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A Multitude of Signaling Pathways Associated with Alzheimer's Disease and Their Roles in AD Pathogenesis and Therapy

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Abstract

The exact molecular mechanisms associated with Alzheimer's disease (AD) pathology continue to represent a mystery. In the past decades, comprehensive data were generated on the involvement of different signaling pathways in the AD pathogenesis. However, the utilization of signaling pathways as potential targets for the development of drugs against AD is rather limited due to the immense complexity of the brain and intricate molecular links between these pathways. Therefore, finding a correlation and cross-talk between these signaling pathways and establishing different therapeutic targets within and between those pathways are needed for better understanding of the biological events responsible for the AD-related neurodegeneration. For example, autophagy is a conservative cellular process that shows link with many other AD-related pathways and is crucial for maintenance of the correct cellular balance by degrading AD-associated pathogenic proteins. Considering the central role of autophagy in AD and its interplay with many other pathways, the finest therapeutic strategy to fight against AD is the use of autophagy as a target. As an essential step in this direction, this comprehensive review represents recent findings on the individual AD-related signaling pathways, describes key features of these pathways and their cross-talk with autophagy, represents current drug development, and introduces some of the multi-target beneficial approaches and strategies for the therapeutic intervention of AD.

Keywords

Alzheimer's disease; Amyloid beta; Tau; Senile plaque; Neurofibrillary tangle; Autophagy; Signaling pathways

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1. Introduction

Alzheimer's disease (AD) is the most common form of age-related dementia with no curative therapy available as of yet due to the limited knowledge on the molecular basis of its pathobiology.[1,2] AD was described for the first time by Dr. Alois Alzheimer in 1906, who reported that his patient Auguste D. started developing personality changes and cognitive deficits (such as aggression, confusion, paranoia, progressive memory decline, and sleep disturbance) in her late 40s, she succumbed to disease 5 years after admission to the clinic, and showed specific extracellular amyloid plaques and intracellular neurofibrillary tangles (NFTs) in the brain histology.[3,4] Despite the painstaking attempts of multiple researchers working in this field for almost 115 years after the first report, and despite the existence of numerous hypothesis and theories, the exact pathological mechanisms of the AD remain poorly understood.[5] This is because the molecular pathogenesis of AD is complex and involves multiple, often interconnected, factors.[5]

The numbers of older peoples are increasing rapidly in the developed and many developing countries, such as China, India, and Latin America. This dominating and ever-increasing aging of the world population enhances the chances of the global increase in the number of AD patients and dramatically increases the related burden. According to worlds Alzheimer's report 2018, about 50 million peoples were living with dementia worldwide in 2018, and this number is expected to reach 152 million by 2050.[6] Furthermore, the total worldwide cost of dealing with dementia in 2018 was US$1 trillion, which is estimated to rise to US$ 2 trillion by 2030.[6] It has also been estimated that 40 million people, mostly older than 60 years, have dementia, and this number is projected to double every 20 years.

The AD is associated with the progressive neurodegeneration caused by the death of neurons in the hippocampus and surrounding parahippocampal region of brain and abnormal accumulation of specific amyloidogenic proteins or protein fragments in the affected brain areas, with these features being commonly considered as the hallmarks of AD. Early-onset AD (EOAD) and late-onset AD (LOAD) are etiologically and epidemiologically different forms of AD.[3,7–9] The EOAD is less common than LOAD, which is the most frequent form of AD with complex etiology that constitute over 95% of all cases.[3,10] EOAD, which is also known as familial AD (FAD), may be inherited in an autosomal dominant manner and associated with a non-dominant cause, such as mutations in APOE4 allele. LOAD, being sporadic AD (SAD) form, is the most common type of the age-related neurodegenerative diseases caused by various (often environmental factors) and affecting 5 million people in the USA alone.[11,12] Compelling evidence generated by numerous experimental, biochemical, neuropathological, and genetic studies revealed that the pathobiology of AD is attributed to many factors of different nature, giving rise to multiple theories and hypotheses on the diverse mechanisms of the AD pathogenesis. However, aging is considered as the most crucial AD risk factor. Next, amyloid cascade hypothesis postulates that the deposition of the β-amyloid (Aβ, which is a 39–43 amino acid peptide derived from the amyloid precursor protein (APP) by β- and γ-secretase cleavage) or senile plaques in the brain plays a vital role in the AD pathology.[13,14] In addition to secretase, several proteins have been identified recently that affect Aβ production and clearance. Furthermore, the FAD is associated with several mutations in genes, such as *APP*,

PSEN1, *PSEN2*, and *APOE4* that are directly involved in the Aβ generation and formation of toxic senile plaques.[4,15] Studies have shown that mutation in presenilin gene promotes aberrant APP processing that leads to the formation of longer and more hydrophobic Aβ proteins.[16] Aβ is produced by the processing of a parent protein APP that contributes to the proper neuronal and cerebral function development. However, aberrant APP processing and Aβ deposition are considered as the first events associated with the AD development.[17,18] Among several other proteins involved in the AD pathogenesis, serious attention is given to the abnormally phosphorylated (hyperphosphorylated) Tau protein that aggregates to paired-helical filaments forming neurofibrillary tangles.[19–25] Therefore, it is not surprising that $A\beta_{42}$ and Tau proteins are considered as well-established cerebrospinal biomarkers for AD.[1] In addition to several factors promoting AD, numerous mechanisms protect the brain from AD, such as clearing of abnormal/misfolded proteins, repairing of cells, and better energy metabolism. Typically, the failure of these protective mechanisms may lead to the emergence of AD phenotype. Furthermore, since Aβ, Tau, ApoE, PSEN1, and GSK3β are associated with diverse signaling cascades that regulate neuronal cell survival and activity, failure of these proteins and misbehavior of their associated signaling pathways are also related to the AD etiology.[1] The autophagy is highly dynamic process, which is inducible by stress stimuli and environmental changes, such as appearance of protein aggregates or damaged organelles, nutrient starvation, and pathogen infection that can resolve cellular demands.[26] Importantly, autophagy is linked to many other signaling pathways, have crucial role in AD pathogenesis, and can be considered as a prominent future drug target.

Therefore, it is evident from the past research that AD represents a multi-factorial disease that involves several cell-signaling pathways. Understandably, the interconnection between these signaling pathways is essential for finding suitable druggable targets. The goal of this review is to highlight different signaling pathways associated with AD pathology, discuss networks interconnecting these signaling pathways, describe interlink between autophagy and other pathways, and consider critical features responsible for the neurodegeneration and their implications for the AD management. Furthermore, we also discuss therapeutic opportunities to enhance the development of new drugs against AD pathogenesis. We hope that this review will help in better understanding of the molecular mechanisms of various pathways involved in AD pathogenesis and their cross-talk with autophagy along with the highlighting of several drug-designing strategies currently employed in this field. Since this review describes a whole cohort of the AD-related signaling pathways, by no means it aims at the exhaustive coverage of all the peculiarities of each pathway. Each of the pathways included in this compendium is itself a subject of numerous focused reviews, and the interested readers are encouraged to look for those specialized reviews.

2. Molecular signaling pathways in Alzheimer's disease

AD is not only the illness of the brain itself, but is also closely associated with whole human body.[1] The complexity of the human brain and unavailability of reasonable animal models are the roots for the unclear pathobiology of AD. Numerous signaling pathways explaining AD pathogenesis have been developed.[27] Among those is the *amyloid cascade hypothesis* that describes the widely accepted pathway for AD pathology, suggesting that the Aβ deposition is the primary cause of AD.[28] In addition to Aβ, *abnormal Tau aggregation*

and formation of neurofibrillary tangles cause toxic effect and lead to the death of neurons.[29] The genetic factors of AD are very complicated. Autosomal dominant familial EOAD is linked to the *genetic mutations* in at least three genes, such as *APP*, *PSEN1*, and *PSEN2*. On the other hand, mutations in *APOEε4* allele represent a genetic risk factor of LOAD.[30] The collapse of various *neurotransmitter systems*, such as those found in cholinergic, glutaminergic, and serotonergic neurons, might lead to the neurochemical abnormalities in the brain that end with the AD development.[31–34] Although healthy mitochondria play various functions in the body, *disturbing mitochondria* have crucial connections with the AD pathogenesis.[35] *Endoplasmic reticulum stress* and *oxidative stress* are strongly associated with neuronal injury in AD.[36,37] Similarly, uncontrolled *neuroinflammation* generated by the release of inflammatory mediators can be associated with the dysfunction, necrosis, and apoptosis of neurons.[38–40] Neuronal survival depends on the elimination of damaged, toxic, and aggregated proteins that are responsible for the neuronal cell death and cognitive decline.[41] The *ubiquitin-proteasomal system*, together with the *autophagy/endosomal-lysosomal system* and *management of protein misfolding by molecular chaperones* are three central protein quality control systems of the cell that play a fundamental role in handling consequences of protein misfolding and aggregation.[42,43] *Autophagy* is a primary intracellular means of removing aggregated proteins and damaged organelles by their degradation.[44] In fact, autophagy is a main regulator of generation and clearance of Aβ and Tau proteins. Thus, perturbed autophagy is a well-established contributing mechanism in the pathogenesis of AD.[45,46] Although in the norm, insulin regulates various central nervous system (CNS) functions, such as neuronal survival, learning, and memory, and also controls peripheral metabolism, the impaired neuronal *insulin signaling* triggers many events associated with the AD pathogenesis.[47] Similarly, cellular Ca^{2+} regulates multiple processes crucial for the neuronal function in the norm. However, abnormal *Ca^{2+} signaling* has been extensively observed in various neurodegenerative diseases, including AD.[48,49] *Neurotrophic factors (NTFs)* are critical components for the maintenance of functions and survival of neurons, but, loss of activity of NTFs exaggerate the effects of Aβ toxicity.[50,51] The brain contains 20% of the total body cholesterol that helps in the neuronal physiology and development; however, disturbance in the *cholesterol metabolism* in the midlife increases the risk of AD pathology.[52,53] Regular activity of β-catenin/Wnt is associated with neuronal connectivity, survival, adhesion, proliferation, and differentiation. On the other hand, the perturbed *β-catenin/Wnt signaling* pathway is commonly reported in AD.[54–56] The peptide hormone *leptin* is involved in the normal glucose homeostasis, control of obesity, food intake, and energy expenditure, and has diverse actions throughout the CNS, such as neuroprotection by various mechanisms, whereas aberrant leptin signaling is also related to AD pathogenesis.[57,58] *Excitotoxicity* caused by excessive activation of N-methyl-D-aspartate (NMDA) receptors causes neuronal death, enhances the production of Aβ and Tau protein aggregation, and finally causes AD.[59] *Blood-Brain Barrier (BBB) leakage* has also been repeatedly reported in AD.[60] Finally, bidirectional communication between the gastrointestinal tract and brain is strongly correlated with AD pathogenesis. Alterations in gut microbiota composition influence not only various gut disorders but also central nervous system maladies, such as AD.[61] The more in-depth understanding of the molecular mechanism in all the signaling pathways involved in AD has been reported here with their therapeutic targets (Table 2) and treatment strategies.

