

MOLECULAR PATHOGENESIS OF ALZHEIMER'S DISEASE: THE CENTRAL ROLE OF AMYLOID AND TAU PROTEINS

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ABSTRACT

Background: Alzheimer's disease (AD) is a major cause of dementia across the globe, imposing a huge social, clinical, and economic burden. Amyloid- β ($A\beta$) plaques (extracellular) and hyperphosphorylated tau (intracellular) are central neuropathological hallmarks according to the current knowledge of its mechanistic understandings. **Discussion:** Hypothetically, the disease pathology starts from cleavage of amyloid precursor protein (APP). Amyloidogenic pathway (β - and γ -secretase cleavage) of APP give rise to $A\beta$, competing with the non-amyloidogenic pathway (α -secretase). The aggregations of $A\beta$ isomerases to form oligomers and fibrils, which disturb neuronal Ca^{2+} homeostasis, induce mitochondrial and oxidative stress, and trigger neuroinflammatory responses of astrocytic & microglial cells. In parallel, tau protein undergoes hyperphosphorylation, abbreviation and misfolds to paired helical filaments, propagates between neurons in a prion-like fashion, ultimately impairing axonal transport and synaptic integrity. Evidences support cross-talk between $A\beta$ and tau pathology rather than separate independent incidents. Accumulation of $A\beta$ accelerates tau pathology by shared kinases like; GSK3 β and CDK5 and calcium signaling dysregulation. For timely diagnosis modern-day research incorporates RNA editing, post-translational modifications, lipid raft biology, multi-omic profiling and proteostasis networks. Clinically, anti-amyloid immunotherapies and strategies featuring tau haven't shown complete success, suggesting need of combined approaches addressing amyloid, tau and neuroinflammatory factors. **Conclusion:** This study emphasizes that amyloid-tau axis not as a whole story of the disease, rather a multifactorial model including dysfunction of mitochondrial RNA and microRNA, and impaired proteostasis. Instead of treating these findings as threat, we should reconcile them with classical amyloid cascade to better understand the disease pathology.

Keywords: Alzheimer's Disease · Amyloid Protein · Tau Protein · Neuroinflammation · Oxidative Stress

1. Introduction:

Alzheimer's Disease (AD) is a progressive neurological disorder (1) which is the major cause of dementia in people older than 65 years (2). Majorly three hypotheses have been proposed to explain the development of AD (3). The earliest of them; "cholinergic hypothesis" associates abnormal synthesis of acetylcholine with AD. However, clinical strategies based on this hypothesis failed to completely cure the disease (4). Another hypothesis is associated with the "hyperphosphorylation of tau

proteins". Neurofibrillary tangles and large fibrils (forming due to hyperphosphorylation of tau proteins) destabilize the microtubular structure of the neuron, which disturbs cellular trafficking and leads to neuronal death (5). "Amyloid Cascade Hypothesis" predominates this field (6) posits that the development of the disease is due to abnormality in the production and clearance of $A\beta$ (7,8,9,10) Accumulation of the $A\beta$ leads to the tau pathology (8,11) and neuronal-toxicity (6). Cascade follows; $A\beta$ deposition, Tau pathology, synaptic dysfunction

in neurons, neuroinflammation, neuronal death, and at the end dementia (8). A recent hypothesis known as the Mitochondrial Cascade Hypothesis proposes that changes in mitochondrial structures with age decide the pathology of AD; neither the A β nor the tau protein is responsible for it. Baseline mitochondrial function and environmental factors play a role in AD progression (7).

Two major pathologies (extraneuronal and intraneuronal) characterize AD. Extraneuronal pathology includes senile plaques which are mainly composed of Amyloid beta (A β) protein and intraneuronal are neurofibrillary tangles made up of hyperphosphorylated Tau protein (12). The disease starts its course with pathophysiological changes that lead to the accumulation of amyloid beta (A β) in the brain years before actual symptoms are observed (1,2). Accumulation of A β is also responsible for tau phosphorylation and its aggregation in neurons, leading to their death (1). Neuronal Cells (like astrocytes & microglia) and proteins (cytokines and chemokines) cause neuroinflammation. This inflammation damages the neuron by damaging its surroundings and leads to its death (13). This neurodegeneration, along with other pathophysiological changes like the accumulation of β -amyloid (A β) and the formation of neurofibrillary tangles by hyperphosphorylation of tau protein provides the hallmark of AD (2). The extraneuronal plaques of amyloid- β (A β) are the earliest neuropathological events in AD (14). Two hallmark lesions that cause synaptic dysfunctions, which correlate with the initial symptoms of memory loss in AD, are: plaques of A β peptide & neurofibrillary tangles (15). At the end, individuals affected by AD completely lose their cognition, with disorientation and even loss of language (16). More than 97% of AD patients face Neuropsychiatric Symptoms (NPS) and disorders during its course. The NPS is associated with extreme cognitive loss, eventually leading to mortality. NPS burdens caregivers by increasing the cost by thousands of dollars annually. Expenditures are expected to rise from billions of dollars in 2020 to a trillion dollars in 2050. A survey in 2019 highlighted millions of informal caregivers provided unpaid care (16).

2. Amyloid Pathology:

2.1. APP processing pathways:

2.1.1. Amyloidogenic:

Physiological levels of amyloid precursor protein (APP) and Amyloid beta (A β) protein are essential for the growth, development, survival, and protection of neurons in the central nervous system (CNS) (17). In the amyloidogenic pathway, APP is cleaved into two fragments: an extracellular soluble APP β fragment (sAPP β) and a membrane-anchored C-terminal fragment (CTF β), by a β -secretase (BACE-1). CTF β is further cleaved by a multiprotein complex, γ -secretase and generates A β peptides (A β 40 and A β 42) (18). Accumulation of amyloid precursor protein (APP) and amyloid- β peptides beyond normal ranges plays developmental roles in AD (19). An increase in the ratio of A β 42:A β 40 leads to "toxic gain of function" because of the A β 42 plaques accumulation, which is toxic (6).

