Insights into the Pathogenesis of Alzheimer's Disease for Better Therapeutics

Anisha Agrawal and Sai Sudha Purushothaman

ABSTRACT

Alzheimer's disease (AD) is characterized by diminishing cognitive skills standing at a zone with no efficient therapeutics for the patients. Early-onset and late-onset AD carry distinct genetic markers, with the epidemiology of 5% and 95%, respectively. The genetic markers for early-onset Alzheimer's disease (EOAD) are APP, PSEN-1, and PSEN-2 locus. These genes contribute to amyloid aggregation, leading to the accumulation of hyperphosphorylated tau fibrils, which triggers neurodegeneration. Multiple genetic factors contribute to late-onset AD, and they range from allelic variants of lipid metabolic pathways to endosomal pathways and innate immune responses. Microglia and astrocytes tend to shift from a neuroprotective to a neurotoxic environment on the onset of Aβ plaques. The current family of therapeutic drugs is limited, challenging the management of AD. This review looks into the etiology of AD and the challenges in finding therapeutic drugs.

Keywords: Amyloid plaques, Tau protein, Neuroinflammation, Genetic markers, Therapeutic challenges

Upsurge Labs, Center for Cellular and Molecular Platforms, GKVK Campus, Bellary Road, Bangalore, India

Correspondence to: Sai Sudha Purushothaman, psai9867@gmail.com; sudha@upsurge.io

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Alzheimer's disease (AD), first reported by Alois Alzheimer in 1906, still stands as the most researched and poorly understood, and has threadbare therapeutics for patients. The setback is rooted in multigenic risk factors that contribute to the cognitive impairment disease. In his article, Alois recorded the pathological investigations observed in the brain of AD patients as accumulation of extracellular amyloid plaques, intracellular neurofibrillary tangles (NFT), dystrophic neurites, and atrophy of the brain.[1] In addition, he reported a higher fibrillation of microglia, implying enhanced neuroinflammation, leading to neurodegeneration (N).[2] Population surveys indicate that people fear AD compared to other fatal diseases. The financial burden in caretaking patients with Alzheimer's disease and related dementia (ADRD) is enormous. Nandi et al.[3] reported in NPJ that in 2020 the annual expenditure reported for the care of ADRD patients in the USA was as much as $196 billion for medical costs and $254 billion in caregiver time, which is expected to increase to about $3.3 trillion by 2060. These factors force the need to understand AD pathogenesis to promote health in the elderly.[3]

AD is a neurodegenerative disease predominant in the aging population, with more than 44 million people affected globally, and the number is expected to exceed over 115 million by 2050.[4] The defining features of AD are declining cognitive skills, non-cognitive behavior, and atrophy of the brain.[5,6] AD is an outcome of a sequential process of amyloid plaque accumulation by Aβ proteins (A), followed by deposition of NFT formed by hyperphosphorylated tau proteins (T) and eventual neuronal inflammation-initiated neurodegeneration (N). As a global burden, there is an immediate need for effective therapies to cure or delay AD.[7] In this regard, there has been a steep increase in disease-modifying therapies (DMT) for AD, tantamounting to an investment of $42.5 billion. However, unfortunately, out of the 235 drug candidates developed, only six have reached commercialization with minimal success.[8] Over 100 years after it was first reported, AD is a challenge on all fronts, from no early diagnosis tools, polygenic risks, lifestyle alterations, and failure to produce successful disease-modifying treatments, and the pathology is still a struggle to scientists.[9] We address in this review, a capsule on AD risks, pathogenesis, and current advances in treatment.

EOAD/LOAD: Same Pathology, But Different Risk Factors

The etiology of AD was believed to be due to β-amyloid (Aβ) aggregates in the brain lesions as observed in the post-mortem of AD patients until its role became controversial, raising the question "Is aggregated Aβ the cause or symptom of Alzheimer's neuropathology?"