2.1. Amyloid cascade signaling in AD

The Amyloid Cascade Hypothesis that was firstly proposed by Hardy and Higgins, in 1992,[28] represents the best defined and widely accepted framework of AD pathogenesis. It postulates that the amyloid beta (Aβ) deposition represents the primary and sole event leading to AD by accelerating downstream deleterious events, such as formation of senile plaques and NFTs thereby leading to the neuronal death that results in the memory loss and finally clinical dementia.[28,62] Although β- and γ-secretase-mediated cleavage of the APP generates several Aβ proteins ranging in length from 39 to 43 amino acids, $Aβ_{40}$ and $Aβ_{42}$ found in the AD brain seem to be the major constituents of the senile plaque.[63,64] Substantial evidence suggested that cognitive decline in the AD might be due to the direct toxic effect of Aβ oligomers on synapses and neuronal network.[65,66]

Aβ is a 4-kDa protein originated from an APP,[67] which is metabolized by competing pathways, such as α-secretase (non-amyloidogenic) pathway and β-secretase (amyloidogenic) pathway. In the α-secretase pathway, the initial cleavage of APP is made by the α-secretase followed by γ-secretase. By contrast, in the Aβ pathway, initial cleavage is made by the β-secretase followed by γ-secretase. In the β-secretase pathway, γ-cleavage mostly generates $Aβ_{40}$ and sometimes $Aβ_{42}$, which is characterized by high cytotoxicity.[68] Cleavage by α-secretase generates large N-terminal peptide called sAPPα and smaller C-terminal fragment called C83. Cleavage with β-secretase forms a large N-terminal sAAPβ and a smaller C99 fragment, which is further cleaved by γ-secretase leading to the release of $Aβ_{40}$/$Aβ_{42}$ to the extracellular space and the APP intracellular C-terminal domain (AICD) into the intracellular space.[69] After synthesis, Aβ is secreted outside the cell where it binds to various isoforms of ApoE, which allow them to undertake degradation and clearance by distinct pathways (proteolysis by the Aβ degrading enzyme (such as insulin-degrading enzyme (IDE) and a neutral endopeptidase neprilysin (NEO)), clearance through BBB, trafficking into the cell).[68] Evidence have been reported that aberrant autophagy leads to disturbance in the processing of APP and aggravate AD pathology.[70] The enhanced autophagy induction increases APP processing that creates conditions favorable for Aβ accumulation in AD brain.[71,72] Therefore, targeting autophagy along with utilization of Aβ aggregation inhibitors may provide better therapy for AD.

Amyloidosis is caused by the gathering and aggregation of amyloidogenic proteins. It has been reported that the self-oligomerization of Aβ molecules might contribute to the neuronal injury and neurodegeneration.[2,73,74] Accumulation and aggregation of Aβ proteins are due to the increase in the Aβ production in neurons and the decrease in the activity of the Aβ degrading enzymes.[11] In normal physiological condition, production and clearance of Aβ are balanced. Conversely, under the pathological condition, increased Aβ production, or decreased Aβ degradation/clearance could result in the raised levels of $Aβ_{1–42}$.[73] It has been reported that soluble oligomers of Aβ are more toxic than fibrillar Aβ at a very early stage of AD.[75,76] Interestingly, the soluble Aβ oligomers formation starts within cells and appearance of such oligomers is strongly associated with the development of dementia-like symptoms in AD brain. These oligomeric species of Aβ interact with the cell membrane and forms pore channel inside the membrane. Also, oligomers induces oxidative stress, mitochondrial alterations, and glial activation.[66] In a recent finding, Aβ oligomers have

been shown to disrupt the blood supply by constricting blood capillaries via interfering with pericytes. In normal physiological condition, pericytes control blood flow by controlling flexibility of capillary walls.[77] This new effect of Aβ oligomers could be explored to develop new therapeutic strategies to cure early AD.

$A\beta_{40}$ is the predominant Aβ species generated by the β-secretase pathway, whereas $A\beta_{42}$ is a less abundant, but noticeably more amyloidogenic form of the Aβ protein. Indeed, $A\beta_{42}$ is the primary Aβ species that contribute to the amyloid plaque formation in all forms of AD.[2,74,78] Senile plaque consists of soluble and insoluble assemblies of Aβ, including soluble dimers, trimers, dodecamers, etc.[2,74] β-Secretase (BACE1) is highly expressed in neurons and cleaves APP at the β-site, which is the first step of Aβ generation. Typically, a high level of BACE1 enhances the production of $A\beta_{42}$ and initiates amyloidogenesis.[79–81] β-cleavage of APP may be up-regulated in LOAD. Interestingly, β-cleavage mainly occurs in endosomes.[3,82,83] PSEN1 and PSEN2 provide catalytic subunit to γ-secretase for APP cleavage. However, cleavage is mediated either by PSEN1 or PSEN2.[4,15,16] Kimberly *et al.* reported that PSEN1 deficiency decreases the production of Aβ, suggesting that PSEN1 serves as the crucial mediator of APP cleavage by γ-secretase.[84] Additionally, presenilin enhancer protein 2 (PEN-2, also known as γ-secretase subunit PEN-2), presenilin-stabilization factor APH-1 (also known as γ-secretase subunit APH-1A), and nicastrin (NCT) are also involved in interaction with presenilin leading to the formation of active γ-secretase.[85–88] PSEN1 mutation generates more toxic $A\beta_{42}$ that leads to the early-onset FAD.[89] Neprilysin and IDE degrade Aβ, whereas their down-regulation raises the levels of Aβ production.[90] Interestingly, both of these Aβ degrading enzymes are reported to be decreased in AD.[68,91,92]

Aberrant levels of Aβ may induce numerous pathological conditions, such as abnormalities in the synapse and neuronal network,[68] distorted hippocampal synaptic plasticity,[93] neuronal network dysfunction.[94] They also can affect synaptic transmission[95] and show inhibitory effects on the presynaptic P/Q Ca^{2+} current necessary for the synaptic plasticity,[96] as well as can affect synaptic structure, composition, and density. Libro *et al.* reported that cannabidiol (CBD) potentiates Aβ and Tau degradation by inhibiting Tau phosphorylation and inhibiting enzymes involved in Aβ processing.[97] Many β- and γ-secretase inhibitors are in phase-II and phase-III clinical trial (Table 2). Additionally, active immunization with the Aβ peptides and their derivatives is in the phase-II and phase-III clinical trial.[11,98–104] This approach was used to develop serum antibody titers to the Aβ peptide that can help in the removal of Aβ from the brain and was shown to cause cognitive improvement in some patients.[11,98–104] Furthermore, passive immunization strategies using antibodies targeting different regions of the $A\beta_{1–42}$ peptide or Aβ oligomers are also currently being tested.[99,105–116] Unfortunately, numerous attempts were made to develop Aβ-targeting drugs for AD have failed. Therefore, for the development of new medication against AD need to consider other targets along with Aβ.

2.2. Tau and neurofibrillary tangles in AD

Tau is the microtubule-binding, intrinsically disordered phosphoprotein abundantly found in central and peripheral nervous systems, where it concentrates predominantly in the

axons of nerve cells and serves as the major constituent of neurofibrillary inclusions.[117,118] Under physiological conditions, Tau binds and stabilizes microtubule in axons, whereas under pathological conditions, this protein gets hyperphosphorylated, and this leads to its detachment from the microtubules and initiates formation of insoluble Tau aggregates followed by the generation of specific neuronal inclusions, paired helical filaments (PHFs) assembled into neurofibrillary tangles (NFTs). The hyperphosphorylation of Tau occurs due to decreased activity of phosphatases and increased activity of kinases.[119] Epigenetic modifications such as histone modification, non-coding RNA regulation, and DNA methylation can regulate tau phosphorylation and AD progression.[120] There are six isoforms of Tau in the brain,[121] containing 352, 381, 383, 410, 412, and 441 amino acids that are expressed in the adult human brain, whereas only one isoform composed of 352 amino acids is expressed in the human fetal brain.[122,123] It has been reported that Tau oligomers with a prefilamentous structure represent the main culprit in the early AD stages.[29,124] Tau pathology is the key driver of the disease progression not only in AD, but also in multiple other neurodegenerative diseases associated with the accumulation of Tau inclusions, which are collectively known as Tauopathies (e.g., primary age-related tauopathy (PART), chronic traumatic encephalopathy (CTE), progressive supranuclear palsy (PSP), corticobasal degeneration (CBD), frontotemporal dementia and parkinsonism linked to chromosome 17 (FTDP-17), Lytico-bodig disease (Parkinson-dementia complex of Guam), ganglioglioma and gangliocytoma, meningioangiomatosis, postencephalitic parkinsonism, subacute sclerosing panencephalitis (SSPE), encephalopathy, tuberous sclerosis, pantothenate kinase-associated neurodegeneration, and lipofuscinosis).[125] However, the molecular basis of the Tau-mediated neurotoxicity is not completely understood.[126] In AD, neurofibrillary lesions are abundantly found that consist of paired helical and straight Tau filaments, whereas other Tauopathies might contain Tau filament with diverse morphologies.[127]

A variety of etiological factors might lead to the abnormal hyperphosphorylation of Tau. This includes diverse pathways, such as Aβ cascade, perturbed glucose metabolism, and impaired phosphorylation and dephosphorylation pathways. Hyperphosphorylated Tau loses its biological activity and disassociates from microtubules. As a result, Tau hyperphosphorylation promotes homooligomerization and intracellular accumulation of this protein. Abnormal Tau is then polymerizing into PHFs and NFTs that accumulate in the body of the neuronal cells, frustrate the affected neurons, and facilitate cell death.[128,129] Prior to the NFTs formation, Tau self-assemble into various aggregation species, such as Tau oligomers, granules, and fibrils.[130] Loss of function of the normal Tau protein and gain of toxic properties by generating multimeric species are strongly associated with the neuronal loss in CNS.[131] Tau undergoes abnormal post-translational modifications during its fibrillation, resulting in altered microtubule-stabilizing properties and decreased solubility.[123] NFTs and other Tau aggregates cause toxic effects to neurons by producing neurotoxic signaling defects and by impeding the normal cell function.[29] PHFs consist of two fibrillar strands of which twist around one another in a helical manner.[122] Goedert *et al.* indicated that multiple human Tauopathies are characterized by different Tau fibril morphologies, suggesting the existence of different molecular strains of aggregated Tau.[132] Although, Tau pathology shows a better correlation with neurodegeneration and cognitive impairment in AD, still Tau-based approaches have not gained much more attention.[133]

Several possible Tau-based therapeutic strategies could be implied in AD, such as: i) Lowering the production of Tau aggregates or efficient removal of misfolded/oligomeric Tau aggregates; ii) Inhibition of toxic oligomers formation; iii) Reduction of the levels of Tau phosphorylation; iv) Increase of the PHFs/NFTs degradation; v) Microtubule stabilization; vi) Maintaining normal Tau conformations; and vii) Reducing levels of mutated Tau. Currently, few drugs have been reported to target Tauopathies (including AD) as shown in Table 2.