2.1.2. Non-amyloidogenic:

Under normal conditions, APP undergoes the non-amyloidogenic pathway (20). In this pathway, α -secretase cleaves the APP within the A β peptide domain by only generating soluble APP (sAPP α) and membrane-bound carboxy-terminal fragment (CTF α) and does not produce A β peptides (18,21). In the mammalian nervous system, ADAMs (A disintegrin and metalloproteases) are a family of multifunctional transmembrane proteins. ADAM10 acts as the α -secretase of APP and is directly linked to AD. It inhibits the production of A β plaques by producing soluble neuroprotective sAPP α , as it cleaves APP within the A β domain. Another member of this family, ADAM17 activates ADAM10 to cleave this APP and helps to initiate the neuroprotective non-amyloidogenic pathway of APP processing (22).

2.1.3. Role of α -, β -, and γ -secretases:

Secretases are a group of proteases that process the amyloid precursor protein (APP) and control the functions associated with microglial (23). These secretases decide whether APP will undergo amyloidogenic or non-amyloidogenic cleavage (20). Under the action of α -, β -, and γ -secretases, APP undergoes proteolytic cleavage and forms soluble amyloid precursor protein alpha (sAPP α), soluble amyloid precursor

protein beta (sAPP β), β -amyloid peptide (A β), and amyloid precursor protein intracellular domain (AICD) along with some other less studied peptides (24).

In non-amyloidogenic cleavage, when cleaved by α -secretase, APP will form soluble APP-alpha (sAPP α) and membrane-bound carboxy-terminal fragment alpha (CTF α) (18,20,21).

In amyloidogenic cleavage of APP, it is cleaved by β -secretase cleaving enzyme (BACE1) and releases two fragments, sAPP β and the C99. The γ -secretase further cleaves this C99 to form AICD and A β peptide (14,20,24).

2.2. Formation and aggregation of A β peptides:

2.2.1. A β 40 vs. A β 42; their aggregation tendencies:

The sequential processing of APP by β - and γ -secretases generates non-amyloidogenic A β 40 and amyloidogenic A β 42 peptides. Two subunits presenilin-1 (PS1) & presenilin-2 (PS2) act as a catalytic of γ -secretase. Mutations in APP, PS1, or PS2 may influence levels of A β 40 and A β 42 peptides. The tendency of longer chains like A β 42 is stronger to associate with membranes than that of A β 40 (6). The monomers assemble themselves to aggregates and the radius of these spherical aggregates depends upon the type of A β . A β 42 forms small and uniformly spherical aggregates, on the other hand A β 40 induces inhomogeneous and comparatively larger aggregates. The small size of A β 42 spherical provide multiple nucleation sites (25). Thus, A β 42 fibers have a higher tendency to form larger clots when compared to A β 40 fibrils. It possibly determines the higher resistance of A β 42 fibers to destabilizing effects (denaturants, ionic detergents, ultrasonication) and this resistance give rise to their characteristic cyto-toxicity (26). Presence of an additional side chain (hydrophobic) in A β 42: accelerates the process of nucleation and of elongation, and starts the formation of S-shaped fibrils. A β 40 along with other short isoforms play a role in the A β 42 suppression from aggregation as A β 40 is less prone from A β 42 to aggregate (27).

2.2.2. Oligomers vs. fibrils; toxicity mechanisms:

Several human diseases develop due to amyloid aggregates by the misfolding of the proteins.

One of the famous is amyloid- β (A β), linked to Alzheimer's disease (AD) (28). The "amyloid hypothesis" explains the onset and development of AD as a result of the events like, an increase in amyloid plaques or soluble A β . Accumulation of plaque and oligomers of A β gives rise to A β pathology which indirectly leads to the cellular metabolic disorders (e.g. oxidative stress and ER stress), synaptic destruction, and neuronal death (29). The toxic effect of the amyloid fibrils is determined by factors like the tendency to form clusters and their stability (26). Cytotoxic effect of amyloid fibrils is mainly concerned with the deterioration of the membranes, cause longer chains like A β 42 oligomers have more tendency to act with the membranes (6,26). A β 42 forms small and uniformly spherical aggregates. These aggregates fuse to form fibrils. Small size of A β 42 aggregates provides multiple nucleation sites for A β 42 fibrillation. Fibrils formed by this procedure are small in diameter, but have greater flexibility (25). Senile plaques are composed of amyloid-beta peptides (A β) of various lengths. These peptides do not carry any specific conformation upon synthesis. But have an ability to acquire a secondary structure by hydrogen bonding and can aggregate as pleated beta-sheets. Despite the fact that synaptic loss and neuronal death are often related to the senile plaques, the plaques are not considered the cause of the disease itself. It is now accepted that the cytotoxic effect of A β is mainly associated with oligomers, while the monomers and fibrils are non-toxic (30).

2.3. Cellular and molecular consequences

2.3.1. Disruption of calcium homeostasis, oxidative stress, mitochondrial damage:

2.3.1.1. Calcium homeostasis:

Intracellular Ca²⁺ acts as a second messenger and is very important for neuronal growth, their differentiation, for action potential, and to maintain synaptic plasticity. Ca²⁺ homeostasis is of vital importance in neurodegeneration mechanisms (31). The calcium hypothesis states that the processing of APP through the amyloidogenic pathway affects the Ca²⁺ homeostasis by an increase in influx from the extracellular to the intracellular environment and by the release of Ca²⁺ from intracellular stores into the cytosol (31,32). An increase in the levels of Ca²⁺ induces

excitotoxicity, whereas reduced Ca^{2+} levels exert neuroprotective effects (32). Studies show that higher levels of Ca^{2+} favor $\text{A}\beta$ -oligomer formation over fibrillar formation. Ca^{2+} promotes the stabilization of $\text{A}\beta$, its insertion into the membrane, and reduces its binding with lysosomes or autophagosomes (34). Accumulation of Ca^{2+} induces the production of $\text{A}\beta$ and hyperphosphorylated tau and their deposition in Aps & NFTs. The transporters in the membranes of the ER, mitochondria, lysosomes, and even in the plasma membrane mediate the Ca^{2+} effects on neurotoxicity, neuroinflammation, neurogenesis, neuronal damage, neuronal protection, synaptic plasticity and autophagy, which leads to cognitive decline in AD (33).