Based on the onset of symptoms, genetics, and disease manifestations, AD is classified into two types:

1. EOAD, which is a Mendelian autosomal dominantly inherited pathology, is reported in people <65 years old and contributes to a mere 1%–5% of AD epidemiology.[10] This small fraction of AD patients carry inherited missense mutation in amyloid precursor protein (APP), presenilin-1 (PSEN-1), and presenilin-2 (PSEN-2).[11,12] The pathology contributed by these markers has been well explored.
2. Late-onset Alzheimer's disease (LOAD), which is a consequence of several genetic risks, also known as sporadic AD, is observed in patients >65 years old and contributes to 95% of AD cases.[10,12] The pathology of LOAD is multi-modal with a strong correlation to APOE4 and is usually caused by an onset of chronic, pathological changes accumulated over time. Other polygenic factors involving aberrant lipid metabolism (APOE4), microglial activation (TREM2), and endosomal trafficking (SORL1) are central to LOAD.[2]

EOAD and LOAD may be the flip sides of a coin, so much so that they appear as an entity, but the difference between these two pathologies goes beyond age and epidemiology. The onset of EOAD is below 65 years of age and accounts for 5%–10% of all AD cases reported. In contrast, LOAD is marked in individuals of 65 years of age and accounts for 90% of AD epidemiology. The progression of the disease is different; patients suffering from EOAD are affected in tasks other than dementia such as written language, executive

function, attention deficit, visuospatial abilities, and motor skills, whereas patients with LOAD show poorer performance on episodic memory and lack visual confrontation, accompanied by impairment of cognitive skills.

Patients with EOAD suffer from memory loss, which is the inability to recall information, and LOAD patients live with memory encoding failure, which is the failure of the brain to process, store, and retrieve information. Also, EOAD is more prevalent in people with mutations in PSEN-1, PSEN-2, and APP, while LOAD is multifactorial with a greater coincidence with the APOE4 allele (Figure 1).[10,12]

Genetic Markers of AD

Predominantly, >150 documented mutations in PSEN-1, 19 mutations in PSEN-2, and 30 mutations in the APP cover >85% of the genetic risk factors of EOAD. In EOAD, PSEN-1, PSEN-2, and APP determine the pathological aggregation of the Aβ peptide in the parenchymatous cells of the brain by improper processing of APP. But in the bigger picture of AD pathogenesis, EOAD contributes to only 1%–5% of disease manifestation, thus making the contribution of APP, PSEN-1, and PSEN-2 relatively less relevant.[13,14] Though the causative of AD epidemiology is still equivocal, homozygous APOE4 has been shown to increase the risk of AD by 85%. APOE4, a critical factor in lipid metabolism, attributes to AD pathology in several ways, as reported in genome-wide analysis study (GWAS).[15] APOE4 binds strongly to Aβ and prevents its clearance. APOE4 competitively inhibits Aβ uptake by low-density lipoprotein receptor-related protein 1 in astrocytes, thereby increasing their load in the CNS. Several other factors contribute to APOE4-mediated AD pathology. Reelin binding to APOE R2 receptor cascades to phosphorylation of NMD2 receptors leading to calcium (Ca^{2+}) influx and long-term potentiation. APOE4 promotes cellular intake of APOE R2, thereby curbing neuronal signaling. Thus, APOE4 contributes to several mechanisms in AD pathology. In addition, other genetic factors have been implicated in the risk of LOAD.[16] Genetic variants of CD33,[17] complement receptor 1,[18] TREM2, surface receptors of myeloid cells,[19] and several members of the endosomal pathway—BIN1, SORL1, and PICALM—have been associated with LOAD.[20] Thus, the role of risk factors in AD manifestation is still nascent, making therapeutic targets for AD painfully challenging.