2.3. Genetic mutations in AD

In the brain, Aβ generation is influenced by the mutation in known genes associated with EOAD such as *APP*, *PSEN1*, and *PSEN2*,[134] along with genes encoding β-secretase and proteins in the γ-secretase complex, such as *NCSTN*, *APH1A*, and *PEN2*.[2] In addition to Aβ peptides, diffuse Aβ plaques abundantly contain various proteins, such as ApoE, clusterin, ACT, and complement proteins, that are playing a critical role in the dynamic balance between Aβ deposition and clearance.[135–139] For example, the ApoE4 interference with the Aβ clearance from brain (which instead processed into neurotoxic fragments and contributed to SAD) was suggested as a major genetic risk factor for an AD.[1,74,140,141] Typically, proteins, such as APP, Tau, and ApoE4 are involved in axonal transport.[51] ApoE2 and ApoE3 have a higher affinity for Aβ, which helps the Aβ clearance by transportation and degradation. By contrast, ApoE4 possesses lower affinity to Aβ, and mainly the mutated forms of this protein induce Aβ accumulation in the brain.[68,142] It has also been observed that genetic mutation in Tau protein generates frontotemporal dementia in the absence of senile plaques, suggesting that mutations in Tau can act as another factor causing AD.[1]

In the 1990s, the first pathogenic mutation was found in the amyloid precursor protein (*APP*). It is recognized now that in addition to APP, there are two more genes (presenilin 1 (*PSEN1*), and presenilin 2 (*PSEN2*)), mutations of which have been implicated in FAD. In fact, these three genes have been described to contain more than 160 highly penetrant but rare FAD-related mutations.[143] The first of these genes is an *APP*, which is located on chromosome 21q21.3, and mutations in which are found in 25 extended families. Despite its overall importance for the pathogenesis of both familial and sporadic forms of AD, the functional repertoire of APP is far from being completely understood (although this protein has been shown to be related to neuronal development and formation and repair of synapses, e.g., being upregulated after neuronal injury). The second FAD-related gene, *PSEN1*, resides on chromosome 14q24.2 and its FAD-associated mutations are found in 315 families, whereas 18 families are known with FAD-related mutations in the *PSEN2* gene, which is located on the chromosome 1q42.13 and has high sequence homology and very similar structural organization to *PSEN1*.[4,144] Scheuner *et al.* reported that the FAD-linked mutations in all cases might increase the extracellular concentration of $A\beta_{42}$, thereby leading to the enhanced aggregation of this protein and triggering the AD.[15] The major biological function of presenilin is control γ-secretase activity which is responsible for proteolytic cleavage of the APP and NOTCH receptor proteins.[145] It has been demonstrated that GSK-3β and β-catenin are the components of the PSEN1 protein complex, where PSEN1 regulates the pool of β-catenin, which is critical for neurogenesis as well as synaptogenesis.[146–148] Intriguingly, the healthy subjects can get AD early, in

case if they have inherited two *ApoE4* genes or aggressive *PSEN1* mutant genes. More importantly, since these genes are primary risk factors for AD, genetic testing (genotyping) is highly advisable to look for mutated *ApoE4* and other susceptible genes.[11] Recently, another pathological role for mutant PSEN1 was reported, which includes reduction in the autophagic cargo elimination that reduces the efficiency of autophagic process.[149] Triggering receptor expressed on myeloid cells 2 (TREM2) specifically expressed in brain microglia have been identified as risk gene in AD.[150] The partial functional loss in TREM2 protein and alteration in microglial cell behavior were reported in LOAD.[151] Susceptibility to LOAD is associated to 20 disease-associated genomic loci, identified in the large-scale genome-wide association studies (GWAS) which was carried out in larger datasets.[152,153] GWAS identifies novel disease-associated genetic variants by simultaneous testing of large number of genetic markers such as single nucleotide polymorphisms (SNPs) throughout the genome.[154,155] Recent GWAS studies identified AD-associated genes such as *PICALM*, *PTK2B*, *SORL1*, *BIN1*, *CLU*, *ABCA7*, *CD2AP*, *CR1*, *SLC24A4 RIN3* locus, *EPHA1*, *MS4A4/MS4A6E*, *INPP5D*, *MEF2C*, *NME8*, *FERMT2*, *CD33*, *CASS4*, *ZCWPW1*, *CELF1*, and *HLA-DRB5 HLA-DRB1* locus.[156] CD2AP, PICALM, BIN1 EPHA1, and CD33 are involved in synaptic functioning, ABCA7, MS4A, CLU, CR1, CD33, and EPHA1 are associated with immune system, CLU and ABCA7 are associated with lipid metabolism.[157]

2.4. Altered neurotransmitter signaling in AD

The AD is associated with the collapse of various neurotransmitter systems caused by the malfunction of cholinergic, glutaminergic, and serotonergic neurons. Therefore, decreased brain levels of neurotransmitters and neuromodulators are among the main neurochemical abnormalities of AD.[31–34] Altered dopamine concentration in the brain is closely associated with the neurotoxicity.[158,159] Nobili *et al.* recently reported the loss of neurons in ventral tegmental area (VTA) at pre-plaque stages in the mouse model of AD and observed memory impairment and disturbed synaptic plasticity.[159] *In vitro* studies on norepinephrine reported that its low concentration can produce neuroprotective effect by acting as antioxidant and decreasing neuroinflammation.[158]

Synapses of the glutamatergic and GABAergic neurons provide excitatory and inhibitory outputs in CNS.[160,161] Alterations in their function and distortions of the related signaling could promote the AD pathogenesis. Dysfunctional glutamatergic signaling increases cellular Ca^{2+} level followed by the promotion of the excitatory pathway that leads to the nerve cell death. The dysfunctional GABAergic transmission leads to an increase in the intracellular level of Cl^{-} ions, which decreases the long-term potentiation (LTP), finally resulting in the impairment of cognition.[162] The loss of presynaptic neuronal structure is responsible for the reduction in the brain level of neurotransmitters (mostly acetylcholine in cholinergic neurons) eventually makes cells to become deafferented due to synaptic and connectivity loss. Importantly, this loss of synapses and connectivity along with reduced levels of neurotransmitters and neuromodulators has been reported to become rather extensive in AD. Furthermore, in AD, failure in rapid ion channel signaling has been reported due to disconnection of the nerve cells, which reduces the release of secondary messengers by G protein-coupled receptors (GPCRs). These signaling events regulate numerous functions in the nerve cells.[31] Lee *et al.* reported that APP

cleavage might be regulated by various signals, such as acetylcholine, neuropeptides, glutamate, and serotonin.[163,164] Therefore, the Aβ peptide generation in the brains of AD patients may cause impaired neurotransmission or reduced neuronal activity.[31] It is extensively observed that GPCRs are involved in neurotransmitter system, which is damaged in the AD brain. Furthermore, the functions of GPCRs have been reported to be disturbed by Aβ peptide.[165] The cholinergic neurons are present in high amount in basal forebrain region of brain that may be reduced or lost in AD. Cholinergic integrity and activity is neuroprotective and essential for cognitive processes.[158] Furthermore, cholinergic transmission has a pivotal role in memory, cognition, and synaptic plasticity. Disruption of acetylcholine-containing neurons substantially contributes to the cognitive decline in AD.[166] It has also been observed that Aβ is more toxic to cholinergic neurons than to other neuron types. Indeed, Aβ efficiently inhibits the cholinergic signaling.[167] M1mAChRs (postsynaptic) and M2mAChRs (presynaptic) receptors are major mAChR subtypes involved in AD.[168,169] Interestingly, neuronal autophagic process is directly regulated by neurotransmitter receptors. The coupling of neurotransmitter receptors with autophagy is crucial for regulation of neuronal function.[170] Aβ-deposition in synapses results in the decreased release of the presynaptic acetylcholine leading to inhibition of the signal transduction and results in the impaired memory and cognition.[165,171] Additionally, reduction in neurotransmitter synthesizing enzymes, such as glutamic acid decarboxylase (GAD) and choline acetyltransferase (CAT) has been found in dementia and AD.[172] Acetylcholinesterase inhibition is the most extensively developed treatment strategy for an AD, which revamps the release of acetylcholine as well as modification of acetylcholine receptors.[173] M1 agonists, such as xanomeline and AF102B, are in the clinical trial where they show a reduction in the Aβ levels in CSF, as well as the development of memory and cognition.[174,175]

Currently, there are two classes of FDA-approved drugs available for AD treatment, which are associated with the regulation of the neurotransmitter signaling.[165] The first class of these drugs includes memantine that acts as a low-affinity voltage-dependent uncompetitive antagonist of the glutaminergic NMDA receptors that inhibit the prolonged influx of Ca^{2+} ions and gives rise to the symptomatic improvement in AD and restores functional glutaminergic transmission, which was disturbed in the AD.[176] Furthermore, memantine can act as a non-competitive antagonist for serotonergic ($5\text{-}HT_3$),[177] cholinergic (nicotinic acetylcholine),[178] dopaminergic (D_2),[179] and sigmaergic (σ_1) receptors.[180] The second class of drugs affecting neurotransmitter systems includes acetylcholinesterase inhibitors (such as rivastigmine, galantamine, and donepezil) that raises the levels of acetylcholine, which are reduced in AD,[181] thereby stimulating presynaptic and postsynaptic muscarinic and nicotinic receptors and leading to an improvement of cognitive function in mild to moderate AD patients.[182,183] However, still, new drugs are under clinical trials, which target neurotransmitter signaling (Table 2 and Figure 2).