2.3.1.2. Oxidative stress:

Misfolded proteins can induce oxidative damage and play a key role in mitochondrial dysfunction, impacting energy utilization (35,36). Both $\text{A}\beta$ proteins and hyperphosphorylated tau proteins affect the mitochondria and lead to mitochondrial malfunction (35). Met35 on $\text{A}\beta$ is a critical acidic residue for the production of ROS, $\text{A}\beta$ -oligomers can also directly induce ROS production by activating an enzyme named NADPH oxidase and stimulate the release of arachidonic acid, which in turn increases the production of NMDARs (N-Methyl-D-Aspartic acid Receptor subtypes) (36). As the level of these ROS increases, oxidative modification of proteins occurs. This oxidative modification consequently results in the loss of the protein function and exposure of hydrophobic domains to the water. These domains aggregate spontaneously, destabilize the function and ultimately death of the cells. Factors like, large amount of polyunsaturated fatty acids in the membrane, dependence on paramagnetic oxygen for survival, and higher metabolic rates, make neurons more vulnerable to the ROS damage (37).

2.3.1.3. Mitochondrial damage:

Mitophagy is the process of selective degradation of damaged mitochondria, during which damaged mitochondria are transferred to lysosomes (38). In the post-mortem of AD patients' hippocampus, the process of

mitophagy was decreased by over 50%, with an increase in the accumulation of defective mitochondria, leading to neuroinflammation (39). mtDNA has limited repairing mechanisms, doesn't possess protective histones, and can generate ROS; these factors make it more susceptible to oxidative damage. In AD patients, mtDNA exhibits tenfold more oxidized bases and thrice the oxidative damage when compared with nuclear DNA. Moreover, mtDNA accumulates mutations from maternal inheritance and from aging as well leads to its damage (40). In AD, Complex IV of ETC experiences a reduction in activity, leading to a drastic fall in MMP & ATP. AD pathological processes destroy the mitochondrial ability of Ca^{2+} homeostasis. Mitochondria produce more ROS under mutations, ultimately leading to neuroinflammation and eventually neuronal death (41).

2.3.2. $\text{A}\beta$ -induced neuroinflammation via microglia and astrocytes:

In AD, the accumulation of $\text{A}\beta$ activates the microglia, continuous release of inflammatory elements by these activated microglia impairs their phagocytic and degenerative capacities (42). Microglia identify and remove the unnecessary neuronal connections in the brain during postnatal development. Unwanted activation of microglial function in adults leads to abnormal neurodegeneration, leading to the early onset of AD (43). Microglia play a significant role in AD pathogenesis. GWAS (Genome-wide association studies) show that mutations in microglial genes, as in TREM2, increase the risk of disease by manyfold (42). In pathological conditions, the large amounts of $\text{TNF-}\alpha$ released by microglia cause neuroinflammation, leading to neuronal dysfunction and cognitive impairment (44). Astrocytes cause an increase in GABA and H_2O_2 due to upregulation of monoamine oxidase-B. Astrocytic functions, like potassium homeostasis, removal of glutamate, Ca^{2+} signaling, and energetic metabolism are impaired in AD (42). The binding of interferon- γ (INF- γ) to its receptor activates the canonical Janus kinase (JAK). JAK activates STAT-1 by the phosphorylation of tyrosine. STAT-1 is translocated to the nucleus and combines with the IFN- γ activation site. Nuclear DNA activates

interferon-stimulated genes (ISGs), promoting the production of pro-inflammatory cytokines (45). The NF- κ B transcription factor is vital for the production of pro-inflammatory factors in the microglia and astrocytes of AD. An inhibitor, I κ B- β , may inhibit the activation of NF- κ B. Many immune receptors activate the I κ B kinase (IKK) complex to phosphorylate and trigger the degradation of I κ Bs. Then, the activated NF- κ B is translocated to the nucleus and promotes the expression of inflammatory genes encoding various factors such as TNF- α and ROS. Both microglia and astrocytes contain TLRs, indicating that NF- κ B is important for neuroinflammation of microglia and astrocytes (45).

2.4. Recent advances:

2.4.1. Role of lipid rafts and membrane composition.

Lipid rafts (LRs) play a crucial role in the pathogenesis of AD. LRs carry several proteins, including β -secretase, γ -secretase, and β -amyloid precursor protein (β APP), contributing to the production of amyloid- β (A β) and amyloid plaques (46). In LRs, cholesterol stabilizes β - and γ -secretases and prevents their degradation, enhancing their activity. Enrichment of cholesterol and gangliosides in LRs promotes A β production. Higher cholesterol levels shift APP localization toward LRs, it favors amyloidogenic cleavage and suppresses α -secretase activity (47). LRs are the site where A β interacts with ApoE and tau, leading to the aggregation of oligomers of A β and hyperphosphorylated tau proteins. The process of amyloid genesis is closely related to the lipid composition in LRs. Additionally, alterations in lipid rafts can affect the function of various membrane-bound proteins involved in synaptic transmission and neuronal signaling, further exacerbating the neurodegenerative process in AD (46).

AD is caused by impaired formation of PM LRs, due to inefficient uptake of cholesterol, which is produced by astrocytes. Reduced formation of PM LRs prolongs Cgen and prevents Cres, with three major consequences.

1. Short-term memory (STM) is not converted to long-term memory (LTM).

2. The cytoskeleton is not linked with the PM properly, causing excessive phosphorylated tau along with mitochondrial problems and disturbing the signaling pathways mediated by PM receptors (including growth factor signaling pathways), and ultimately neurodegeneration.
3. Finally, increasing the production of cholesterol by neurons.

In many cases, this is not sufficient to produce PM LRs and stimulates chronic A β production, leading to membrane A β cation channels that induce calcium toxicity and to A β aggregation. In other cases, neural cholesterol production does manage to establish PM LRs, with intact plasticity accompanied by excessive A β (48).

