Navigating the amyloid landscape: Insights into Alzheimer's pathogenesis and emerging treatment paradigm

Aniket Singh[1], Nibedita Banik [2]
Department of Chemistry, Chandigarh University, NH-05, Mohali, Ludhiana Chandigarh highway-140413, India
[1]anisin1357@gmail.com [2]nibedita.e11769@cumail.in

Abstract
Alzheimer's disease (AD) presents a complex array of symptoms, including cognitive decline, memory impairment, and behavioral changes. Extensive research has underscored the pivotal role of amyloid aggregates in AD pathogenesis. These beta-amyloids, aberrantly folded proteins that aggregate into insoluble fibrils, accumulate in the brains of AD patients, leading to the formation of senile plaques and neurofibrillary tangles. This comprehensive review delves into the multifaceted role of beta amyloids in AD, elucidating their molecular origins, aggregation mechanisms, neurotoxic effects, and potential therapeutic avenues. By unraveling the intricate mechanisms governing amyloid-related pathology, this review aims to deepen our understanding of AD and pave the way for targeted therapeutic interventions.

Key words: Beta-amyloid, Alzheimer's disease, senile plaques, therapeutic interventions.

Introduction
Alzheimer's disease is a central nervous system centred neurodegenerative disease which is one of the major disorders causing dementia, loss of memory, in human beings. This condition is mostly prevalent in people of age more than 60 years. A study of the disease in 2016 indicated that approximately >46.8 million people of age older than 60 years were affected from this disease [1]. AD is of two types i.e. familial and sporadic meaning that it can be either taken up from the parent generation or form on its own due to abnormal protein deposition or plaque formation in the brain. The familial AD is observed in less than 5% of the overall AD patients. However, the sporadic type of this disease occupies the major part of approximately 95%. The latter, forms in the late phases of life in a human i.e. above 60 years of age. As of now, there are about 50 million people suffering from this disease and the number is supposed to triple by 2050 [2]. These numbers have attracted a multitude of scientists and doctors in order to find the cure of the disease which seems to be a distant dream even after years of research and drug trials. The main reason of it being that the brain is a very sensitive tissue itself to treat. The neurons, forming the major part of the nervous system, are permanent and non-dividing in nature.

AD pathology and treatment approaches suggest AD as a very deeply rooted disease such that the structural plaques and tangles of this disease are spread in the peripheral as well as the interior parts of the neurons and synapses. This makes the surgical treatment nearly impossible. The treatment using drug administration seems a viable therapeutic aid along with behavioural therapies and lifestyle interventions.

The structural peptide components resulting in the formation of the disease consist of two major types: the Beta amyloid plaques and Tau Neurofibrillary tangles. However, the pathogenesis studies also mark some other causes that are responsible in a way or other in AD. Numerous alternative theories regarding the pathogenesis of AD have been suggested and investigated, including disruptions in the acetylcholine system, over-phosphorylation of tau protein, axonal damage, and neuronal depletion [3]. Decades of study of the diagnosis and treatment of AD has focussed on the role of Beta-amyloids as the paramount in the formation of disease and hence the treatment efforts were also aligned with the anti-amyloid drug development.

Beta-amyloids are the secondary beta proteinaceous structure i.e. sheet like structure that arise from amyloid precursor proteins (APP). These Beta-amyloids form plaques, also known as senile plaques, upon significant deposition around the synapses. The senile plaques consist of extracellular accumulations of beta-amyloid protein in various morphological variants, which encompass neurotic, diffused, dense-cored, classic, and compact types of plaques. Enzymes involved in proteolytic cleavage, such as α-secretase and beta-secretase, play pivotal roles in the generation of beta-amyloid deposits from the transmembrane amyloid precursor protein (APP) [4,5,6]. This deposition results in the decreased potential of neurotransmission of nerve impulses and hence affect the neuronal network of the brain. This review dives deep into the origin, structural features and causative actions of the Amyloid plaques. We will also discuss the latest trends in the therapeutics of AD mostly the once gaining success in the anti-amyloid category.