2.5. Mitochondrial dysfunction in AD

The mitochondrion is the critical organelle in neurons, which has numerous functions, such as ATP generation, control of energy efficiency, reactive oxygen species (ROS) generation, apoptotic signaling, and calcium homeostasis.[35,184] It has been reported

that mitochondrial transport decreased in AD brain.[35,185] As a result, mitochondrial dysfunction is a primary and early event in pathological cascade of AD.[35,185] The normal physiological function of mitochondria depends on their intact structure needed to maintain the electrochemical gradient. However, structurally damaged mitochondria with the lost internal structure and change in morphology have been observed in AD brain.[186–188] Furthermore, mitochondria found in AD brain are characterized by the reduced efficiency of ATP production, increased levels of ROS and oxidative stress, lost Ca^{2+} buffering capacity, and released pro-apoptotic factors eventually leading to the induction of apoptosis. All these factors trigger apoptosis of neuronal cell by associating with various cytoplasmic factors.[184] Studies in yeast have been reported that cellular proteostasis is maintained by mitophagy and mitochondrial proteases and their dysfunction leads to protein misfolding disease.[187] Mitochondria may combine growth signaling and nutrient signaling pathways to regulate energy production and Ca^{2+} homeostasis and regulate apoptosis.[189] Functional mitochondrial abnormalities, which include the aberrant respiratory chain, defective enzyme activity, impaired energy metabolism, generation and accumulation of ROS, increase in the BACE-mediated cleavage of Aβ, increased brain amyloidosis, increase in generation of NFTs, dendritic arborization, disturbance in oxidative phosphorylation (OXPHOS), impaired Ca^{2+}-signaling, increased mtDNA mutations, defective mitochondrial bioenergetics, mitochondrial dynamics, and mitochondrial trafficking, are all known to play a key role in AD pathogenesis.[49,184,187,190–200] Evidence suggested that progressive accumulation of mitochondrial Aβ can be associated with the mitochondria-mediated toxicity. It has also been suggested that mitochondria may play a central role in Aβ-induced oxidative damage and neuronal damage. Transfer of the intracellular Aβ into mitochondria occurs via a receptor-dependent pathway. Furthermore, intra-mitochondrial Aβ accumulation directly affects mitochondrial respiratory enzyme activity (Table 1) and leads to the mitochondrial dysfunction followed by the neuronal damage.[192] It has also been reported that hyperphosphorylated Tau and NFTs in AD patient causes mitochondrial dysfunction and axonal transport inhibition.[201]

Mitochondrial ROS (Table 1) can increase the Aβ level, and Aβ can interact with mitochondria, which eventually cause mitochondrial dysfunction.[202] In EOAD, mitochondria produce O_2* and H_2O_2 free radicals that inhibit cellular ATP generation, whereas in LOAD, Aβ generation increased by the enhanced BACE activity followed by the Aβ entry to the mitochondria generates free radicals and disturbs electron transport chain (ETC), which decreases ATP, leading to the nerve cell damage and cognitive impairment.[194] In addition to Aβ, overexpressed and aggregated Tau are also involved in disturbed mitochondrial transport.[203] Mitochondria play a critical role in both necrotic and apoptotic cell death, and its dysfunction is an early feature of AD.[192] Indeed, mitochondrial trafficking is crucial for the function and development of synapses and dendrites growth, which are observed to be impaired in the AD brain.[204,205] Furthermore, AD brains have been observed with the increased mitochondrial autophagy due to the autophagosome accumulation.[206,207] Mitochondrial fission and fusion are critical for the normal function of this organelle, which seems to be disturbed in AD.[196,208] The components of γ-secretase complex have been found in mitochondria and further studies are required to confirm its association with AD pathogenesis.[188] During mitochondrial dysfunction, autophagy plays important role

for maintaining cellular homeostasis through the clearance of dysfunctional mitochondria through autophagic process (mitophagy).[209] The agents that improve mitochondrial function and protect the neuronal cell from the death caused by the mitochondrial dysfunction could be a potential therapy against AD.

2.6. Endoplasmic reticulum stress in AD

The endoplasmic reticulum (ER) is involved in various cellular processes, such as maintenance of Ca^{2+} balance, protein folding, and quality control of nerve cells. ER stress can induce environmental and genetic insults. Interestingly, all the elements of ER stress can alleviate AD pathology.[210] ER consists of stress sensors (such as serine/threonine-protein kinase/endoribonuclease IRE1, PRKR-like endoplasmic reticulum kinase (PERK), and cyclic AMP-dependent transcription factor ATF-6 alpha (ATF6)) that recognize protein misfolding in ER and produce unfolded protein response (UPR). UPR is a protective cellular mechanism of ER against stress response. Conversely, prolonged UPR activation leads to the apoptotic neuronal death. Extensive activation of UPR has been observed in the AD brain. Interestingly, UPR is activated in nerve cells, but not in the glial cells of the AD brain.[210] It was observed that phosphorylated UPR proteins, such as pPERK, peIF2α (eukaryotic translation initiation factor 2 subunit 1), and pIRE1α were increased in the AD brain neurons.[211] Under ER stress condition, the UPR-related proteins are hyperphosphorylated that leads to their dysfunction and death of nerve cell.[212,213] Furthermore, ER stress may aggravate the effects of a mutation in PSEN1, APP processing, Aβ production, and accumulation, as well as tau phosphorylation followed by the neuronal death.[214–216] Typically, PSEN1 mutation generates Ca^{2+} imbalance in the ER lumen and disturb ER homeostasis.[212] The reduced Ca^{2+} level in ER results in the dysfunction of the protein folding process that elicits prolonged UPR activation.[217] In agreement with these findings, Mota *et al.* observed the presence of ER stress markers and impaired ER Ca^{2+} homeostasis in the neurons of AD brain.[216] Additionally, ER stress also induces inflammatory responses via the inflammatory caspase-induced signaling pathways and causes inflammation of nerve cell.[210,212] A large body of evidence indicates that pathological condition of the AD, such as impaired Ca^{2+} homeostasis, oxidative stress, apoptotic cell death, intracellular Tau, and extracellular Aβ deposition may be caused by the ER stress and vice versa.[210] Study by Abisambra *et al.* demonstrated that the accumulation of tau interferes with ER-associated degradation and triggers activation of the UPR that represents tau disrupts protein quality control in the ER.[218] Furthermore, Murakami *et al.* reported that response to ER stress could be localized to the dendrites that may provide a link to axonal degeneration and synaptic loss.[219]

There is also a connection between ER stress/UPR activation and autophagic pathology in AD brain. A recent report shows that ER stress activates autophagy but not the UPS in the neuronal cells suggesting that autophagy is the key degradational pathway following the activation of UPR.[220] ER stress and autophagy play an important role in regulating brain function. Recent studies have suggested that these UPR signals may be linked to autophagy. There is evidence that autophagy ameliorates ER stress by eliminating accumulated misfolded proteins. Both abnormal UPR and impaired autophagy have been implicated as a causative mechanism in the development of various neurodegenerative

diseases.[221] Nijholt *et al.* observed the connection between UPR activation and autophagy in AD brain. Furthermore, they also reported that ER stress activates autophagy but not the proteasome in neuronal cells suggest that autophagy is the key degradational pathway following UPR activation.[220]

2.7. Oxidative stress-related signaling in AD

Oxidative stress is the condition of imbalance in the production of antioxidants and free radicals, such as ROS and reactive nitrogen species (RNS), that plays a critical role in neurodegeneration and cognitive impairment.[222–224] Importantly, brain is highly prone to oxidative stress since it is highly rich in lipid content and consumes a large amount of oxygen which leads to increased ROS production. Additionally, neuronal membranes are rich in polyunsaturated fatty acid that makes them more susceptible to ROS.[225] At the cellular level, oxidative stress occurs from a variety of sources, such as mitochondrial dysfunction, and leads to oxidation of lipid, protein, and DNA damage.[226] An indication of oxidative stress in the AD has been displayed through oxidation of nuclear and mitochondrial DNA, oxidation of lipids and proteins, advanced glycation end products and the formation of toxic species such as peroxides, alcohols, and aldehydes.[227–231] However, it is still unclear what can serve as an exact source of the oxidative source in AD,[232] although mitochondrial abnormalities in the AD are considered as the main source of oxidative stress.[232] Memory impairment is associated with a decrease in the defense activity of the brain and plasma antioxidants.[233] Evidence shows that there is a strong correlation between the levels of antioxidant enzymes, lipid peroxides, Aβ plaques, and NFTs in AD.[234,235] Oxidative stress mediates abnormal aggregation of Aβ and Tau proteins, facilitates Tau hyperphosphorylation, which further produces neuronal damage by additional ROS generation. Furthermore, it was also reported that cells with the excess levels of Tau protein have a higher susceptibility to the oxidative stress.[236] The effect of the presence of imbalanced oxygen radicals is massive oxidative damage of various biological molecules, which is found in AD, such as lipid peroxidation, the formation of adduction products, free carbonyls, advanced glycation end products (AGEs) and nitration.[235,237,238] AGEs are commonly found in amyloid plaques and are responsible for the nerve damage and pathogenesis of AD. Furthermore, extracellular aggregation may be caused by the enhanced oxidation of the glycated proteins.[226,239] AGEs are responsible for cross-linking of Aβ peptide that leads to the formation of Aβ fibril and eventually plaque formation, followed by the neuronal cell death by ROS and cytokines. Additionally, AGEs are also involved in nerve cell death by direct (chemical) and indirect (cellular) free radical production, which further elevates oxidative stress levels.[226] DNA strand damage was also reported to increase the levels of free carbonyls in neurons and glia of AD brain.[240] Fascinatingly, numerous antioxidants produce a significant improvement of memory and cognition in an animal model of AD.[232] Neuronal stress produces ApoE4, which is cleaved into neurotoxic fragments that induce an effect on neuronal Aβ production and clearance, also produces mitochondrial dysfunction.[11] Accumulation of misfolded amyloid protein activates UPR through ER stress kinase. Phosphorylation of signaling protein eIF2α affects synaptic function and cognitive process, whereas the IRE1α/JNK pathway may feed forward to the enhanced deposition of the amyloid protein.[241] Oxidative stress is associated with mitophagy in AD and other neurodegenerative diseases. Reactive nitrogen species (RNS)

and ROS act as inducer of autophagy or mitophagy which has protective roles in cell survival.[242] Therefore, regulating the balance between oxidative stress and autophagy may provide better treatment for AD. The drugs have completed preclinical assessment for AD, such as Dantrolene, Edavorene, and GSK2606414, which act by inhibiting activation of PERK to ameliorate proteotoxic reactions.[203] Some drugs are in different phases of clinical trials that targeting oxidative stress (Figure 2) such as ARC-031, Lu-AF-20513, curcumin, quercetin, nilvadipine, SK-PC-B70M, HX-106, EGCG (Table 2). These drugs are showing effective treatment in AD patients and more drugs must enter in clinical trial targeting oxidative stress.