2.4.2. Post-translational modifications (PTMs) of APP and A β :

After synthesis proteins undergo modifications like acetylation, phosphorylation, or methylation (49,50,51,52). In AD, APP, Tau protein and A β protein undergo abnormal PTMs, which leads to their aggregation and accumulation, resulting in neuronal death and neurodegenerative diseases (50,51,52). A β is derived by sequential cleavage APP, APP is cleaved by BACE-1 (β -site APP-cleavage enzyme-1) and then by γ -secretase. During the procedure, APP and BACE-1 can glycosylated and phosphorylated, which effects the APP cleavage and plays a crucial role in the trafficking and then maturation of BACE-1. Presenilin (key component of γ -secretase) is phosphorylated to regulate the degradation of A β by microglia. Apart from all this, the aggregation and toxicity of A β can be enhanced by the process of glycation (49). The affinity of tau to tubulin is regulated by various PTMs, encompassing phosphorylation, acetylation, glycosylation, methylation, nitration, oxidation, ubiquitination, and SUMOylation. Tau phosphorylation is most studied among these PTMs. Acetylation and some other PTMs can also impair the functions of tau, promoting tau monomer aggregations (52). The aggregation of amyloid- β and hyperphosphorylation of tau protein are hallmarks of AD (50,51). These PTMs are associated with weakening of memory, cognitive impairments with reduce in synaptic

plasticity and thus contributing in the rapid progression of AD (51).

2.4.3. Emerging imaging and biomarker approaches (e.g., A β -PET)

Biomarkers like A β -PET and CSF have improved the accuracy of the diagnosis of dementia in AD. Currently, it is being used in the diagnosis of cognitive impairment and to ensure the presence of abnormal A β , which is essential before initiating the anti-A β therapy (53). A β -PET is effective in diagnosing the progression of AD and can provide highly valuable information for clinical purposes. The effectiveness of A β -PET can be improved by combining it with the glucose metabolic features of brain ¹⁸F-FDG-PET images (54). The detection of A β and tau with A β -PET or CSF has limitations, cost, limited availability, and their invasiveness. Blood-based biomarkers show somewhat better results in clinical trials, like AHEAD 3-45 use plasma A β 42/40 to rule out individuals unlikely to be A β +ve. Recently, phosphorylated tau-217 (p-tau-217) is effective for prescreening, as it is elevated in A β +ve individuals (55). Disease-modifying therapy (DMT) is a vital concept in AD therapeutics development. Mostly DMT drugs, currently in clinical trials, are anti-A β drugs, such as aducanumab and lecanemab (29).

3. Tau Pathology:

A group of biochemically, clinically, and morphologically heterogeneous neurodegenerative diseases (cognitive decline and dementia, etc.) due to abnormal tau filaments (56,57). Extracellular amyloid- β plaques and intracellular neurofibrillary tangles of hyperphosphorylated tau are the hallmarks of accumulation due to neurofibrillary tangle misfolding (58). These misfoldings lead the adverse effects on major brain regions as the disease progresses (59,60). Tau mutations like MAPT mutation also influence these misfoldings faster aggregation in AD patients (61).

3.1. Tau structure and physiological function;

Tau protein is a microtubule-associated protein (MAP) encoded by MAPT gene on chromosome 17q21 to give stability to the cytoskeleton and microtubules in neurons of CNS but in humans

there are 6 different forms of Tau due to alternative splicing of 2,3,10 exons (62,63). Neuron-specific tau gene has 16 exons but 6 isoforms appear in CNS. In PNS, high-molecular-weight big tau (2340-base-pair cDNA & 733 amino acid residues) with the exon 10 form 4R isoforms and tau without exon 10 yield 3R isoforms (64).

These tau isoforms differ in primary structure due to inclusions and exclusions in specific exons. These primary sequences show that tau consists structurally of two-thirds N-terminal acidic portion with proline-rich region and one-third C-terminal tail. These isoforms, referred as τ 3L, τ 3S, τ 3, τ 4L, τ 4S, and τ 4 are differ by the number of microtubule-binding repeats (MTBRs) with exon 10 inclusion (4R tau: 0N4R, 1N4R, 2N4R) and exon 10 exclusion (3R tau: 0N3R, 1N3R, 2N3R,65). Moreover, 2 and 3 exons encoded polypeptide sequences add acidity to tau, whereas exon 10 encodes a positively charged sequence that contributes to the basic character of tau protein (66).

In the adult human brain, 3R /4R ratio is ~1 but 4R binds microtubules (MTs) threefold more strongly and assembles MTs more effectively than 3R (67). These bindings need 3R/4R tau and acidic C-terminus of tubulin interaction to promote microtubule assembly and stabilization. The C-terminus of tubulin contains three repeated sequences to bind, while adult-specific tau isoforms have a fourth one too, which creates a jaw effect that makes the binding stronger (68). In addition, tau forms β -sheet structure in amyloid fibrils with microtubules by forming 2 and 3 repeat stable hairpin shape to stabilize microtubules (69). However, these bindings are affected by tau mutations and PTMs such as hyper-phosphorylation that leads to disturbed MT function, fast axonal transport and neurodegeneration (70).

Tau protein is transported and evenly distributed by diffusion through microtubule lattice and cytosol, and also co-transported from the cell body to axon through dynein and kinesin motors during slow axonal transport. But excess of tau blocks kinesin-1 binding sites on MTs which impairs synapses that may contribute to axon degeneration in AD (71).

3.2. Hyperphosphorylation, truncation, acetylation, and aggregation into paired helical filaments (PHFs):

PHFs-tau's 19 sites, except Ser-262, associated with multiple sclerosis and instability are localized to N and C terminals. The phosphorylated tau degradation occurs by CHIP (carboxyl terminus of Hsc70-interacting protein). TauC3 phosphorylation disturbs CHIP which causes abnormally hyperphosphorylated tau, microtubule disassembly, axonal transport impairments, and truncation ultimately leading to cell death in AD (72).