By Evolution, APP Does Have Cellular Functions

One of the vexing issues of APP is the inability to pin specific functions to the single-pass transmembrane protein with a large ectodomain, transmembrane

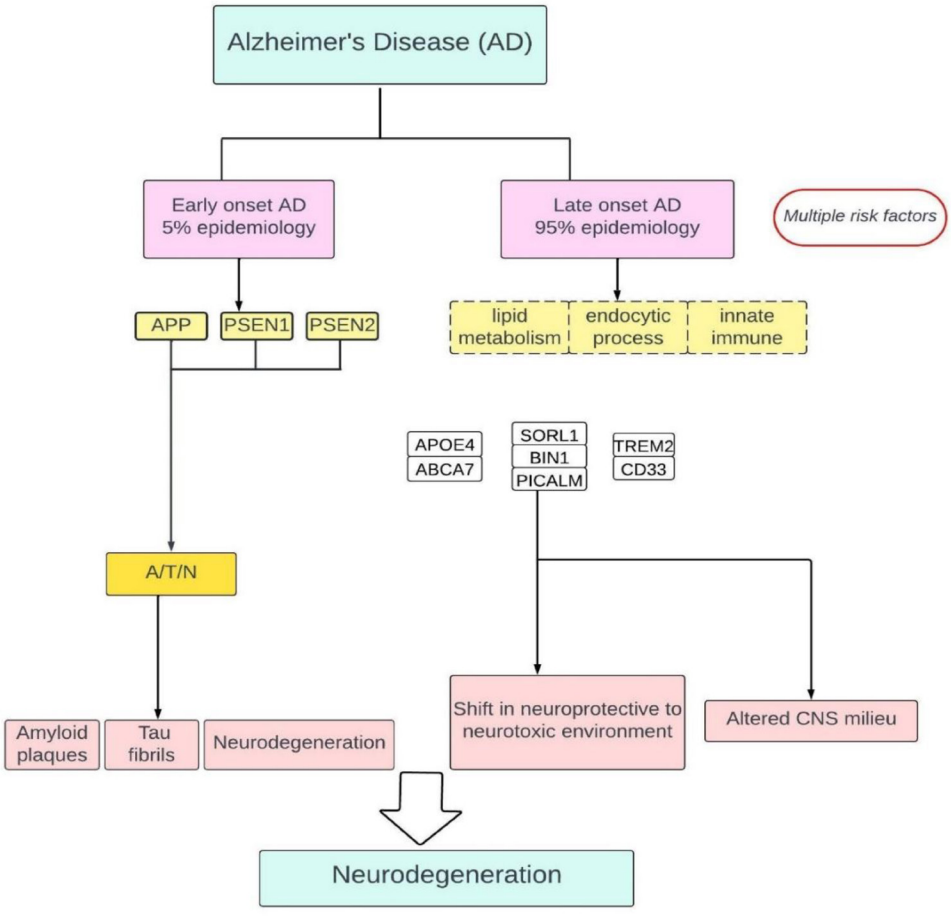

Fig 1 | Genetic risk factors in mediation of early-onset and late-onset AD

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domain, and C-terminal fragment (CTF). APP functions as an adaptor molecule without enzymatic properties, and nearly 200 molecules bind to the ectodomain. APP is unique as it functions both as a receptor and as a ligand—it is a receptor to several ECM proteins such as heparin and collagen whose downstream processes are not well documented; sAPP acts as a ligand by binding to cell adhesion molecules, growth factor receptors, and GPCRs.[21,22] sAPPα has been shown to possess neurogenetic and neuroprotective functions in mouse models. This molecule regulates GABA release and thus works in long-term potentiation. The APP intracellular domain (AICD) regulates gene expression in cell signaling pathways and cytoskeletal molecules. APP is reported in the epigenetic modification of immediate early genes potentiating memory. Though APP KO is not lethal in mice, it does show neuromuscular defects and decreased brain size.[23] APP is processed by different types of secretase, giving rise to peptide fragments with diverse biological functions, both physiological and pathological.