Molecular origins of Amyloids

Since Alois Alzheimer's initial delineations of pre-senile dementia in 1907 [7], the development of senile plaques (SP) and neurofibrillary tangles (NFT) has been viewed as the hallmark pathological characteristics of AD. To understand the whys related to the formation of these plaques and tangles, one must understand the molecular basis of them. The Amyloid-beta Precursor Protein has garnered significant attention in research circles owing to its pivotal role in the formation of pathological cortical plaques in AD [8]. This protein is part of a gene family with ancient evolutionary roots and constitutes a member of a highly conserved group of type-1 transmembrane proteins [9-11]. Within vertebrate species, the APP family comprises potentially three homologues: APP, amyloid precursor like protein 1 (APLP-1), and amyloid precursor like protein 2 (APLP-2). In the genomes of invertebrate species, a solitary homologue exists, known either as amyloid precursor like 1 protein (APL-1) or APP-like 1 protein (APPL-1). These findings suggest the APP as a naturally found protein of the animal cell. In the brain, the amyloid precursor protein (APP) is involved in many different processes, including metal ion balance, transport and signaling, cell adhesion, neuronal development and repair, proteolytic processing, and synaptic plasticity. However, alterations in the sequence of APP and its associated enzymes have been separately linked to familial early-onset AD, typified by swiftly advancing cognitive decline and substantial accumulation of Abeta plaques [12].

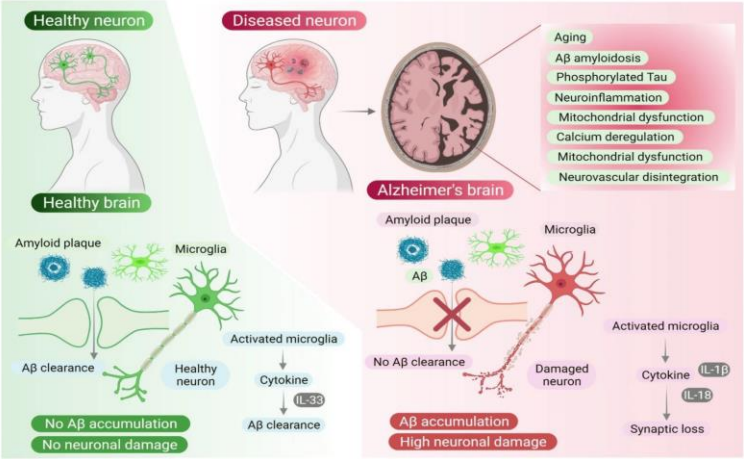

Figure 1. Visualizing the Impact: Healthy Brain vs. Alzheimer's Brain

Animal studies indicate that Abeta peptides could arise in reaction to cellular deterioration. For instance, impairments in the nucleus basalis of Meynert (nBM) in rat models lead to increased synthesis of APP in cortical neurons [13]. An increase of APP leads to the threshold breakage of the cell to accommodate the peptide. This result in cleavage of the peptide sequences leading to formation of fragment with no particular function and in turn accumulating extracellularly. The pathophysiology of AD is complex, with significant pathological markers identified. Among these, Beta-amyloid accumulation is considered the primary driver of neurodegeneration. Other factors, such as tau pathology and neuroinflammation, ultimately lead to Beta-amyloid buildup. For instance, microglia, the brain's innate immune cells, mediate neuroinflammation by producing cytokines like IL-33, IL-8, and IL-1β. Microglial activation initiates neural inflammation, with IL-33 promoting Beta-amyloid clearance, while IL-8 and IL-1β contribute to synaptic dysfunction. This molecular mechanism highlights the intricate nature of AD. A better look at the difference between a normal brain and AD patient’s brain is shown in the figure below [14].

Another causative component of AD related molecules are the Tau neurofibrillary tangles. The genesis of tau neurofibrillary tangles (NFTs) begins with the intricate interplay of various cellular processes, where aberrant phosphorylation and conformational changes in tau protein disrupt its normal function. Tau, a vital microtubule-associated protein (MAP), stands as the primary component within the paired helical filaments (PHF) and straight filaments constituting the neuronal neurofibrillary tangles observed in AD. A solitary gene governs tau, giving rise to diverse isoforms through processes like alternative splicing and post-transcriptional modifications [15]. The Tau proteins which get hyperphosphorylated are of three categories: (1) During the pre-tangle phase, a variant of neurofibrillary tangles (NFTs) emerges, marked by the accumulation of phosphorylated tau proteins in the somatodendritic compartment, devoid of the formation of paired helical filaments (PHF). (2) Mature NFTs represent another category, characterized by the aggregation of tau protein filaments and the displacement of the nucleus towards the soma's periphery. (3) Extracellular tangles, also known as ghost NFTs, manifest as a consequence of neuronal loss attributed to high levels of filamentous tau protein, exhibiting partial resistance to proteolysis. [16,17]