2.8. Neuroinflammatory signaling in AD

Although neuroinflammation is known to play a remarkable role in the AD, the debate is still going on whether it is harmful or protective. In the body, inflammation is generally intended to be protective. However, excessive inflammation and chronic response may lead to cell damage and various pathological developments.[243,244] The ROS formation, enhanced activation of microglia and other immune cells, nuclear factor kappa B (NF-κB), and expression of cytokines are associated with neuroinflammation in AD.[244,245] Misfolded/aggregated proteins trigger innate immune response characterized by the release of inflammatory mediators by binding to microglia/astroglia. Importantly, Aβ peptide promotes microglial and astrocytes activation through the action of scavenger receptors, chemokine receptors, and generates inflammatory mediators.[246,247] Microglia and astrocytes play a pivotal role in neuroinflammation by releasing various pro-inflammatory elements, such as chemokines, IL-2β, IL-6, IL-12, INF-γ, TNF-α, NO, ROS, and O_2^- (Table 2) causing oxidative stress, nerve cell necrosis, apoptosis, and dysfunction of neurons. Hence, this pathway could represent a risk factor for SAD.[38–40,248] Senile plaques and NFTs are physically associated with inflammatory markers, such as C-reactive protein (CRP) and transforming growth factor beta (TGFβ), that generate neuroinflammatory stress.[249,250] The chronic activation of microglia is associated with the increased Aβ level followed by hyperphosphorylation of Tau and production of NFTs.[247] Excitotoxicity or neuronal stress leads to the increased APP expression and increased release of sAPP. Eventually, enhanced production of Aβ and sAPP activates microglia to release IL-12 and IL-23, which bind to microglial receptors P19 and P40 that enhance the release of IL-1β. IL-1β again causes an increase in the APP level, which further enhances Aβ plaque production in the brain.[251] Glial cells express a family of TLRs and CD14, which play a central role in the innate immunity that activates transcription factor NF-Kβ and leads to the release of the pro-inflammatory cytokines. Interestingly, both receptors are critical for the interaction of glial cells with Aβ and the release of pro-inflammatory cytokines.[252–254] The pro-inflammatory cytokines, such as IL-1, enhance the APP synthesis and amyloid deposits and stimulate further cytokine production by activation of microglia. The specific cytokines IL-1, IL-3, IL-6, and TNF-α, have been reported to be elevated in brain tissue homogenates from the AD patients, and heightened IL-1 immunoreactivity has been detected in the CSF of the AD-afflicted individuals.[255,256] Reports also suggest that autophagy/mitophagy reduces neuroinflammation in the brain and increases microglial phagocytosis.[257] Thus, agents acting via modulation of autophagy may reduce autophagy and act as a promising therapy for AD. Several drugs investigated for AD, such as Ginkgo biloba, resveratrol,

and cerebrolysin, have been examined for their anti-inflammatory activity in AD.[258–260] Furthermore, the preclinical studies on the animal models of the AD and numerous clinical trials with the long-term use of non-steroidal anti-inflammatory drugs (NSAIDs) show reduced Aβ accumulation and are associated with the decreased risk of AD.[247,261] Human intravenous immunoglobulins (IVIgs) obtained from the pooled plasma of healthy blood donors, which are in phase-III clinical trial, were shown to reduce the harmful inflammatory processes as well as enhance Aβ clearance.[11,262]

2.9. Ubiquitin-dependent proteasomal system in AD

Abnormal/misfolded proteins are processed by cellular quality control systems such as molecular chaperones, ubiquitin-proteasome system (UPS), and Autophagy.[42,263] UPS is the ubiquitin-dependent proteolytic system, which degrades 80–90% of normal as well as abnormal/misfolded intracellular proteins.[264,265] The inhibition of proteasome function leads to the accumulation of cellular waste/misfolded proteins such as Aβ and Tau (Figure 1A **right panel**).[266] Conversely, accumulated misfolded proteins also inhibit proteasome function, thereby leading to AD.[42,267] Aβ self-aggregates into oligomers that inhibit the proteasomal pathway and stimulate the formation and accumulation of hyperphosphorylated Tau.[42] Recently, different studies have reported that UPS affects the AD pathogenesis.[268,269] UPS works with three families of the ubiquitination-related enzymes, such as E1 (ubiquitin activating), E2 (ubiquitin conjugating), and E3 (ubiquitin ligating) enzymes.[42] In the neuronal cell, UPS is a large ATP-dependent proteolytic machine having an important role in the progression of the protein-misfolding-related diseases. The 26S proteasome consist of one 20S core particle and two 19S regulatory particles.[264] Importantly, misfolded proteins are recognized and degraded by the 26S proteasome via the sequential process that includes misfolded protein ubiquitination, deubiquitination, and unfolding followed by cleavage in the 20S core with the proteolytic enzyme activity (Figure 1A **left panel**).[263,270] Proteasome degrades Aβ and Tau. However, it has also been reported that $A\beta_{40}$ binds inside the 20S proteasome and inhibit its chymotrypsin-like activity. Additionally, Tau accumulation also inhibits 26S proteasome and reduces abnormal protein degradation.[42,271–273] In AD brain, the accumulation of ubiquitin-protein-conjugates (mutant UBB+1) is first observed in NFTs.[274,275] Furthermore, PHFs of Tau proteins are also reported as being involved in the impairment of proteasomal activity.[276] It has also been proposed that the accumulation of mutant ubiquitin, oxidation of specific deubiquitinating enzymes (DUBs), and down-regulation of E1 and E2 enzymes may lead to the neurodegeneration and AD.[42,277] Recent study has been reported that the disturbance in polyubiquitination of the protein is associated with neurodegeneration in AD.[278] Importantly, UPS plays a critical role in synaptic plasticity, and evidence also proved synaptic dysfunction in AD brain.[42] Over-expression of APP mutant isoforms is associated with the decrease in UPS activity.[279] UPS is also responsible for the degradation of mutated presenilin, which is the main culprit in the development of AD.[280] Moreover, evidence suggest that altered proteasome activity activates autophagic process.[257] The ubiquitin-specific hydrolase UCHL1 involved in the modulation of autophagosome-lysosome fusion[281] indicates that these both pathways are depending on each other's effect. Thus, targeting drugs for activation of UPS may provide better therapeutics against AD. Resveratrol is in Phase III clinical trial that restores proteasomal activity against Aβ accumulation (Table 2). Furthermore, Betulinic acid, IU1,

and PAP1 stimulate proteasomal activity, which has completed preclinical assessment against AD.[203]

2.10. Autophagy and endosomal-lysosomal system in AD

The lysosome is a digestive organelle that facilitates the clearance of mutant and aggregated Aβ and reduces its aggregation.[282] In this pathway, Aβ and Tau aggregates are entrapped or generated in endosomes, and then autophagic vacuole is delivered to the lysosome for its degradation by lysosomal enzymes (Figure 1B **left panel**).[283] Interestingly, increase aggregation of Aβ and Tau inhibits autophagy and endosomal-lysosomal system and, subsequently, decreases the clearance of Aβ and Tau (Figure 1B **right panel**).[284] Alteration in the endocytic pathway leads to increase in the cellular density of lysosomes and alters expression of genes, which enhance the level of lysosomal hydrolases.[282] Endocytic vacuoles enriched with PSEN1 and APP can produce Aβ. Typically, the elevated APP levels can alter endosomal function.[285] Lysosomal degradation has two different routes. One is the endocytic pathway, which degrades extracellular abnormal/aggregated proteins, and second is the autophagic pathway, which degrades intracellular aggregated proteins.[41]

It was also pointed out that the macroautophagy function is impaired during the AD. PSEN1 play a key role in autophagy, and some FAD-linked PSEN1 mutations have loss of function effect on macroautophagy leading to the accumulation of autophagy vacuoles (AVs) and to the impaired protein turnover. Typically, increased autophagy induction and defective clearance of Aβ-aggregates create conditions favorable for Aβ accumulation in AD.[207,286] Abnormally accumulated Aβ peptide has been reported in the autophagy-endosomal-lysosomal vesicles. Importantly, the lysosomal activity modulators show a good effect in the treatment of neurodegeneration.[42,287] Defective endosomal sorting and lysosomal function may work together with intracellular (endosomal) Aβ accumulation. Therefore, dysfunction in endocytosis seen in the AD brain represents a possible basis for the accelerated β-amyloidogenesis in the more than 90% of all AD cases.[288,289] It has been observed that stimulation of lysosomal activity in TgCRND8 mice caused a noticeable reduction of the Aβ levels by enhancing Aβ clearance via the autophagic pathway.[279] One of the key players in the regulation of autophagy is the serine/threonine kinase known as mammalian target of rapamycin (mTOR). Activation of mTOR is associated with inhibition of autophagy, decreased Aβ clearance, enhanced Aβ generation and deposition by modulating the APP metabolism, upregulating β- and γ-secretases, and thereby causing the AD pathogenesis.[290,291] In fact, alteration of mTOR signaling and autophagy have been reported to occurs at the early stages of AD.[292] mTOR is the downstream effector in Akt/PTEN signal transduction pathway and disturbance in the coordination of Akt and PTEN signal transduction is linked with AD.[293] Rapamycin is a mTOR inhibitor that ameliorates the AD-like cognitive deficit by activating autophagy and inhibiting Aβ accumulation.[282] AMP-activated protein kinase (AMPK) is the regulator of cellular energy homeostasis is also reported to be engaged in the AD pathogenesis. AMPK activation decreases mTOR activity leading to facilitation of autophagy and promoting lysosomal degradation of Aβ (Figure 1B **left panel**).[294] Maintaining cellular homeostasis by boosting autophagy-lysosome pathway, enhancing lysosomal hydrolase activity, and improving retrograde axonal transport of endolysosomes may protect brain against neurodegeneration.