Enzymatic Processing of APP

APP enters either the non-amyloidogenic or amyloidogenic pathway depending on whether the transmembrane is enzymatically cleaved by α or β secretase, respectively, which is dependent on the mutations carried by the individual. In healthy individuals, APP enters the non-amyloidogenic pathway where α-secretase processes APP to yield soluble ectodomain APPα, and an 83-amino acid fragment carrying the C-terminus fragment (CTFα), which is further processed by γ-secretase to give a p3 fragment and an AICD fragment.[21] In contrast, when APP enters the amyloidogenic pathway, it becomes a substrate for β-secretase to yield a 99 amino acid CTFβ which is internalized and follows the endocytic pathway to generate fragments of 40 and 42 amino acids (Aβ40 and Aβ42) by γ-secretase.[24] The amyloidogenic and non-amyloidogenic pathways yield AICD fragments that can translocate to the nucleus to regulate gene expression. The Aβ 42/40 amino acid peptides self-aggregate to form plaques in different regions of the brain. The other prime reason for the abnormal accumulation of Aβ is the slow clearance of Aβ, which forms extracellular aggregates, and finally plaques. The insoluble Aβ aggregates trigger the formation of intercellular NFT, astrocytosis, microgliosis, and chronic inflammation (Figure 2).[25]

Failure of the Amyloid Cascade Hypothesis, Emergence of Other Genetic Risks

In 1992, Hardy and Higgins put forward the hypothesis that deposition of amyloid β protein is the mainstream for AD pathogenesis and all other features such as NFT, brain damage, and dementia are an output of Aβ.[26] Thirty years later, we are disappointed that millions spent on AD research could not find a therapy but inversely proved that Aβ is not the foundation of AD pathogenesis, at least in late-onset AD. This stems from the reports of Aβ deposits in post-mortem reports of people who died without dementia. These patients showed diffused rather than fibrillary Aβ deposits, with no neuroinflammation. Many studies indicate no correlation between failure of cognitive skills and increased amyloid

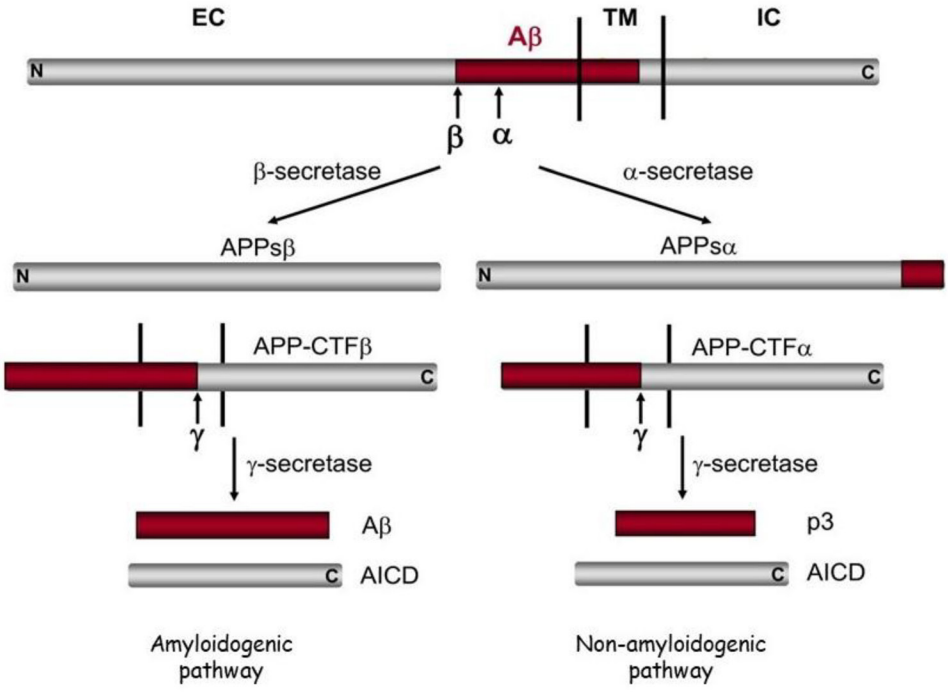

Fig 2 | APP processing via amyloidogenic and non-amyloidogenic pathways

Courtesy: Zheng H, Koo EH. Biology and pathophysiology of the amyloid precursor protein. Mol Neurodegener. 2011;6:27. https://doi.org/10.1186/1750-1326-6-27

deposits in the brain. Amyloid-β PET scanning reports show the presence of Aβ deposits in normal individuals with very mild cognitive defects.[27] A surprising observation was that older patients who had abundant atherosclerotic plaques in the coronary arteries but no heart disease developed AD in later life, especially >85 years. Another clinical observation was that patients with neoplastic changes in the prostates, but without a clinical diagnosis, later developed AD-related dementia. This initiated several genome-wide analyses to investigate if AD was a post-morbidity disease of genes regulating lipid metabolism.