AD is caused by mutations in the genetic composition of the patients early in the life for the familial type and later on in the sporadic. Both the sporadic and familial AD are caused by similar mutations. Genetic mutations result in the changed behaviour in the Amyloid forming APP. These factors also include changes in the presenilin 1 and presenilin 2 genes [18]. The alterations in the APP results in the aggregation of Beta-amyloid. On the other hand, mutations of presenilin 1 and 2 causes the decreased clearance rate of Beta-amyloid aggregates by making them more hydrophobic. [19-21]. By hydrophobicity we understand that if a chemical compound show hydrophobicity than it is more susceptible to elimination from the excretory path way through favourable dissolvability. Similarly for a protein aggregate it is essential to have a hydrophilic nature to get dissolved for transportation in humas system. The ApoE4 protein is a well-known risk factor in sporadic type AD. Apolipoprotein E4 (ApoE4) is one of the three major isoforms of the apolipoprotein E protein, crucial for lipid metabolism. It is characterized by having arginine residues at specific positions, which differentiates it from other isoforms like ApoE3 and ApoE2. ApoE4 is known for its less efficient clearance of amyloid-beta peptides from the brain, contributing to the development of AD. It also impacts neuronal repair and lipid transport, and is associated with a higher risk of cardiovascular issues. The structural differences of ApoE4 affect its interactions with lipids and receptors, resulting in its unique physiological effects. Constituting approximately 15% of the entire ApoE pool, APOE4 disrupts the removal of Beta-amyloids from the brain. Distinguished by amino acid replacements at positions 112 and 158, ApoE4 features two arginine residues, whereas ApoE3 possesses two cysteines, and ApoE2 harbours both arginine and cysteine at these specific positions. [22]

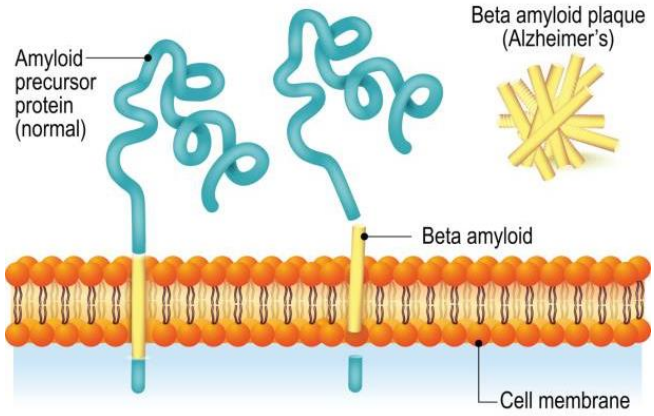

Figure 2. Source of Beta-amyloid aggregation through APP
(CREDIT LINK: https://www.istockphoto.com/portfolio/ttsz?mediatype=illustration)

Amyloid Aggregation Process

Protein aggregation can involve folded or globular proteins, as in transthyretin (TTR) linked amyloidosis, where the misfolding process results in the development of partially unfolded states, or it can involve naturally unfolded or inherently disordered systems, as amyloid-beta peptide in AD. Assemblies of monomeric units that adopt highly disordered structures, well-defined fibrils with cross-beta structure, or native-like conformations that originate from unfolded, partially unfolded, or folded monomeric states, respectively, are the typical

oligomeric species formed during the amyloidogenic pathway. Because these various aggregate forms form in well-defined clinical states and provide an important expression of the multiplicity of processes, structures, and morphologies observed during protein aggregation and disease progression, they are associated with amyloid diseases. [23]. The various conformational states that proteins can adopt in a functional living system include a very intricate set of kinetic barriers and thermodynamic equilibria that are finally determined by the amino acid sequence of the protein. While intrinsic amino acid sequences and biological contexts work together to maintain proteins in their natural, soluble forms (a non-amyloidogenic pathway), proteins can also interconvert into cytotoxic, non-functional protein clumps (amyloidogenic pathway) in specific situations. A few neurodegenerative illnesses are included in this list of misfolding and aggregation in peptides that have been discovered and investigated for a variety of diseases (Table 1). The mechanism of Beta-amyloid senile plaques has been largely explained by the aggregation process of these disorders. In order to identify the specific gene sequences causing misfolding and develop APIs that can target those sequences, a thorough and methodical analysis of the aggregation of these peptides is essential.