Hyper-lysine/dysregulated acetylation also plays an important role in the inhibition of tau and MTs hairpin folding, impaired tau-mediated stabilization of MTs, enhances tau aggregation, and disease pathogenesis due to the removal of lysine positive charge (73).

Tau has high β -sheet content and large hydrophobic surface but loss of acetylated α -tubulin destabilizes MTs. Truncated tau K18 and K19, lysine-cysteine spacing, and PHF6 hexapeptides drive tau aggregation (74). Flexible and unstructured tau is triggered by polyanions, then accumulates itself, and creates β -sheets that form PHFs at a specific pH 5-10 (75).

3.3. Propagation and “prion-like” spreading of tau:

Tau propagation begins with the misfolded tau donor cell to the recipient cell by recruiting normal tau into β -sheet aggregation in prion-like ways that enable the spread of tau pathology to distinct parts of the brain (76,77). Sonication experiment proved that prions also amplify by fragmentation which increases tau propagation (78). A rodent model experiment was performed to observe the tau propagation in relevance to human tau. That results in developing similar NFTs as human and co-aggregation of both rodent and human tau protein when expression is on or off if once, they co-aggregate (79).

3.3.1. Interaction with cellular systems:

Different portions of cells work differently and play their role in perfect cell functioning, but in Alzheimer's disease, these cellular systems become paralyzed in performing their functions. Here are some examples of malfunctioning: Mitochondrial dysfunction, synaptic

degeneration and Tau-induced inflammation and autophagic/lysosomal dysfunction. Mutations like missense (cluster near microtubule binding site) and splicing errors (altering 3R/4R repeats by affecting exon 10) caused by PTMs, axonal transport defects, synaptic loss by dysregulation in actin regulatory protein and soluble oligomers of beta-amyloid ($A\beta$), neuroinflammation, and oxidative stress etc., are the reasons for tau aggregation and pathogenic tau propagation (80,81,82). These actins' irregular binding leads to cognitive decline, motor issues and cerebellar/brainstem dysfunction (83). Our brain, which needs disproportionately high energy (ATP), is highly affected by disruption in mitochondrial homeostasis, leading to oxidative stress, neurotoxic neurofibrillary tangles, extreme nervous system damage (temporo-parietal brain regions), cognitive impairment, ATP starvation in the brain, impeding the autophagic clearance of mitochondria in neurons and cell death in AD (7,38,84). Moreover, synaptic degeneration is also the most derived correlate of cognitive decline, where amyloid- β triggers malfunctioning in synapses and makes glial cells (microglia and astrocytes) worse in this decline (85).

Where mutated tau tends to self-aggregate and form PHFs, substantial aggregation of tau involved in lysosomal and autophagy dysfunction which are the major contributors to the etiology of AD. Lysosomal vesicles consist of hydrolases, proper cellular machinery (integral membrane β - and γ -secretases) to generate amyloid-beta (86,87). PSEN1, a genetic mutation, affects v-ATPase maturation and Ca^{2+} homeostasis which promotes lysosomal faulty acidification. This faulty acidification contributes significantly to the accumulation of Amyloid- β ($A\beta$). This accumulation stops autophagy and promotes the accretion of noxious protein extracellular $A\beta$ plaques and intracellular neurofibrillary tangles (NFTs) in the hippocampus and cortex of the brain (88,89).

3.4. Tau isoforms and alternative splicing (3R/4R tau):

Tau protein consists of a balanced 3R:4R ratio by alternative splicing, essential for normal brain functioning. But in AD, its proportion is

disrupted by exon 10 mis-splicing due to a mutation in MAPT gene on chromosome 17q21 and this mixing in 3R:4R ratio causes neurodegenerative diseases like Alzheimer's, with predominantly 4R mild disease and 3R severe pathology (90). Clinically, 50 MAPT mutations have been identified, of which one-third affect exon 10 splicing. This mis-splicing is also influenced by different polymorphisms, spliceosomal protein activity and RNA-binding proteins that contribute to isoform-specific impairments and pathological aggregation (91).

3.5. Cross-Talk Between Amyloid and Tau:

A bidirectional interaction of A β and tau has induced tau aggregation in PHFs, but interestingly, tau aggregation, A β plaques, expression of mutant tau, tangle formation and microglial activation, responsible for the release of proinflammatory cytokines, such as interleukin-1 β and tumour necrosis factor- α (TNF- α), are also due to over-expression of APP and PSEN1 that was shown in APPS1 transgenic mice models (APP KM670/671NL, PSEN1 L166P) (92,93). Data from aging rhesus monkeys show abnormal tau phosphorylation, disrupted APP-containing endosomes, and overall genetic (APP-gene mutation, PSEN1), and environmental factors (oxidative stress, hyperphosphorylation, and prions) are responsible for A β deposition, loss of synapses and neurons and calcium dysregulation. In addition, gut microbes, for example, Eubacterium rectale, Porphyromonas gingivalis, and Lactobacillus rhamnosus, etc., are also important in altering Astrocytes into reactive Astrocytes, proinflammatory cytokines and reactive oxygen species (ROS) for the origination of AD (94,95).

3.5.1. Shared signaling pathways: GSK3 β , CDK5, and calcium signaling:

GSK3 β , CDK5, and calcium are the core factors for normal brain cell functioning but their disruption, hyperactivation, or high influx may result in severe neuronal problems in Alzheimer's disease as described later: Glycogen synthase kinase-3 β (GSK-3 β) enzyme, activated by tau phosphorylation, its hyperactivation by hyperphosphorylation compromises the cAMP transcriptional activity, downregulates nerve

growth factor (NGF) which may result formation of neuronal plaques, A β plaques, irregularities in long-term memory and declined microglia-induced inflammatory responses, and contribute to various pathological processes in AD (96,97). Similarly, cyclin-dependent kinase-5(CDK-5) enzyme is also hyperactivated by p35 cleavage into p25 in AD. It accumulates in the frontal lobe and induces decreased ability to bind to microtubules, hyperphosphorylation, cytoskeleton disruption, morphological changes, and apoptosis in vivo and vitro (98,99). Ca²⁺ is also the key factor in forming fibrils, A β aggregation, and alters the unfolded A β 1-42 to β -sheet structure, by large influx, increased intracellular calcium concentrations (100).