Nilotinib is currently being tested in a phase II trial for AD that can augment the autophagic machinery by increasing levels of parkin, E3 ubiquitin ligase.[295] Small molecules associated with regulation of autophagy and endosomal-lysosomal pathways, such as Rapamycin, Temsirolimus, Arctigenin, GTM-1 (act by mTOR inhibition), and Trehalose (act by AMPK activation), have completed preclinical assessment for AD.[203]

2.11. Protein misfolding and molecular chaperones in AD

Molecular chaperones are the most decisive components of the cellular protein quality control system that acts as a first-line defense against protein misfolding and aggregation.[42] Molecular chaperones assist in the folding and refolding of damaged proteins, prevent protein misfolding, and target severely damaged proteins to degradation.[296] Perturbed proteostasis manifested in protein misfolding and formation of toxic aggregates within affected neurons is the important feature of AD pathology. In fact, the misfolding of proteins leads to the formation of toxic aggregates that produces neurotoxicity via cellular stress pathways.[297] In response to that, the ER activates the UPR that leads to the up-regulation of ER molecular chaperones and folding enzymes that play a vital role in unfolding and refolding of the misfolded proteins to their natural states or directing them to degradation. In this way, molecular chaperones have a very crucial role in the diseases associated with neurodegeneration and protein misfolding.[296,298] The heat shock proteins (HSPs), such as HSP60 and HSP70, are the main classes of chaperones that prevent the accumulation of misfolded conformers and inhibit intermolecular aggregation.[296] The mammalian brain expresses over 200 different chaperones and co-chaperones that are found mainly in the nucleus, cytoplasm, and cellular organelles, which are then tailored due to cellular stress. In addition to that, each cell type expresses different sets of chaperones and co-chaperones.[299,300] Chaperones are classified into six conserved classes according to their molecular size or function: HSP40, HSP60, HSP70, HSP90, HSP100, and the small HSPs (HSP10, HSP27, 15 to 30 kDa).[299] HSP70 and HSP90 inhibit the formation of Aβ and its aggregation.[296] HSP40 acts as co-chaperones of HSP70 and maintains ATPase activity important for HSP70. HSP90 is the most abundant molecular chaperone in the cell that plays a vital role in controlling protein misfolding and maintains cell cycle, as well as cell growth and development, and other essential activities of the cell. Furthermore, HSP90 activates more than 200 HSP90-client proteins required for cell signaling. HSP100 is also bound to the aggregated or misfolded protein to ensure correct folding. Aβ and Tau are the two misfolded proteins in AD, and HSP70 and HSP90 interact with both of these proteins and degrade them through UPS.[299] Surprisingly, few protein aggregates are degraded by the lysosome based on the size of aggregates, the degree of misfolding, and peptide sequence and other aggregates are selectively tagged by ubiquitin for the proteasomal degradation. HSPs help to degrade the proteins by carrying them to the UPS.[299] Dou *et al.* reported the reduced formation of NFTs and reduced accumulation of misfolded and aggregated proteins after up-regulation of molecular chaperones in the brain.[301]

Extracellular chaperones such as clusterin, haptoglobin, and alpha-2-macroglobulin (α2M) have been reported to inhibits misfolded protein aggregation.[302] Clusterin interact with amyloidogenic proteins at their aggregation states such as prefibrillar states and mature fibrils. Further studies have shown that clusterin suppresses especially the elongation step

of $A\beta_{42}$ aggregation.[303] Additionally, the molecular chaperone of Brichos family (proSP-C Brichos) shows $A\beta_{42}$ aggregation inhibition by suppressing secondary nucleation. Combined used of Clusterin and Brichos shows additive effect on $A\beta_{42}$ aggregation inhibition[303] Anavex 2–73 is a small molecule that inhibits the intracellular sigma-1 chaperone protein and has completed phase II clinical trial for the treatment of AD [https://www.labome.com/method/Alzheimer-s-Disease-Clinical-Trials.html]. Curcumin was shown to promote the increase in the Hsp70 and Hsp90 activity that inhibited or delayed amyloid formation and reduced neurodegeneration[42] PU-DZ8 (HSP90 inhibitor), and YM-08 (HSP70 activator), which acts by reducing accumulation of Tau protein in the brain, have completed preclinical assessment for an AD.[203] Minimizing protein misfolding and aggregation by targeting chaperones and components of the UPR system is the promising therapeutic approach for the development of anti-AD drugs.

2.12. Insulin signaling in AD

Insulin resistance is associated with insulin receptor (IR) internalization, reduced IR activity, tumor necrosis factor receptor (TNFR) activation, glycogen synthase kinase three beta (GSK-3β) activation, reduced IDE activity, and increased levels of the inhibitory serine phosphorylation.[304,305] Impaired insulin signaling and glucose distribution, as well as hyperinsulinemia, are among the critical risk factors for the AD. The decrease in glucose metabolism and increased radio-ligand uptake detect abnormal deposits of Aβ protein on Positron Emission Tomography (PET).[11] However, debates are still going whether AD impairs insulin signaling or insulin resistance produces AD.[306] Additionally, altered insulin signaling, inflammation, and distorted metabolism are key features of both AD and diabetes mellitus (DM).[307] Many pieces of evidence have shown that decreased level of insulin in cerebrospinal fluid (CSF) and reduced expression of IRs are observed in AD.[308,309] Insulin and insulin-like growth factor 1 (IGF-1) plays a pivotal role in CNS by regulating learning, memory, and neuronal survival. The condition of hyperglycemia increase peripheral insulin utilization and results in the reduction of the levels and transport of insulin in the brain. Defective insulin signaling also leads to the neuronal energy deficit and generates other metabolic insults. Insulin resistance stimulates GSK-3β activity that enhances the hyperphosphorylation of Tau and causes oxidative stress. In its turn, oxidative stress again generates mtDNA damage and mitochondrial dysfunction, and triggers the nerve cell apoptosis, and leads to dementia.[47] Brain is an insulin-sensitive organ.[310] Intranasal administration of insulin reported with improvement in learning and memory in animal AD models and humans.[311,312] In a normal brain, insulin binds to its receptor, which causes phosphorylation of insulin receptor substrate 1 (IRS-1). This triggers activation of PI3-K and AKT that inhibits activation of GSK-3β and results in the synaptic plasticity, memory and cognition. Moreover, IDEs also degrades accumulated Aβ.[304] In the AD, aggregation of Aβ leads to the TNF-α activation that activates TNFRs, followed by activation of stress kinases, such as c-Jun N-terminal kinases (JNKs), resulting in the inhibitory serine phosphorylation of IRS-1, which inhibit PI-3K and AKT activation leading to the GSK-3β activation followed by the Tau hyperphosphorylation and NFTs formation.[304] Interestingly, Aβ oligomers also facilitate internalization of IRs through CK2/CaMKII pathway, resulting in reduced levels of IRs on the cell surface.[304,313–316] Typically, insulin resistance decreases the level of IDE, which further reduces Aβ degradation. Collectively, all these events

result in the impairment of nerve growth, learning, memory, and synaptic plasticity.[304] It was reported that decrease PI3K/AKT-mediated activation of glucose transporters (GLUTs) and their decreased expression in the AD could produce glucose hypometabolism.[47] In addition to the removal IRs from cell surfaces, Aβ oligomers increase TNF-α and activate various stress kinases, such as JNK, protein kinase R (PKR), and IκB kinase (IKK), cause inhibitory serine phosphorylation.[317] Faulty activation of N-methyl-D-aspartate receptors (NMDARs) by Aβ-oligomers leads to the increase in the Ca^{2+}influx that results in the augmented excitotoxicity, oxidative stress, disturb signaling, and impairs synaptic plasticity.[307] Inhibition of IRS-1 has been observed in a transgenic mouse model of AD.[318] On the other hand, glucagon-like peptide-1 receptor (GLP-1R) activation may provide neuroprotection against the AD.[319] Hence, insulin and GLP-1R agonists are now in the clinical trial for the AD treatment. Exendin-4 is one of the GLP-1R agonists that has been reported to restore impaired brain insulin signaling and decrease Aβ accumulation, as well as improves cognition.[318,320,321] The administration of intranasal insulin (INI) to reduce brain insulin resistance is under evaluation. Disturbance in biliverdin reductase-A (BVR-A) level leads to insulin resistance in AD.[322] Recent study by Barone *et al.* reported that INI stimulates insulin signaling by activating BVR-A.[323] Impaired glucose metabolism associated with the accumulation of advanced glycation end products (AGEs) stimulates Aβ accumulation and NFTs formation, which further causes mitochondrial dysfunction and oxidative stress.[306]

Normal insulin signaling is important for neuronal development, survival, and synaptogenesis.[324] In AD, insulin signaling is defective and coincident with the abnormalities associated with reduced levels of IRS mRNA, Tau mRNA, IRS-associated PI3-K, phospho-Akt (activated), increased GSK-3β activity, and formation of NFTs and Aβ plaques.[25,304,325–327] The decrease in the neuronal glucose metabolism particularly in temporoparietal and frontal association area, due to the blood-brain barrier and cerebral microvasculature alterations, reduces energy production in the brain, reduces levels of Tau O-Glc-N-acylation, affects the production and clearance of Aβ and Tau phosphorylation, and leads to neurodegeneration and AD.[328–330] The insulin resistance is linked to autophagy, where autophagy protects pancreatic β-cells from apoptotic cell death and preserves their structure and function. Therefore, insulin resistance can be inhibited by activating autophagy.[331]

Furthermore, insulin deficiency may distort cholesterol metabolism in the brain.[332] Cholesterol regulates both generation and deposition of Aβ, with elevated cholesterol increasing Aβ levels in the AD.[333] The ε4 variant of the apolipoprotein E (APOE4) is the important component and regulator of the very-low-density lipoprotein (VLDL) homeostasis, serve as principal cholesterol carrier in the brain and are among the major genetic risk factors for the AD.[334,335] Soluble Aβ interacts with APOE associated with VLDL particle, and this interaction promotes Aβ aggregation into the amyloid fibrils[52] (see below for further discussion of a correlation between the distorted cholesterol metabolism and AD).

