated with neuroprotective effects and increased Aβ clearance. These findings suggest that modulation of AβDPs may represent a promising therapeutic strategy for limiting amyloid accumulation in AD. In addition to enzyme-based approaches, gene therapy and immunotherapy have also been explored to improve Aβ clearance and potentially slow disease progression.[44]

Among emerging therapeutic strategies, immunotherapy has attracted considerable attention because of its encouraging outcomes in animal models and clinical studies. Early landmark investigations by Dale Schenk and colleagues demonstrated that immunization of PDAPP transgenic mice with fibrillar Aβ42 significantly reduced amyloid plaque formation and slowed the progression of amyloid pathology in both young and older animals. These promising findings initiated extensive research into immunotherapeutic interventions for AD.[45]

Immunotherapy for AD mainly includes two approaches: active immunization and passive immunization. Active immunization involves vaccination to stimulate the body's immune response against Aβ, whereas passive immunization uses externally administered monoclonal antibodies directed against Aβ peptides.

Studies in transgenic mouse models indicated that anti-Aβ immunization could reduce synaptic degeneration, enhance cognitive performance, and promote Aβ clearance from the brain.[46]

The first major active immunization trial involved AN1792, a vaccine containing full-length Aβ42 peptide. Although this vaccine successfully reduced amyloid plaques and improved memory deficits in experimental studies, the clinical trial was terminated because approximately 6% of participants developed meningoencephalitis, despite showing decreased Aβ accumulation. Due to these safety concerns, attention shifted toward passive immunization strategies.[47]

Passive immunization using monoclonal antibodies demonstrated several advantages, including improved antigen specificity, favorable pharmacokinetic properties, and reduced toxicity. Systemically administered monoclonal antibodies were shown to reduce circulating soluble Aβ through the "peripheral sink" mechanism, thereby limiting Aβ deposition in the brain. In addition, passive immunotherapy may directly dissolve existing Aβ aggregates and inhibit the formation of toxic fibrils and oligomers. As a result, numerous monoclonal antibodies are currently being investigated in clinical trials as potential disease-modifying therapies for AD.

A reverse translational medicine approach has also been explored, based on the isolation of naturally occurring anti-Aβ antibodies from cognitively healthy elderly individuals. One important example is Aducanumab, a human IgG1 monoclonal antibody that selectively targets aggregated Aβ. Aducanumab has demonstrated dose-dependent reduction of amyloid plaque deposition and has shown potential to slow cognitive decline in patients with AD.[48]

v. Based on the Tau Hypothesis

Apart from amyloid-β (Aβ), the Tau protein is considered another major contributor to the pathogenesis of Alzheimer's disease (AD). The tau hypothesis proposes that abnormal aggregation of hyper phosphorylated tau leads to the formation of neurofibrillary tangles (NFTs), one of the characteristic histopathological hallmarks of AD. Tau is a hydrophilic and intrinsically unfolded microtubule-associated protein predominantly present in neuronal cells of the brain, where it plays a critical role in maintaining microtubule stability and axonal transport. Six different isoforms of tau are expressed in the adult human brain, and their varying affinities for microtubules influence their tendency to aggregate into NFTs. Consequently, alterations in tau gene expression and alternative splicing mechanisms have emerged as important therapeutic targets in tauopathies.[49][50]

Numerous preclinical investigations have shown that pathological tau can initiate and propagate abnormal signaling cascades within neurons, thereby contributing to neurodegeneration. Under physiological

conditions, tau is mainly localized in neuronal axons; however, in AD and related tauopathies, tau abnormally accumulates not only in axons but also in dendrites and neuronal cell bodies. Tau undergoes several post-translational modifications, including phosphorylation, acetylation, glycosylation, and ubiquitination, which promote its oligomerization and aggregation.[51] Among these modifications, phosphorylation is considered the most critical event in tau pathology. Excessive phosphorylation converts tau into paired helical filaments, which subsequently aggregate to form NFTs.[52]

Hyper phosphorylated tau loses its normal affinity for microtubules, leading to destabilization of the neuronal cytoskeleton and impairment of axonal transport. These alterations ultimately contribute to neuronal dysfunction, neurodegeneration, and cell death. Because of the central role of tau hyper phosphorylation in AD progression, several therapeutic approaches have been investigated to restore microtubule stability and preserve neuronal integrity.[53] These include inhibitors of tau phosphorylation, particularly kinase inhibitors targeting Glycogen synthase kinase-3 beta, phosphatase modulators, and microtubule-stabilizing agents. Compounds derived from Paclitaxel, such as Epothilone D, have shown potential because of their ability to penetrate the brain and stabilize neuronal microtubules.[54]

In addition to targeting phosphorylation, inhibition of tau aggregation has become another important therapeutic strategy for reducing tau-associated neurotoxicity. Preventing the assembly of toxic tau oligomers and fibrils may help minimize neuronal damage and slow disease progression. Furthermore, enhancement of pathological tau clearance through immunotherapy has emerged as a promising treatment approach. Tau-directed immunotherapies aim to facilitate the removal of abnormal phosphorylated tau species and reduce NFT burden in the brain.[55]

Recent studies have also highlighted the role of microRNAs in regulating tau expression. miR-219 has been shown to bind to the 3′ untranslated region of tau mRNA and suppress tau protein expression.Reduced levels of miR-219 have been reported in AD, suggesting that restoration of miR-219 activity may represent a novel therapeutic strategy for controlling tau pathology and slowing neurodegeneration.[56]

II. Conclusion

Alzheimer’s disease is a progressive neurodegenerative disorder in which amyloid beta (Aβ) and tau protein play central roles in disease development and progression. Accumulation of amyloid beta peptides leads to the formation of extracellular amyloid plaques, which disrupt neuronal communication, induce oxidative stress, and trigger inflammatory responses in the brain. These pathological changes initiate neuronal damage and create conditions that promote further neurodegeneration.

Tau protein, normally responsible for stabilizing microtubules in neurons, becomes abnormally hyper phosphorylated in Alzheimer's disease. This altered tau aggregates into neurofibrillary tangles (NFTs), causing disruption of intracellular transport, neuronal dysfunction, and eventual cell death. The spread of tau pathology is strongly associated with cognitive decline and memory impairment observed in affected patients.

Current evidence suggests that amyloid beta and tau proteins act synergistically, where amyloid accumulation may trigger tau abnormalities, accelerating neuronal degeneration and disease progression. Understanding the complex interaction between these two proteins has significantly improved knowledge of Alzheimer's pathogenesis and has guided the development of targeted therapeutic strategies. Although complete cure remains unavailable, ongoing research focusing on amyloid beta clearance, tau stabilization, and neuroprotection offers promising directions for early diagnosis, disease modification, and improved management of Alzheimer's disease in the future.

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