3.5.2. Combined neurotoxicity and feedback loops:

A β -aggregation in the brain is a feedback loop in AD that exerts multiple malfunctions and diseases which were already discussed earlier. Mainly, cellular prion protein (PrPC) inhibits BACE1, an enzyme that produces A β . In pathological conditions, PrPC binds with A β oligomers, loses its inhibition ability and leads to A β o-PrPC complexes that activate Fyn kinase, tau phosphorylation, NMDAR dysfunction, A β production by modulatory factors (cAMP and cGMP), and ultimately neurodegeneration (101,102).

3.5.3. Systems biology and network models:

The imbalance between reactive oxygen species (ROS) and reactive nitrogen species (RNS) causes oxidative stress which is amplified by activation of NADPH oxidase. However, neuroinflammation has three stages: the early-stage links A β plaques and tau tangles. Blood-Brain Barrier (BBB) permeability increases with age, trauma, and infection which helps to accumulate A β . The intermediate stage involves prolonged activation of microglia (Astrocytes) and this activation releases inflammatory mediators. The last stage exhibits ultimate neuronal death and cognitive decline called dementia (103,104).

4. Emerging Insights and Therapeutical Implications:

Alzheimer's Disease (AD) is the most complex multifactorial neurodegenerative disorder and

common cause of dementia, it is characterized by senile plaques composed of Amyloid beta protein and neurofilament tangles derived from the hyperphosphorylation of tau-protein (105).

4.1. Novel protein

Beyond Amyloid plaques and tau tangle, Novel mechanism in Alzheimer's disease (AD) include early disruption in cellular waste disposal, altered immune response (such as role of IL-2), and new peptide divers (T14), Additionally, the impact of the gut microbe, sleep, hearing, and particular protein (DEK) deficiency are explored pointing to a complex interplay of pathways influencing neuronal health and function (105) Over 55 individuals suffer dementia, and every 20 years, this figure is expected to quadruple. By 2050, 131.5 million individuals worldwide are predicted to develop Alzheimer disease and associated dementias, creating a serious health emergency (106).

4.2. Anti-Amyloid Therapy:

A β peptides in the extracellular area make up amyloid plaques. The transmembrane protein known as Amyloid precursor protein (APP) is the source of $\alpha\beta$. Pathological $\alpha\beta$ is produced when beta-secretase and Y-secretase break the APP. Neurotoxicity is caused by $\alpha\beta$ accumulation. Reducing $\alpha\beta$ buildup has emerged as treatment goal for AD (107).

4.3. RNA-Editing:

A biochemical mechanism called RNA-editing adds an additional layer of diversity to RNA. Millions of sites have been identified as being altered in human APOB gene in 1987. Over 10,000 exonic sites were found in study of B cell from 27 different people. ADAR1, ADAR2, ADAR3 are the three main genes that encodes ADAR protein. Cardiovascular disease, autoimmune and anti-inflammatory disorders have all being linked to ADAR-related RNA editing. One of the most frequent post-transcriptional changes in eukaryotic cells in ADAR, also known as A-I editing, which is the deamination of adenosine-inosine in double stranded RNA (dsRNA) mediated by the adenosine deaminase acting on RNA family of enzymes. It may produce a variety of protein isoform and influence the cellular destiny and translation probability of RNA. RNA editing is

tightly controlled depending on the tissue (108,109).

4.3.1. Biology of ADAR enzymes and A-to-I editing:

Adenosine is converted to inosine in double stranded RNA (dsRNA) by adenosine deaminases that work on RNAs. Activation of nuclear factor kappa B-regulated genes, interferons and dsRNA sensors. Here, We used the available RNA sequence file to examine whether alternations resulting from adenosine-to-Inosine editing were linked to the existence of Alzheimer's disease in the entire pre-frontal cortex, the entire hippocampus, and the cortical vasculature (110). According to several basic papers, ADARs2 ratio decreases in vulnerable areas and cell type specific conversion (e.g., significant augmentation in P110 vs P150 in certain, models) and ADARs1 diminishes with brain aging and Alzheimer disease. A python based program known as the SPRINT toolkit. Served as the primary identification tool. It takes sequence file and generates text files with the following details for every change site:1. genomic location, 2. Edit type (e.g., A-to-G and C-to- G), strand or (+ to -), 3. Total number of reads per site and number of alternations per site. Data such as the number of samples in groups with shared editing sites, the mean numbers of reads and edits for each editing site, the editing sites common and unique to group pairings, and the editing sites per gene were all synthesized using Mathematica program (110,111).

4.3.2. Micro-RNAs:

A family of non-coding RNAs known as Micro-RNAs is crucial for controlling transcription, translation and gene expression. MicroRNAs can attach to proteins to be released into the extracellular space, where they can be transported to their target cell via vesicles. MicroRNAs are important for cell signaling and communication (112). Due to their great therapeutic promise in neurodegenerative disorder, micro-RNA based treatment have garnered a lot of interests lately. In the brain, a number of modulatory micro-RNAs plays a crucial and critical role in regulating gene expression following transcription. Promoting the production of protective micro-RNAs are

less neurotoxic than other gene silencing technique. MicroRNAs involved in post-translational phases and gene expressions of several AD disease, according to recent studies on transgenic mice, it has been discovered that some micro-RNAs level decreased throughout AD cell stages. Among these is microRNA 132, which is markedly diminished in the intermediate stages of AD. Additionally, it has been demonstrated that microRNA 132 reduction significantly worsen the molecular and functional pathologies brought on by AD. Moreover, it has been discovered that increasing the expression of microRNA 124 in cerebral cortex and hippocampus enhances cognitive function in AD rats (112,113).