2.13. Altered lipid/cholesterol metabolism in AD

The brain contains highest (20% of the total body) cholesterol level, where it serves as the key component of the nerve cell membrane and is required for the receptor-ligand interactions, synaptic function, normal neuronal development, and physiology.[52,53] The disturbance in lipid metabolism results into abnormal levels of certain lipids in the plasma, brain and cerebrospinal fluid.[336] Importantly, the formation and clearance of Aβ are regulated by cholesterol.[52] It has been reported that the high levels of cholesterol in the midlife may increase the risk of AD pathology.[337] Studies of the cellular and animal AD models with high cholesterol levels revealed the increased production and aggregation of Aβ peptide.[52] Various biochemical, molecular, AD model data suggested that alterations in ApoE, which is the key apolipoprotein in plasma and brain, may induce AD pathology.[52] Kuo *et al.* reported that individuals with ApoE4 genotype demonstrated an increase in susceptibility to AD due to high cholesterol level.[338] It is not surprising that hypercholesterolemia and atherosclerosis increase the risk of the AD due to the presence of high cholesterol levels in these conditions.[52,339] ApoE and cholesterol metabolism are strongly involved in deregulation, biogenesis, and assembly of Aβ protein. Typically, ApoE interacting with the high-density lipoprotein (HDL)-like particles (which are a heterogeneous group of lipoproteins composed of various lipids and proteins and that act as an important player in the reverse cholesterol transport pathway) inhibits aggregation of Aβ. Conversely, free ApoE enhances Aβ aggregation.[74] LRP (low-density lipoprotein (LDL) receptor-related protein) is a multi-ligand receptor that interacts with the Kunitz-type proteinase inhibitor (KPI) domain of $APP_{751/770}$ and enhances the internalization of Aβ.[340] ApoE binds to Aβ and stimulates internalization of Aβ by binding with the LDL receptor.[341,342] Cholesterol is first released into a cell, then, is incorporated into intracellular membranes, where it stimulates machinery responsible for the APP processing leading to Aβ production and aggregation.[52] Habchi *et al.* recently demonstrated that cholesterol associated with lipid membranes can efficiently accelerate $Aβ_{42}$ aggregation by increasing its primary nucleation rate by up to 20-fold.[343] In addition, recent study on FAD PS1 ΔE9 cells shown that the elevated cellular cholesterol level is associated with the disturbed APP processing.[344] Jin *et al.* reported the presence of AD symptoms such as brain atrophy, brain metabolic and structural changes in high cholesterol fed rabbit.[345]

ApoE-linked Aβ moves into the endocytic lumen. Typically, Aβ entry inside the cell does not necessarily lead to its breakdown.[52] Aβ gets released from ApoE and aggregates in the endocytic lumen and then is secreted outside the cell in the more toxic form.[342] In comparison with other ApoE isoforms, lipid-free ApoE4 significantly enhances Aβ fibril formation.[346] Furthermore, lipid rafts, which are membrane domains enriched in the cholesterol, promote interaction of APP with β-secretase, which is considered as the primary culprit for Aβ generation. Therefore, disturbance in the integrity of lipid rafts may affect numerous signaling pathways and generates neuronal death.[53] For maintaining the cholesterol homeostasis in brain, it is converted into 24(S)-hydroxycholesterol (24OHC). However, several studies reported enhancement in level of 27(S)-hydroxycholesterol (27OHC) and reduction of 24OHC in the AD brain.[347] Enhanced cholesterol levels reduce the efficiency of degradation processes, such as autophagy. Fusogenic ability of autophagosome and lysosome is disturbed due to the cholesterol-enrichment within the

endosomes-lysosomes.[348] Consequently, maintaining normal cholesterol level can enhance autophagy-mediated degradation of Aβ aggregates in AD brain.

Recently, a clinical trial has been started to test the effects of lowering of neuronal cholesterol levels as a means for the treatment of AD (Table 2).[52] The corresponding agents reducing cholesterol levels are showing promising results against the AD. Therefore, cholesterol-lowering agents, such as statins and Acyl CoA: Cholesterol O-acyl transferase (ACAT) inhibitors could become valid agents for the prevention and treatment of AD.[52] For example, statins were shown low cellular cholesterol levels that favored the α-secretase APP processing pathway leading to the decreased Aβ production and secretion.[349–355] Thus, targeting statins to reduce cholesterol level could be a potential target for AD.

2.14. Calcium signaling in AD

Perturbed cellular Ca^{2+} regulation is the critical and early event associated with the AD pathogenesis.[356] Ca^{2+} is an important regulator of the various neuronal processes associated with extracellular stimuli and intracellular responses.[357] The Ca^{2+} regulates numerous cellular processes that are crucial for the normal neuronal function, such as neuronal physiology, growth, differentiation, neurotransmitter release, generation of the action potential, membrane excitability modulation, ATP production, cognition, as well as short-term and long-term synaptic plasticity.[49] The Ca^{2+} signals are maintained by process such as store-operated Ca^{2+} entry (SOCE) and its dysregulation leads to perturbed intracellular Ca^{2+} signaling in neuronal and glial cells.[358] Recent studies in AD mouse models reported that the downregulation of neuronal store-operated calcium entry (nSOCE) is associated with disrupted postsynaptic contacts and memory formation.[359] Thus, activation of nSOCE could be a potential target for AD therapy. Additionally, deregulation of the Ca^{2+} homeostasis creates the Ca^{2+} overload in the nerve cell, which results in the mitochondrial dysfunction and neuronal cell death. Furthermore, abnormal Ca^{2+} efflux from ER and mitochondria in various neurodegenerative diseases has been reported.[48,49] The abnormal accumulation of Ca^{2+} in the synaptic region was also linked to the impaired Ca^{2+} regulation.[360] Increased $A\beta_{42}$ level, disturbed Ca^{2+}signaling, and aberrant expression of Ca^{2+}signaling proteins have been reported in the animal models of a FAD as well as found in the samples of the post-mortem sporadic AD brain.[49] Collectively, inhibitors and stabilizers of Ca^{2+} signaling are potential drug candidates in AD treatment.[49]

Presenilin interacts with the inositol trisphosphate receptor (InsP3R),[361] which is a membrane glycoprotein complex acting as an inositol trisphosphate (InsP3)-activated Ca^{2+} channel. This presenilin-InsP3R interaction modulates the gating activity of this Ca^{2+} release channel.[361] FAD-associated mutant forms of PSEN1 and PSEN2 exert stimulatory effects on InsP3R channel activity that result in perturbed cellular Ca^{2+}signaling.[361] Evidence also suggests that the Aβ oligomers initiate neuronal cell damage by channel-dependent disruption of the integrity of plasma and intracellular membranes leading to the Ca^{2+}dyshomeostasis.[362] Disturbed amyloid metabolism leads to disturbance in Ca^{2+} signaling followed by neuronal hyperactivity.[363,364] Aβ fibrils generate glutamate-independent inward current, which further dysregulates Ca^{2+} homeostasis that induces neuronal cell death.[365] Blocking Ca^{2+} channels to reduce neuronal hyperactivity showing

effective treatment in AD patients and few Ca^{2+} channel blockers are in clinical trial for AD (Table 2).

2.15. Excitotoxicity in AD

Glutamate is a principle excitatory neurotransmitter in the brain that, being released from presynaptic terminals, mainly acts on the post-synaptic NMDA receptors. Excitotoxicity mainly occurs due to increased release and decreased uptake of glutamate neurotransmitter.[366] All the neurons in CNS contain the NMDA subtype of ionotropic L-glutamate receptors that can affect post-synaptic influx of Ca^{2+}.[367] Neurochemical and neuropathological studies of the early-stage AD brain showed the distortion in the L-Glu-mediated pathway.[367] Excessive activation of NMDA receptors by glutamate causes excitotoxicity followed by nerve cell death due to the excess release of glutamate in synapse and influx of Ca^{2+} inside the cell.[368] This results in the activation of catabolic enzymes, free radical generation, and mitochondrial dysfunction. Furthermore, hyperactive NMDA receptors and excessive release of glutamate enhance the production of pathogenic Aβ and Tau protein.[59] Extracellular Aβ and intracellular NFT deposition lead to the modification of the glutamate receptors and causes the excitotoxic neurodegeneration.[369] Therefore, although NMDA receptors are generally neuroprotective, their over-activation causes cell death. NMDA receptors can be found in both presynaptic and postsynaptic locations on the neurons. These differently located NMDA receptors might have very different physiological roles. One illustrative example of this phenomenon is given by the cAMP response element binding (CREB) protein, which is one of the cellular targets affected by the dysregulation of NMDA receptors.[370] CREB is the prototypical signal-regulated transcription factor that plays an essential role in the maintenance of LTP, learning, memory, and synaptic plasticity.[371,372] The activity of CREB is regulated by phosphorylation, changes in which can be triggered by a variety of cellular signaling events, such as an increase in intracellular Ca^{2+} via activation of NMDA receptors, or activation of receptor tyrosine kinase by growth factors. Here, synaptic NMDA receptors promote calcium entry leading to the induction of the CREB phosphorylation, whereas extrasynaptic NMDA receptors show the opposite effects and initiate the CREB shut-off pathway.[370] Transcriptional activity of CREB and associated LTP generation are decreased in AD mostly due to the Aβ-induced inactivation of PKA that leads to the decreased phosphorylation of CERB at residue Ser133.[370] Madeira *et al.* recently reported the increased in level of glutamate and glutamine in the CSF of AD patients. Thus, CSF measurements of glutamate/glutamine level may act as a biomarker for the detection of AD.[373]

The hypothesis in which Glutamate-mediated neurotoxicity is involved in the pathogenesis of AD is widely accepted, and drugs, such as memantine, which reduce the neurotoxic effects of glutamate, have therapeutic potential for AD.[374] Memantine is a non-competitive NMDA antagonist currently prescribed for the moderate-to-severe cases of AD.[76] The combined use of memantine with acetylcholinesterase inhibitor drugs found to be beneficial, since cholinergic and glutamatergic dysfunction occurs at early stages of AD.[375,376] Memantine is approved by USFDA and is in extensive clinical use in Europe since 1982 for the treatment of moderately severe to severe cases of AD.[377] Excitotoxicity is also linked to autophagy, in which hyperstimulation of non-NMDA glutamate receptors activates

lysosomal enzymes and induces autophagic process.[378] The drugs which can modulate different aspects of excitotoxic mechanism along with autophagic activation can prevent neurodegeneration and may provide beneficial therapy against AD.