	Neuro-degenerative Disease linked with protein misfolding		
Neuro disease	**Precursor protein**	**Peptide sequence length**	**Strucatural Organization**
Alzheimer's disease	Amyloid alpha precursor variants	37-44	IDP
Spongiform encephalopathies	Prion protein or its fragments	208	IDP or alpha helical
Parkinson's disease	alpha-synuclein	140	IDP
Amyotrophic lateral sclerosis	Superoxide dismutase 1	153	Beta sheet
Huntington's disease	Huntingtin with polyQ expansion	3144	IDP
Neuroferritinopathy	Ferritin	175 or 183	Alpha helical
Familial British dementia	ABri	34	IDP
Familial amyloid polyneuropathy	Transthyretin variants	127	Beta sheet

Table 1. Neurodegenerative diseases linked with protein misfolding and aggregation [24,25]

There are the following types of Amyloid aggregation processes-

Aggregation through a nucleation dependant process: The process of amyloid formation, known as nucleation-dependent mechanism or nucleation–elongation polymerization, follows a characteristic sigmoidal curve over time and comprises three sequential stages: (1) initial lag or nucleation phase; (2) elongation, growth, polymerization, or fibrillation phase; (3) equilibrium, stationary, or saturation phase [26,27]. During the nucleation phase, transient, critical nuclei assemble, serving as seeding intermediates for additional monomeric subunits to attach, facilitating the formation of oligomers with cross-beta structure. This phase is characterized by similar rate constants for monomer addition and dissociation, resulting in a slow overall nucleation process and serving as the rate-limiting step in fibril formation. The nucleation phase can be expedited or bypassed by introducing pre-formed aggregates or fibrillar species, a phenomenon referred to as seeding [28,29]. Subsequently, in the elongation phase, monomers, nuclei, and oligomers interact further, assembling into prefibrillar structures that rapidly mature into ordered fibrillar structures known as protofibrils. As this phase yields more stable protofibrils, it represents a faster and thermodynamically favourable process.

Finally, in the saturation phase, characterized by low and relatively constant monomer concentration, protofibrils assemble into mature amyloid fibrils with varied morphological structures and levels of polymorphism [30,31]. The mechanism of nucleation dependent aggregation follows two steps-

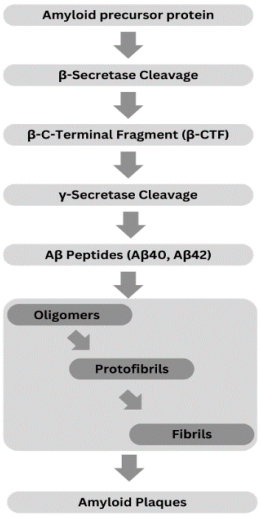

Figure 3. Formation and Aggregation Pathway of Amyloids

Primary elongation-

Two primary nucleation mechanisms exist: homogeneous and heterogeneous. Homogeneous primary nucleation involves the aggregation of monomers in bulk solution, while heterogeneous primary nucleation occurs when monomeric subunits associate on the surface of different objects, such as reaction container walls, other proteins, phospholipid bilayers, or the air–water interface [32-34]. Structurally, the nucleated polymerization (NP) mechanism represents the simplest form of primary nucleation. In this process, amyloidogenic monomers aggregate to form nuclei, which then grow into amyloid protofilaments and protofibrils predominantly through monomer addition [35-37]. This mechanism is favoured at relatively low protein concentrations where monomeric species are prevalent in solution.

Secondary elongation-

While the concept of a simple homogeneous primary nucleation mechanism is attractive and observed in various scenarios, it is not universally applicable [38,39]. Several studies have highlighted that the simple homogeneous nucleation model fails to adequately explain certain experimental aggregation kinetics data [40,41]. This model overlooks other nucleation mechanisms and events, including fibril-catalysed secondary nucleation, which is a monomer-dependent process, and fibril fragmentation, which is monomer-independent [42,43]. Fibril-catalysed secondary nucleation involves nucleus formation on the surface of an existing oligomer, without the involvement of a foreign surface as seen in heterogeneous primary nucleation. This mechanism appears to be heavily influenced by the structural compatibility of the amyloid precursor protein [44]. In a few instances the seeds are already present and, in such cases, the primary nucleation becomes irrelevant and the step can be skipped.