Mitochondrial Dysfunction:

Maternally inherited organelles called mitochondria are essential for cell survival, energy metabolism, oxidative stress and calcium homeostasis. It has been suggested that AD is a metabolic illness. Crucially, both fundamental research and clinical investigations have shown a substantial link between microbial activation and metabolic impairment in AD (114). Age dependent accumulation of mitochondrial DNA (mtDNA) altered mitochondrial membrane potential, excessive mitochondrial ROS production decreased mitochondrial adenosine triphosphate (ATP), disrupted electron transport chain (ETC), increased mitochondrial fragmentation, and impaired mitophagy in microglia and other brain cells are just the few abnormalities found in AD. Furthermore, long term-exposure to $\alpha\beta$ and p-tau causes deregulated expressions of gene linked to late-onset AD. Additionally, treatments that target fundamental mitochondrial function, such qualities control (QC) have a lot of therapeutic potential (113,114,115).

Microglial mtDNA and AD:

Microglial mtDNA depletion levels in three brain areas varying AD pathogenic vulnerability and matching disease phases were shown to be likely correlated in a recent in a recent study that evaluated microglial mtDNA depletion in the human AD brain. In many clinical diseases, microglial dysfunction is caused by abnormalities in microglial mtDNA. Research

conducted on congenic mtDNA mice showed that microglial mtDNA polymorphism directly control microglial activation, AB phagocytosis (116). Toll-like receptor 9 (TLRP9), cytosolic cycle GMP-AMP synthase stimulator of interferon gene, and NOD like receptor family pyrin domain containing 3 inflammasomes are some of the ways that microglial may detect the release of mtDNA from injured cell. NLRP3 inflammasomes and the IFN-related pathways are activated when oxidized mitochondria DNA binds to TLR9 on the Endo lysosomal membrane. Following internalization by adjacent microglia, mtDNA attaches to cGAS to trigger the cytosolic DNA-sensing, cGAS-STING pathway, which increases IFN- β production. Additionally, human microglia are treated with mtDNA generate a significant quantity of ROS to trigger the NF-kb pathway release an excess of pro-inflammatory cytokines, exacerbating the inflammatory milieu to cause tissue damage and cell death. As a result, more damage associated molecular patterns (DAMPs) are released, which in turn trigger others microglia to spread a vicious cycle of neuroinflammation (116,117). Mitochondria has its unique circular genome called DNA, human DNA contains 15,569 base pair and 37 coding genes, including 22 tRNA, 2 rRNA, and 13 polypeptides. In AD, microglial mtDNAs are vulnerable to various damages particularly ROS generated nearby (118).

5.Future Insights

5.1 Integrating omics (proteomics, transcriptomics, metabolomics):

The establishment of a molecular map of the brain would be a great step towards understanding the complex pathology of AD. For this purpose, an integrative approach, combining the use of microscale omics (for biomolecular analysis) and macroscale imaging technology (to capture locational profiles), may be a powerful tool. Omics encompasses the various levels of distinct molecular layers, including the genome, transcriptome, metabolome, and proteome. The results are then collected by the application of omics. Processing of imaging technologies is achieved using appropriate procedures, which include the feature extraction by the use of machine learning, followed by data integration to develop a molecular map of the brain, by a similar

feature detection function (119). Even though available knowledge provides enough insights about the single genetic variations associated with A β or tau PET. Future genomics studies require the deep exploration of rare and structural variants, through sequencing of the whole-genome. In addition, analytic frameworks designed for modeling gene-by-environment interactions are the need of the time, and are linked with the advancements in epigenomics. Quantitative trait loci studies can significantly enhance the precision, and the confidence for detecting functional variants relevant to AD and AD-related processes (120).

A study of the relation between genetics and dementia risk factors, and the processes associated with them, is important. The advancements in blood-based biomarkers have made widespread monitoring feasible, and preventative initiatives are being designed using digital tools for remote cognitive and behavioral tracking. Precise preventive methods should be developed that align risk reduction with optimal therapeutic allocation by establishing at-risk cohorts based on cardiovascular and genetic risk factors interactions (121). In addition, integration of proteomic data with other omics approaches is essential for the comprehensive understanding of the pathogenesis of AD. Approaches like metabolomics, transcriptomics, and genomics are of central importance in it. Development and refinement in the bioinformatics tools and the machine-learning algorithms that are capable of handling the complexity and the scale of proteomic data can assist in this regard. With the advancement in proteomic technologies, their application in clinical trials and their integration with other omics can enhance the effectiveness and precision in the diagnosis and therapeutic approaches in AD (122).

Early Detection Biomarkers and Personalized Medicines:

The multi-omics knowledge houses following three important developments in the diagnosis and timely treatment of AD;

First one is the multi-omics datasets, which would be a hallmark towards the development of better genetic and molecular biomarkers. For example, improvements in the CSF and blood

biomarkers increase the accuracy of early detection of AD.

Secondly, the discovery of new biomarkers is very helpful in indicating and measuring the readouts, which helps us to monitor disease progress, drug efficiency, and treatment responses more precisely.

Last but not least, the discovery of drugs with specific targets like genes, alleles, transcript isoforms, or specific cells will help in developing new and more effective therapeutics towards AD (123).