APOE4 Cascade Hypothesis Ruling the LOAD

After many studies, it has been reported that gene variants in the cholesterol metabolism, inflammatory pathways of the brain, and endosomal pathways may be contributors to AD.[28] It has been reported that the formation of senile plaques is a consequence of either overproduction or poor clearance of Aβ. Genetic variants of lipid metabolism are surprisingly involved in the development of AD in the elderly. APOE is predominantly expressed in astrocytes, and the allelic variant, APOE4, has been shown to affect the clearance of Aβ[29] in a study by Fortea et al., where the correlation of APOE4 and AD was investigated in 3,297 brain donors from National Alzheimer's Coordinating Center cohorts and 10,039 from clinical cohorts.[29] APOE exists in three allelic forms—ε2, ε3, and ε4. Heterozygous for ε4 increases LOAD risk by nearly three–fourfold while homozygous for ε4 increases LOAD risk by about 12-fold. Nearly all APOE4 patients showed either high or intermediate AD neuropathological change. This was further studied by biomarkers of clinical cohorts, and it was observed that people homozygous for APOE4 carry a lifetime risk for AD. The different allelic APOE variants modulate the Aβ homeostasis through differential binding to Aβ and consequently promoting different levels of fibrillogenesis. Individuals with APOE4 exhibit decreased Aß clearance from the brain with the degree in the order APOE4 > E3 > E2. In a study by Castellano et al.,[30] mice breed crossed with hAPP and hAPOE4 showed poor clearance of Aß estimated by microdialysis.[30] In most cases, the decrease in clearance of soluble Aß precedes the amyloid deposition. APOE4, along with variants of PICALM, a protein involved in clathrin-mediated endocytosis, showed dramatically decreased Aß clearance and thereby promoting AD. APOE4 has also been implicated in tau processing in neurons.[31] Other lipid metabolic genes include ABCA7, a lipid transporter whose loss of function increases AD risk by nearly threefold.[32] ABCA7 is involved in membrane trafficking, and the loss of function of the transporter alters APP processing, and routes the protein to the amyloidogenic pathway to form excess Aβ in mice leading to insoluble and aggregated Aβ, and finally amyloid plaques. In people with this genetic background, there is no change in the processing of APP, suggesting that APOE and ABCA7 are involved in the clearance of Aβ.

Other Risk Factors of LOAD

True to the observation that activation of microglia determines AD pathogenesis, GWAS exposed another major risk factor, TREM2, triggering receptor on myeloid cells-2 and contributing to major pathologies of AD, extracellular Aβ, and intracellular tau.[33] Individuals carrying the TREM2 variant R47H are at higher risk of AD. Studies with knock-out or R47H mutant of TREM2 exhibited reduced activation of microglia at the vicinity of the Aβ plaques, which results in faster spreading of Aβ and facilitates the seeding and spreading of senile plaques. Other risk factors of late-onset AD map SORL1, BIN1, and PICALM of endosomal vesicular trafficking.[34]

Tau Protein Hypothesis

Along with extracellular amyloid plaques, tau proteins are responsible for the rapid progression of AD. Tau protein, a trigger for NFT, displays spatial and temporal distribution onset by Aβ. Tau proteins are microtubule-associated proteins encoded by MAPT and exist in six isoforms generated by alternate splicing of exons 2 and 10. In healthy individuals, tau protein is phosphorylated at different regions regulated by kinases/phosphatases and helps in the assembly of tubulin to form microtubules and their subsequent stabilization. However, when tau phosphorylation is imbalanced, it gets hyperphosphorylated, becomes insoluble, and aggregates into filament bundles. This leads to the formation of pair helical filaments assembling into NFT, a feature of tauopathies that alters neuronal function.[35]