The nucleation-independent mechanism of protein aggregation represents an isodesmic or linear polymerization model, which can be illustrated by a simple paradigm for the formation of spherical oligomers or linear multimers [45]. This model operates through an infinite series of steps with uniform rate constant, regardless of the aggregate size, leading to an exponential polymerization curve without a lag phase. Once aggregation initiates, the process follows a downhill-polymerization trajectory. Here, aggregation progresses through a series of energetically favourable steps, facilitating the successive addition of amyloidogenic monomers to the growing aggregate, all without the necessity of a multimeric nucleus. This model underscores the intrinsic propensity of amyloidogenic proteins to self-assemble into higher-order structures in a highly efficient manner, driven by favourable thermodynamic conditions and molecular interactions. Furthermore, experimental evidence suggests that this mechanism may play a significant role in the rapid formation of toxic oligomeric species implicated in neurodegenerative diseases such as Alzheimer's and Parkinson's.

Electron microscopy analysis of nerve biopsy specimens from patients with Transthyretin Amyloidosis, Variant (ATTRv) amyloidosis has revealed a potential chronological sequence of amyloid fibril formation and subsequent tissue damage [46,47]. Initially, globular structures appear within the extracellular electron-dense material. These globular structures seem to evolve into mature amyloid fibrils, as elongated fibrillar structures are often observed nearby (Figure 2) [48].

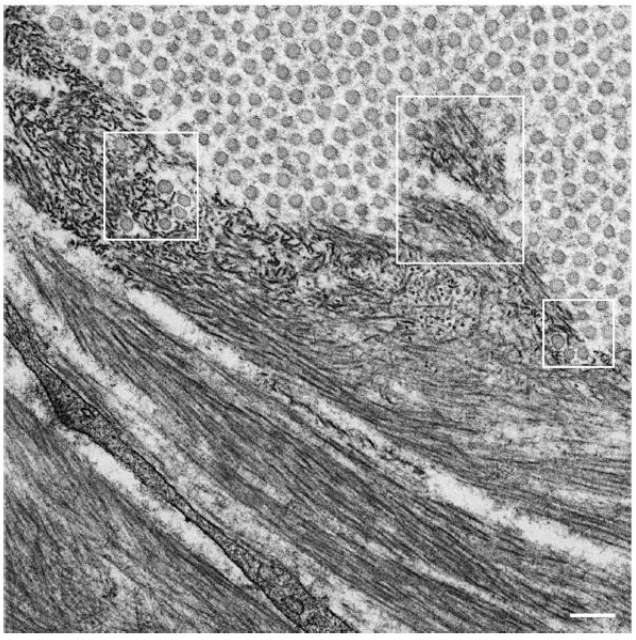

Figure 4. This image shows the photographical look at the amyloidosis process and results of the aggregates. This plaque formation is responsible of more such diseases out of which the image is from a ATTRv patient. [49,50]

Neurotoxic Effects of Amyloid Aggregates

A growing body of research has demonstrated the toxicity of various amyloid-beta (Beta-amyloid) species in vitro and in vivo, supporting the idea that age-dependent accumulation contributes to the pathogenesis of AD [51]. The buildup of beta-amyloid is believed to be neurotoxic, causing oxidative stress, inflammation, synaptic dysfunction, nitrosative stress, and progressive neurodegeneration [52]. This neuronal damage is crucial for the progression of AD, with Beta-amyloid being the main component of senile plaques [53]. To study the neural degeneration seen in AD, many studies have injected beta-amyloid peptide into the brain ventricles of mice and rats [54]. Although limited, research suggests that neuroinflammation in A beta-AD mice may affect peripheral immune responses by releasing inflammatory cytokines through a compromised blood-brain barrier. Our study aims to assess peripheral immunological parameters and the impact of Beta-amyloid induced neuroinflammation [55].