Even though we have made considerable progress in the fluid and imaging biomarkers, more precise biomarkers that are capable of capturing the heterogeneity of disease are needed for the time being. These biomarkers would be capable enough to categorize the patients based on the protein expression variation, PTMs, and aggregation quality. Early diagnosis and better monitoring of the progression of the disease would help us to design better treatment responses (124). Research based on CSF AD biomarkers suggests that innovative biomarkers can be used as noninvasive indicators. The discovery of blood-based biomarkers enabled us to timely diagnose, track the disease progression, and design the care better suited to them. It is difficult to identify the best biomarkers as the exact starting process of AD is unknown, but when combined with other risk factors it may revolutionize the early detection of AD (115). Emerging treatments include monoclonal antibodies (e.g., lecanemab and donanemab), kinase inhibitors, BACE modulators, and gene therapies targeting ApoE. Drugs capable of crossing the Blood-Brain Barrier are essential cause without this ability many strategies may fail. Approaches like intranasal delivery, focused ultrasound, receptor-mediated transport, or nanoparticles can revolutionize AD therapeutics, as they have an ability to cross the BBB (125). These emerging biomarkers have limited use in clinical trials due to improper access to advance technologies, lack of assay standardization, absence of a universally accepted reference range, and variable pre-analytical handling. By addressing these issues, we can enhance test reliability and improve clinical applications. Future research focuses on large-scale, longitudinal studies, and to identify the best-

suited biomarkers. This may help to develop techniques for early detection and timely treatment of the disease (126). With the advancement in technologies and interdisciplinary techniques, personalized care is promised in the AD therapeutics. Treatments can be made easier by timely disease diagnosis using enhanced imaging and biomarkers. The main goal is to decrease disease progression by advancements in disease-modifying treatments; industrial, research institutes, and clinical work must be combined. To improve mental health education and treatment, it is crucial to emphasize caregiver assistance. There is still a healthy need for new research and policies, public awareness, and state-of-the-art technologies to work in coordination to improve AD care and therapeutics in the near future (127).

Reconsidering amyloid-tau-centric view:

Future research into neuroinflammation should explain the nature and mechanisms involved in AD progression. Modern strategies should be adopted to design diagnostics and the pharmacotherapy of inflammation in AD. Early detection of the development of neuroinflammation is vital for the timely diagnosis of AD. Many drugs and methods are in clinical trials, and their introduction will be a turning point in treatment (13). Modulation of microglial signaling pathways carries enough therapeutic potential; in future our focus should be enhanced phagocytosis instead of reducing the inflammation. Pathways like NLRP3 inflammasome are helpful to reduce neuroinflammation and neurodegeneration. In microglial targeted therapies it is crucial to maintain the safety, so that off target effects can be minimized by optimizing the timings of interventions. Promotion of cross-disciplinary collaboration and usage of advanced technologies should be considered in future. Studies tracking microglial activation in individuals at risk can provide insights into disease progression, while cross-species comparisons will enhance translational relevance (128). Microglia are the main source of neuroinflammation, releasing cytokines, causing synaptic loss, neurodegeneration, and an increase in the levels of A β and p-tau. Future research needs to discover potential

inflammatory targets and to study their effect on the overactivation of microglia. AD diagnosis can be more precise by developing anti-inflammatory treatment strategies, and by combining anti-inflammatory drugs, along with the biomarkers for inflammation (129). Future research is highly focused on the overactivation of microglia and astrocytes and the release of cytokines, as important pathogenic factors in neurodegenerative diseases. In the Nervous system, the chronic inflammatory processes contribute to the onset of AD, Parkinson's disease, and even multiple sclerosis. Strategies to control the inflammatory process, like microglia modulators, cytokine inhibitors, or factors to inhibit the inflammasome activation, can provide significant advancement in AD therapeutics. Therapies targeting inflammatory pathways can slow down or even inhibit AD-related inflammation. In the future, the development of biomarkers that allow the early detection of inflammation and, introduction of therapeutics at a stage where they are most effective will be important. Combining the immunomodulatory approaches with innovative methods such as gene or cell therapy provides a promising path forward in the treatment of AD (129).

Conclusion

The Alzheimer's disease pathology is a result of interconnected processes in which amyloid- β and tau remain the two most extensively studied and mechanistically relevant factors. Studies have shown how an imbalance in APP processing generates A β 42 species that isomerize to form soluble oligomers and insoluble fibrils; this happens when the protective α -secretase pathway (non-amyloidogenic pathway) is replaced by pathogenic β - and γ -secretase cleavage (amyloidogenic pathway). These species are active neuronal homeostasis disturbers, causing an imbalance in calcium signaling, introducing oxidative and mitochondrial stress, and activating the chronic neuroinflammatory response of the microglia and astrocytes. Tau is a protein whose role is to maintain the microtubular network of the neurons, in parallel to the amyloidogenic pathway of APP, tau undergoes abnormal hyperphosphorylation, acetylation, truncation, and misfolding into

helical filaments. This destroys the normal functioning of the tau proteins along with its pathological capacity of propagating between neurons, a mechanism that explains the stereotyped, stage-wise tau pathology often seen in AD brain. The field has come far ahead of treating amyloid and tau as independent processes. Recent studies now support genuine cross-talk, where A β accumulation reduces tau-hyperphosphorylation threshold and aggregation through disturbed Ca²⁺ homeostasis and pathways like GSK3 β and CDK5. This amyloid-tau cascade, integrated with other neuroinflammatory feedback loops provides a more integrated system for disease progression. Such integrated models help to explain why strategies designed to target a single node yield more clinical benefits, and why field is shifting its focus to combination therapeutic strategies.

Even though the central, amyloid-tau axis is not the whole story. Emerging insights suggest a well-distributed and multifactorial model of neurodegeneration comprising RNA editing and microRNA dysregulation, mitochondrial RNA dysfunction, impaired proteostasis and chaperone networks, and the broader contribution of glial and systemic inflammatory factors. It'll be even more productive to follow both new insights and the classical knowings synergistically than comparing. This point is supported by the partial successes and notable failures of anti-amyloid and anti-tau monotherapies. Clinical benefit ultimately depends upon the timely diagnosis (before the neuronal damage) and combining classical knowledge with the modern-day understandings of the disease. In the future, the integration of proteomic, transcriptomic, and metabolomic data, alongside refined imaging and fluid biomarkers such as A β -PET and phosphorylated tau assays, promises to enable earlier diagnosis, better patient stratification, and truly personalized therapeutic regimens. Complementary developments in lipid raft dynamics, 3R/4R tau isoform biology, and RNA-level regulatory mechanisms including ADAR-mediated editing and microRNA dysregulation expand the toolkit for detecting at-risk individuals well before overt cognitive decline manifests. Ultimately, the logical development of successful, disease-modifying

therapies for Alzheimer's disease depends on a mechanistic understanding of amyloid and tau biology.

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