Environmental Factors as a Causative of AD

Other than the genetic markers attributed to AD, environmental hazards have been widely implicated in its epidemiology. Various environmental toxins such as pesticides, industrial wastes, heavy metals, and household detergents increase the gene-to-environment ratio in AD manifestations. Many of the toxins can cross the blood-brain barrier and alter the conformation of critical proteins such as Aβ and tau, triggering the onset of senile plaques. Diet is another major environmental factor that regulates the gut microbiota in the health of individuals. The gut-brain axis links the enteric nervous system and the brain and is a key player in both neuronal development and neuroinflammation. Neuromodulators such as catecholamines, 5-hydroxytryptamine, and GABA are produced by many bacterial species of the gut microbiota. Short-chain fatty acids and branched-chain amino acids are regulators of neuronal health.[36]

Neuroinflammation Hypothesis

To date, the genetic risk factors for AD center around APP processing and clearance, vesicular trafficking, and astrocytosis and microgliosis. The cornerstone of AD prognosis resides with neuroinflammation-mediated N. Alzheimer (1901) first reported the existence of abundant glial cells in the neuritic plaque vicinity. The inflammatory response works as "yin and yang"—as self-defense by protecting the brain from toxic substances, and switches to

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chronic inflammatory response, fueling N. In the CNS, microglia and astrocytes are the prime mediators that propagate Aβ aggregation of amyloid plaques. Post-mortem reports of AD patients reveal that the Aβ plaques are surrounded by a remarkably high number of reactive astrocytes and activated microglia, suggesting their role in AD pathogenesis. Astrocytes and microglia, subsets of glial cells, carry diverse properties, both in health and in pathology. Astrocytes create neural circuits and synaptic activity by linking far-apart neurons, which otherwise never connect with each other.[37,38] They also provide energy for neurons, afford synaptic plasticity, and maintain homeostasis of neurotransmitters in the CNS. Astrocytes along with pre-synaptic and post-synaptic neurons form the tripartite synapses to perform inter-neuronal communications. Astrocytes communicate with the external environment by the release of gliotransmitters such as glutamate, and ATP, via calcium-dependent secretory vesicles. An aberrant Ca^{2+} signaling mediates the pathology of AD. Experimental data show that cultured astrocytes undergo calcium signaling on exposure to β amyloid.[37] This triggers the release of glutamate from the synaptic vesicles, causing abnormal and extended neuronal depolarization. On polarization by factors such as Aβ, TNF-α, and IL-1α, the cytosolic Ca^{2+} levels increase in astrocytes, which causes morphological and physiological changes by a process called reactive astrocytosis. This further leads to the release of Ca^{2+} from the secretory vesicles initiating a calcium wave.[38] They switch to different phenotypes—the proinflammatory A1 phenotype, which is neurotoxic, or the anti-inflammatory A2 phenotype, which provides neuroprotection. The characteristic appearance of reactive astrocytes is their hypertrophic appearance, presence of glial fibrillary acidic protein (GFAP), and vimentin, which is an indication of hypertrophy.

Astrocytes and microglia are involved in bidirectional signaling that release neurotransmitters and growth factors required for neuronal function. However, enhanced Aβ release promotes prolonged activation of microglia resulting in chronic inflammation leading to the release of inflammatory cytokines. Microglia carry pattern recognition receptors (PRRs) to which Aβ binds, which promotes its clearance as a neuroprotective effect. Chronic inflammation leads to the expression of danger-associated molecular patterns, which trigger self-perpetuating proinflammatory reactions leading to the formation of senile plaque with dead cells. IL-1, TNF, and C1q released by activated microglia trigger further neuroinflammation by astrocytes amplifying the neurodegenerative process. Technically activated microglia can exhibit M1 and M2 phenotypes, with the former involved in neurotoxicity. Astrocytes are the glial cells involved in Ca^{2+} storage and signaling; dysregulation of Ca^{2+} signaling results in the increased activity of calcineurin, leading to enhanced expression of IL-1 and TNF. The cumulative response of astrocytes and microglia results in accelerated Aβ pathology (Figure 3).