Synapse loss in AD was first described in the early 1990s by DeKosky and Scheff using electron microscopy, and by Terry and Masliah through densitometry of immunostained synaptic proteins. These studies identified synapse loss in the frontal cortex, temporal cortex, and the dentate gyrus of the hippocampus, establishing it as the strongest pathological correlate of dementia [56]. Notably, the entorhinal cortex, which is one of the earliest and most severely affected regions in terms of neuronal loss and tangle formation, does not show a reduction in synapse density in the remaining neuropil although there is significant synapse loss in its target zone within the dentate gyrus [57]. The connection between amyloid pathology and local synapse loss was primarily explored using animal and cell culture models.

The brain parenchyma that surrounds dense plaques is poisoned, which results in a variety of symptoms that could lead to synapse loss and dysfunction. Numerous neurites in the vicinity of plaques have enlarged, dystrophic morphologies and frequently include phospho-tau aggregates as well as a variety of cellular components, which are probably the result of cellular transport disruptions [58]. In animal models of AD, the normally rather straight courses of axons and dendrites are disturbed around amyloid plaques, potentially affecting synaptic signal integration [59]. Additionally, there is a significant amount of gliosis and associated oxidative stress near plaques, which may also play a role in the alterations to synapses [60]

Senile Plaques and Neurofibrillary Tangles

The discovery that eliminating endogenous tau in mutant APP-overexpressing mice by crossing them with a tau knockout line prevented Ab-associated cognitive deficits and decreased the susceptibility to seizures induced by a GABA antagonist provided an early indication that synapse dysfunction depended on the actions of both Beta-amyloids and tau [61]. Subsequent research [62] revealed that tau's regular function in attracting fyn kinase to the postsynaptic density in response to Beta-amyloids at the synapse is what causes this protective impact of tau decrease. Soluble Beta-amyloids oligomers extracted from the human AD brain cause tau hyperphosphorylation and neuritic degeneration in cultured neurons [63]. Mechanistically, the Mandelkow group's study on neuronal culture offered tantalizing evidence for the significance of both mitochondria and calcium when they found that regions of the dendrite to which tau has been missorted, calcium levels have been elevated, microtubules have

been disrupted, and mitochondrial distribution has been impaired are the specific areas of the dendrite to which dendritic spine loss induced by exogenous Beta-amyloids occurs [64].

Evidence suggests that tau pathology is crucial for Beta-amyloid toxicity in vivo. Crossing tau knockout mice with hAPPJ20 mice, which overexpress human APP mutations causing familial early-onset AD, revealed that loss of tau genes did not affect plaque accumulation but protected against learning, memory deficits, and excitotoxicity typical of the APP strain.[65] This indicates that Beta-amyloid triggers a tau-dependent pathway leading to synaptic dysfunction, and reducing tau could potentially prevent cognitive decline in AD. Further studies confirmed that eliminating tau in AD model mice protects against Beta-amyloid accumulation's harmful effects. In mice overexpressing mutant human APP and presenilin-1 (PS1), tau knockout prevented memory impairment, synaptic and neuron loss, and premature death. Interestingly, tau-deficient APP/PS1 mice had lower plaque burdens, suggesting that tau influences Beta-amyloid, hinting at a pathological feedback loop between Beta-amyloid and tau. [66-69]

One protein linking Beta-amyloid to tau is fyn, a nonreceptor tyrosine kinase that enhances NMDA receptor activity and is targeted to postsynaptic sites in dendrites by tau, which binds fyn directly [70]. Fyn was correctly targeted in wild-type mice but not in mice overexpressing truncated tau or lacking tau genes. Memory deficits, seizures, and premature death in APP_{Swe} mice were alleviated by misdirecting fyn through truncated tau expression or tau gene knockout. Normally, tau is enriched in axons, but Beta-amyloid causes tau redistribution to the somatodendritic compartment [71], accompanied by excess fyn, which increases NMDA receptor activity and harmful calcium levels, leading to neuron damage [72,73]. Reducing dendritic fyn might protect neurons from Beta-amyloid-induced, tau-dependent NMDA receptor hyperactivity. Strategies like tau gene knockout or truncated tau expression in mice are impractical for humans, but antisense oligonucleotides to reduce tau expression might be viable. This approach targets neuron-specific tau, potentially avoiding harm to non-neuronal cells, though delivering these oligonucleotides past the blood-brain barrier remains a challenge.

Amyloids and neuroinflammation

One of the main theories for the etiology of AD is that Beta-amyloid causes neurotoxicity that is mediated by inflammatory cytokines. Activated glial cells generating pro-inflammatory cytokines, inflammatory mediators, free radicals, iNOS, NO, and chemokines are among the mechanisms of Beta-amyloid-induced neuroinflammation that have been seen both in vivo and in vitro [74,75]. Primary microglial cells produce IL-1α when exposed to Beta-amyloid42 and Beta-amyloid40 oligomers and fibrils [76], but human monocytes primed with Beta-amyloid release more IL-1β and IL-6 when C5a complement is activated. The Beta-amyloid-associated proteins C1q and SAP increase the number of cytokines secreted by microglia [77]. The p38αMAPK pathway is essential for the generation of cytokines that promote inflammation. When exposed to Beta-amyloid, microglia from animals lacking p38αMAPK produce less pro-inflammatory cytokines, suggesting that p38 MAPK inhibitors such as CNI-1493 may be useful in treating AD [78].

One of the main causes of neuroinflammation in AD is microglial activation brought on by Beta-amyloid [79,80]. A characteristic that is common to this neurodegenerative illness is glial activation, which is triggered by neurotoxicity from environmental exposures, including Beta-amyloid . Research substantiates that Beta-amyloid elevates the expression of several markers associated with microglial activation [81,82]. Through the regulation of glia maturation factor, Beta-amyloid-induced glial activation leads to the generation of inflammatory cytokines/chemokines and neuronal injury. Microglial activation to Beta-amyloid is modulated by astrocytes and pro-inflammatory molecules such iNOS, NO, and ROS [83]. Beta-amyloid-activated microglial cells that have had their cathepsin B gene silenced exhibit reduced neurotoxicity, suggesting that cathepsin B is a mediator of the neuronal death that these cells cause [84].

Pharmacological data demonstrates that blocking Beta-amyloid-induced microglial activation decreases Beta-amyloid deposition, ameliorates behavioural impairment in vivo, and decreases the production of inflammatory cytokines [85-88]. For example, minocycline suppresses the production of IL-1β, IL-6, TNF-α, and Beta-amyloid deposition, improving cognitive performance in APP-tg mice [89]; atorvastatin limits Beta-amyloid-induced microglial activation and associated LTP deficits [90]; and vasoactive intestinal peptide inhibits Beta-amyloid-induced neurodegeneration by limiting microglial activation through blocking p38MAPK, p42/p44MAPK, and NF-κB signalling cascades involved in the transcription of inflammatory mediators and free radical production [91].

Emerging diagnostic and therapeutic approaches

Pathological alterations in AD start decades before symptoms manifest. AD is a neurodegenerative disorder characterized by senile plaques, neurofibrillary tangles (NFTs), and synaptic loss. Understanding the development of a disease and creating successful therapies depend on early diagnosis and long-term surveillance. Numerous biomarkers have been suggested, however their specificity, dependability, and sensitivity are all limited. Beta-amyloid deposition is an early characteristic, but with time, its levels equalize, raising doubts about its usefulness in monitoring the course of the illness. On the other hand, neurodegenerative symptoms are more closely associated with tau buildup. Tau PET imaging has potential, but it needs further testing. Diverse AD symptoms have distinct tau spreading patterns, which might be useful for tailored interventions while also increasing complexity. Instead of focusing on characteristics unique to AD, general imaging methods like FDG-PET and structural MRI evaluate more general disease alterations. While not specific to AD, brain atrophy shown by MRI signifies considerable neurodegeneration. FDG-PET detects absorption of glucose, which is associated with hypometabolism and synapse loss in AD, although strokes and brain traumas can also cause impaired glucose metabolism. Moreover, glucose absorption can be a better indicator of astrocyte activity than neuronal function. Advances in AD research and treatment depend on our ability to comprehend and enhance these diagnostic instruments. The development of tailored medicines and patient outcomes will be greatly impacted by increased specificity and early detection capabilities [92].

To date, five drugs have been approved for AD treatment. Four are cholinesterase inhibitors (CIs)—donepezil, rivastigmine, and galantamine, with donepezil also for severe AD. Tacrine has been discontinued in the US due to severe liver toxicity. Memantine, an NMDA receptor antagonist, protects neurons by inhibiting glutamate activity. These drugs only alleviate symptoms without modifying the disease. Developing effective disease-modifying therapies is urgent and necessary [93].