Microglia, the immune sentinel glial cells, observe finite change in the brain and appear ramified with features carrying small cell bodies with highly motile processes.[39] But factors such as necrotic debris, or proinflammatory cytokines, activate microglia with morphological changes to large cell bodies with amoeboid processes. Aβ aggregates trigger unrestrained activation of microglia with an output of excess production of

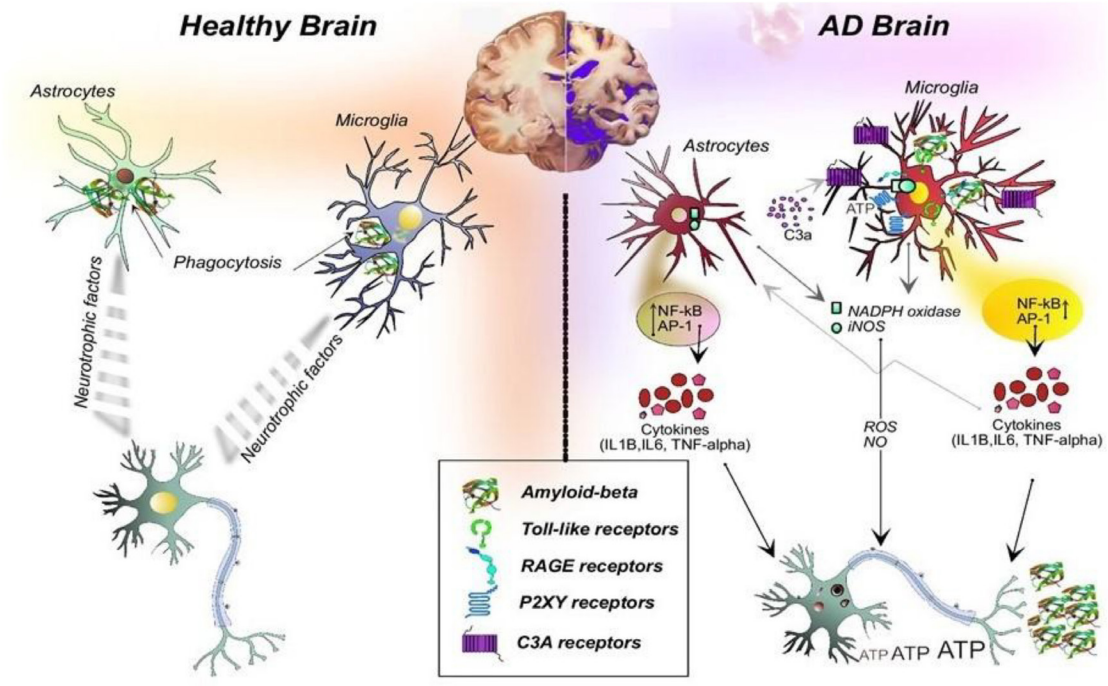

Fig 3 | Neuroinflammation-mediated neurodegeneration in Alzheimer's disease. Singh D. Astrocytic and microglial cells as the modulators of neuroinflammation in Alzheimer's disease. J Neuroinflamm. 2022;19:206. https://doi.org/10.1186/s12974-022-02565-0 Copyright link

reactive nitrogen and oxygen species, proinflammatory cytokines that promote amyloidogenesis. Aβ aggregates interact with PRRs such as Toll-like receptors (TLRs) and receptors for advanced glycoxidation end products, NOD-like receptors (NLR) expressed on microglia and astrocytes inducing transcriptional of inflammatory genes.[40] Animal studies have shown that Aβ binding to TLR4 activates microglia to release increased inflammatory cytokines, downregulate phagocytosis, and enhance plaque deposition. Aβ peptide activates NLRP3 to form an inflammasome complex to trigger the caspase pathway.[41] Microglia also express purinergic receptors P2Y12 and P2Y6 that bind nucleotides released by damaged cells.[42] Activated astrocytes can activate microglia, resulting in a chronic inflammation cascade.[43]

Biomarkers for Early Diagnosis of AD

Early diagnostics in AD was primarily clinical phenotype; however, this is at an advanced stage of the disease prognosis, and an early diagnosis is mandatory for treatment. Different biomarkers for AD include PET scan, genome sequencing, physiological evaluation such as gait, biochemical evaluation of Aβ, tau, and phosphorylated tau in CSF, blood, urine, and saliva. FDG PET exhibits hypometabolism in the parietal and medial temporal regions. Amyloid PET identifies amyloid plaques in AD patients with 92% sensitivity and 100% specificity. Another imaging tool is the tau PET, which visualizes the NFT and is predominantly used in research. Magnetic resonance imaging (MRI) shows structural changes in the brain such as atrophy of gray matter, a representative of N. Biomarker detection of Aβ and tau peptide fragments in CSF can identify pre-symptomatic AD patients. However, the high costs of PET imaging and invasive CSF diagnostics promoted the development of simplistic blood biomarkers.[44] Assays that can determine Aβ42/40, different fragments of phosphorylated tau and GFAP have been made available. However, these biomarkers must be correlated with the clinical symptoms of the disease.

AD Therapeutics, the Road Ahead

There are several molecules and immunotherapies that have been efficient in pre-clinical studies but have failed to move to clinical studies. Also, several AD therapeutics were discontinued during clinical trials due to poor efficacy or due to toxicity.[45,46] For example, gosuranemab-targeting tau protein failed at the phase II clinical trial. In diseases such as AD with different genetic factors, it is challenging for a single drug to act as a remedy. The first line of drugs for AD was anti-cholinesterase aimed to increase acetylcholine levels. However, drugs such as tacrine, donepezil, rivastigmine, and galantamine provide only symptomatic relief. NMDA receptor activated by simultaneous binding of glycine and glutamate is required for memory and learning. However, over-activation of the NMDA receptor results in the excessive influx of Ca^{2+} ions into the neurons, enhancing AD pathology. Memantine, an NMDA antagonist has shown to provide a short-term relief for AD patients. Both acetylcholinesterase inhibitors and NMDA antagonists failed to provide long-term relief leading to the development of DMT, which focuses on the progression of AD. These therapeutics focus on the elimination of Aβ accumulation and clearance, and tau fibrillation. A report on Alzforum.org mentions that out of the 298 molecules that are under clinical trials for AD, 76 are targeted against Aβ peptide. These anti-Aβ therapies work under different mechanisms that include reduction of Aβ production, inhibit AB aggregation, and increase clearance of Aβ aggregates and neutralization of soluble Aβ monomers to promote elimination. Immunotherapies that include lecanemab, aducanumab, and donanemab are approved by FDA. However, many of them show side effects with abnormalities in the brain observed by MRI and are collectively known as amyloid-related imaging abnormalities. Remternetug and SHR-1707 are other Aβ monoclonal antibodies under clinical trials. Tau NexGen is an international trial encompassing a cohort of 168 participants with a greater risk of EOAD due to mutations that would cause overproduction of Aβ. These patients were administered tau-reducing antibody E2814 and lecanemab. The costs for AD treatment are expensive, with one year cost of lecanemab administration amounting to $26,500 and that of aducanumab costing $56,000.[47–49] Current research is focused on approved DMT drugs with more efficacy, and lesser cost to treat AD.

Considering the heterogeneity in AD contributed by polygenic factors, personalized medicine becomes the focus of future therapeutics. Targeting immunotherapies towards Aβ may alleviate the symptoms but will fail if the neuroinflammation is not suppressed. Therefore, the future towards early diagnosis of the disease and combinatorial drug therapy.

Conclusion

AD, which is one of the trademarks of aging, has been a challenge that has no solution to date. The genetic risk factors are very distinct for early-onset and late-onset AD, but loss of cognitive skills is the primary pathology of AD. The triplet of Aβ, tau, and neurodegeneration are the mediators of the disease. AD is promoted by either overproduction or delayed clearance of Aβ42/40. LOAD individuals strongly correlate with the APOE4 allele, which regulates several pathological features such as poor clearance of Aβ aggregates and a propensity to trigger a chronic inflammatory response. With a better understanding of AD pathogenesis and risk factors, the search for therapeutics seems extremely hopeful.

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