As of March 2023, 298 AD therapies are in clinical trials, with 76 targeting the Beta-amyloid peptide or its aggregates. Two FDA-approved antibody-based drugs are aducanumab and lecanemab. BACE1 inhibitors like LY2886721 reached Phase 2 trials but were halted due to liver toxicity [94]. Other BACE1 inhibitors, including atabecestat [95], elenbecestat [96], lanabecestat [97,98], and umibecestat [99], failed due to off-target effects and low blood-brain barrier penetrance [100].

γ-secretase inhibitors (GSIs) have serious side effects by affecting proteins like Notch (101,102), leading to the development of γ-secretase modulators (GSMs) which regulate enzyme activity. Promising candidates like SGSM-36 [103] and EVP-0962 reduced toxic Beta-amyloid42 levels without affecting Notch signaling but were discontinued in clinical trials.[104]

Immunotherapy, a promising strategy, involves synthetic peptides or monoclonal antibodies to decrease brain Beta-amyloid load and slow disease progression. Current vaccines in trials include ALZ-101 (Phase 1) [105], ACI-24 (Phase 2) [106], ABvac40 (Phase 2) [107], and UB-311 (Phase 3) [108]. UB-311, shown to generate Beta-amyloid antibodies and improve cognitive function, received fast-track designation by the FDA for Alzheimer's treatment in May 2022.

Amyloid PET scans demonstrate that anti-amyloid monoclonal antibodies (MABs), a class of disease-modifying treatments (DMTs), influence the neurobiology of AD by decreasing amyloid plaque in the brain [109-112]. Secondary biomarkers in plasma and cerebrospinal fluid (CSF) such as phosphorylated tau (p-tau), total tau, and neurogranin are also impacted by these therapy [113,114]. With a 30% fall in the Clinical Dementia Rating—Sum of Boxes (CDR-SB) and a 32% reduction in the integrated AD Rating Scale (iADRS) shown in certain trials, clinical trials show notable decreases in cognitive and functional deterioration [115]. Trials using lecanemab similarly revealed a 27% decrease in CDR-SB [116]. Subpopulations with large reductions in amyloid plaque had delayed declines, suggesting a dose-dependent response, even though some studies did not fulfill main goals [117]. Although there is disagreement about the therapeutic importance of a 30% decline decrease, simulation modeling points to possible 7.5-month prolongation of the moderate cognitive impairment period [118,119]. Additionally, lecanemab therapy may prolong mild AD phases by around 2.5 years, saving a significant amount of money and maintaining patient autonomy [120,121]]. The advantages of DMT therapy are predicted to rise with time since it is believed that the medication will permanently modify the course of AD [122,123].

The development of anti-amyloid vaccines and small molecule medications may be influenced by the effectiveness of anti-amyloid monoclonal antibodies, indicating the viability of altering the course of AD [124]. The investigation of therapeutic targets other than amyloid, including as tau biology, neuroinflammation, and synaptic plasticity, is encouraged by this success.

Decreases in tau levels in plasma and cerebral fluid after amyloid plaque removal emphasize the significance of tau-related alterations, encouraging the creation of tau-targeted therapies. Furthermore, the activation of microglia by anti-amyloid MABs raises the possibility of a treatment strategy that specifically targets these cells. Moreover, this achievement might serve as a model for the creation of medications that target aggregated proteins in other neurodegenerative illnesses [125,126]. Anti-amyloid MABs represent a major breakthrough in the development of disease-modifying medicines for AD and other neurodegenerative diseases, boosting confidence and investment from stakeholders [127].

Conclusion

In conclusion, our journey through the intricate amyloid landscape unveils profound insights into Alzheimer's pathogenesis and heralds a paradigm shift in treatment approaches. The amyloid hypothesis stands resilient amidst ongoing scrutiny, guiding our understanding of AD's complex mechanisms. The advent of anti-amyloid monoclonal antibodies (MABs) represents a significant leap forward, illuminating new avenues for therapeutic intervention and offering hope to those affected by AD. However, our quest for effective treatments must extend beyond amyloid-centric viewpoints, embracing a holistic understanding of AD pathophysiology. Collaborative efforts, innovative strategies, and personalized care approaches are essential as we navigate this challenging terrain. By harnessing the transformative potential of anti-amyloid MABs and integrating diverse perspectives, we move closer to a future where the burdens of AD are alleviated, enriching the lives of individuals and communities worldwide.

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