2.16. Aberrant neurotrophic factor signaling in AD

The AD is also strongly associated with the deficits in the axonal transport and deregulation of several neurotrophic factors (NTFs). NTFs are small proteins that maintain nerve cell morphology, neurogenesis, synapse formation, neuronal survival, axonal guidance, as well as proper architecture and function of the brain during embryonic development.[51,379] NTFs are produced in neocortex and hippocampus then are reversibly transported to the basal forebrain containing cholinergic neurons, where they play a number of roles in maintaining functionality and survival of neurons.[51] Brain-derived neurotrophic factor (BDNF), nerve growth factor (NGF), neurotrophin-3 (NT-3), and neurotrophin-4/5 are the most eminent members of the mammalian neurotrophin family. However, reduced in the level of BDNF, NGF, and NT4/5 were reported in the hippocampus of AD patients.[379]

Pro-neurotrophins are first synthesized and bind to their receptor $P75^{NTR}$. Cleavage of pro-neurotrophins generates active neurotrophins, which bind and activate selectively one of three types of tyrosine kinase (Trk) receptors (TrkA, TrkB, or TrkC). NGF binds to TrkA receptor, BDNF and NT-4/5 bind to TrkB receptor, and NT-3 binds to TrkC receptors, which then lead to the accelerated downstream cell signaling.[51] Numerous studies demonstrated the involvement of BDNF and NGF in AD pathology.[51,380,381] It has also been reported that loss of the activity of NTFs may aggravate the effects of Aβ on the production of pathological conditions of dementia.[50] BDNF is widely distributed throughout the CNS and is a critical component required for the function and survival of cortical, hippocampal, dopaminergic and cholinergic neurons.[382,383] BDNF and TrkB stimulate LTP in the hippocampus, which is found to be reduced in the AD. LTP involves the formation of synapses at the dendrite spines of axonal collaterals.[50,384,385] It was recently shown that up-regulation of BDNF might rescue learning deficits and cognitive impairment in $Aβ_{42}$-induced AD.[385] Xiang *et al.* recently reported that the reduction in BDNF level induces Tau pathology by activating asparagine endopeptidase (delta-secretase) in AD.[386] Combined use of BDNF, NGF, and NT4/5 for the treatment of AD may be an attractive therapeutic perspective.

2.17. Alterations in Wnt/β-catenin signaling in AD

Wnt signaling is involved in various cellular key processes, such as survival, adhesion, proliferation, differentiation, and apoptosis taking place in neuronal as well as glial cells. Importantly, Wnt signaling regulates neuronal connectivity by controlling the formation of the synapses, axon remodeling, and dendrite morphogenesis.[54–56] Recent studies revealed that the demolition of the Wnt signaling components is prominently occurring in AD.[387–393] Granno *et al.* recently identified the downregulation of Wnt/β-catenin signaling in down syndrome hippocampus.[386] Wnt binds to its Frizzled (Fz) transmembrane receptors associated with the LRP5/6 or interacts with the atypical receptor tyrosine kinases RYK or ROR2, and IGF1R (tyrosine kinase receptor type 1 or IGF (insulin-like growth factor) receptor) and activates three different pathways, which play various roles in different

neuronal functions.[55,189] The first of these pathways is the Wnt/β-catenin or canonical Wnt pathway, which regulates transcription through β-catenin. The second pathway is the Wnt/Ca^{2+} or non-canonical pathway, which is modulated by intracellular Ca^{2+} release that regulates gene transcription. Finally, the third Wnt-based pathway is the Wnt/PcP-JNK or Wnt cell polarity pathway, in which the JNK plays a crucial role in cytoskeleton remodelling, dendrites development, and complexity.[394,395] It has been reported that Wnt modulates both pre- and postsynaptic regions of the mammalian nervous system and affects synaptic wiring and plasticity. Furthermore, Wnt signaling is responsible for the neuroprotection from the toxic effects of Aβ oligomers.[395] The FAD patient has been reported with the inherited form of AD caused by the PSEN1 mutation leading to the reduced β-catenin level.[148] The increased Wnt antagonist levels have been observed in the brain of AD mouse model.[396] Wnt secretes glycoprotein and regulates diverse function in neuronal development by receptor-mediated signaling pathways.

Typically, Wnt protein is required for cellular proliferation, development, neurogenesis, axon guidance, neuronal migration, dendrite development, and synaptic formation.[391,392,395] Interestingly, the neurotoxic effects of Aβ oligomers can be reversed by the Wnt ligands, such as Wnt-3a.[395] Direct binding of Aβ to CRD-Fz5, a Wnt-binding receptor, inhibited canonical Wnt signaling pathways and thereby revealed that Aβ is directly associated with the Wnt impairment.[393] Killick *et al.* reported that AD developed after the Aβ-driven up-regulation of various genes induced Clusterin/p53/Dkk1/Wnt-Pcp-JNK pathway. Evidence also suggests that Wnt inhibitor DKK-1 overexpression results in Tau hyperphosphorylation, β-amyloid toxicity, and cognitive deficits.[397] ApoE4 was reported to be inhibited in the canonical Wnt signaling pathway in the PC12 cells.[398] Wnt signaling activation inhibits GSK-3β that causes accumulation of β-catenin in the cytoplasm eventually leading to an increase in transcription of the Wnt target genes, which results in the neuroprotection.[387,391] Interestingly, Wnt signaling involves GSK-3β activation/inhibition, and therefore it is linked to autophagy. GSK3β inhibition leads to AMPK activation that decreases mTOR signaling and further enhances the activation of autophagy.[189] Several antioxidants, anti-inflammatory compounds, PPARα and γ agonists, and agents leading to the activation of the M1 muscarinic receptor and PKCare known to regulate Wnt/β-catenin signaling and promote neuroprotection against Aβ-driven pathology.[392]

2.18. Leptin signaling and AD

Recent studies revealed that the pleiotropic endocrine hormone leptin has diverse actions throughout the CNS and can be related to the link between obesity and AD.[57] Leptin is a peptide hormone secreted from peripheral adipocytes and brain is involved in glucose homeostasis and regulation of obesity, energy expenditure, and food intake.[58] Leptin produces neuroprotective effects by improving cognitive function, inhibiting Aβ production by inhibiting BACE1 and reducing GSK-3β-mediated Tau hyperphosphorylation. Additionally, leptin plays a role in controlling the neuronal morphology, hippocampal synaptic plasticity, synaptic transmission, and neurogenesis.[399] Under the normal conditions, leptin receptors are highly expressed in the brain areas associated with learning and memory, such as the hippocampus. Leptin produces its function by binding to leptin receptor (LEPR or OBR) that facilitates numerous signaling pathways, such as ERK pathway, PI3K/Akt/

mTOR pathway, and JAK/STAT pathway and regulates various cellular functions. In the hypothalamus, leptin regulates glucose homeostasis and food intake that reduces the risk of diabetes, obesity, and AD. Furthermore, in the hippocampus, leptin increases neurogenesis, synaptogenesis, and neuronal survival. Besides, leptin downregulates BACE1, reduces Tau phosphorylation, and increases Aβ clearance. All these leptin effects occur by activation of JAK/STAT, PI3K/Akt, and AMK/SIRT pathways.[58]

Also, leptin is involved in neuroprotection by shielding against oxidative stress and glutamatergic cytotoxicity, improving cell survival, inhibiting apoptotic cell death, and by enhancing the proliferation of hippocampal progenitor cells.[400] Circulating leptin is critical for reducing the risk of dementia and AD.[401] However, low circulating leptin levels are associated with energy impairment, as well as affect the AMPK activity, Aβ processing and Tau phosphorylation by the action of GSK-3β.[402] A significant increase in the leptin levels in CSF and hippocampus has been observed in AD patients. Furthermore, leptin receptor proteins have also been observed in NFTs. Disruption of leptin-induced signal transduction occurs due to the presence of free leptin that is unable to bind OBRs since it gets reduced due to NFT-induced disturbances in intracellular trafficking network. This leads to cognitive decline.[403] Maioli *et al.* reported that although the leptin signaling is disturbed in AD, the leptin levels in CSF remained intact.[404]

Leptin regulates body weight and systemic metabolism, and changes in the body weight and obesity increase the risk of the AD. Leptin helps degrading Aβ protein by increasing IDE involved in Aβ degradation. Additionally, leptin increases Aβ clearance by LRP-1 mediated uptake of ApoE-bound Aβ.[405] Furthermore, leptin reduces the expression of BACE1, which is the main culprit in the synthesis of Aβ protein and senile plaque by activation of SIRT1 signaling pathway.[58,406] It has been reported that leptin injection in a transgenic mouse model of AD reduced brain pathology and improved cognitive performance.[402] Studies in the cell cultures as well as in animal models revealed that leptin reduces the amount of extracellular Aβ and intracellular Tau phosphorylation in neuronal cells.[407] It was also shown that leptin supplementation reduced Aβ production and Tau phosphorylation.[58] Corem *et al.* recently reported that deficiency of leptin receptors induces the disturbance in blood-brain barrier (BBB) function,[408] that may further associate with AD pathogenesis. All these observations suggest that modulation of leptin signaling can be considered as a potential target for the development of the anti-AD drugs.

2.19. Blood-brain barrier (BBB) and cerebrovascular dysfunction in AD

The blood-brain barrier (BBB) regulates the homeostasis of the CNS by controlling the molecular exchange between the brain parenchyma and blood flow and keeps neurotoxic plasma-derived components, pathogens, and cells out of the brain.[409] Leakage of the BBB leads to an influx of cells, microbial pathogens, and neurotoxic blood-derived debris that generate immune response and inflammation in CNS.[60] Numerous studies on animal models suggest that Aβ and Tau lead to damage of BBB and abnormalities in blood vessels.[410] Importantly, in the pathogenesis of AD, BBB dysfunction and cerebrovascular lesions coexist with senile plaques and NFTs. The disruption of BBB can be detected by measuring the appearance of the plasma- or serum-derived molecules in brain parenchyma.

In fact, the presence of various plasma proteins (albumin, IgG), increased levels of the hemoglobin-derived peptides, and increased prothrombin quantities have been observed in the brain of AD patient, suggesting BBB dysfunction in AD. Furthermore, increased CSF/serum or CSF/plasma ratios of albumin serve as a critical hallmark of the BBB damage. Pericytes regulate BBB integrity and clearance of metabolite. However, coverage of microvessels by pericytes was shown to be significantly reduced in AD brain, again indicating the BBB disruption.[60,411–413] BBB operates with the neurovascular unit (NVU) and its dysfunction, such as pericyte degeneration, astrocyte depolarization, loss of tight junction (TJ) integrity, diminished endothelial transport, thickening of basement membrane, are the hallmarks for BBB dysfunction. It has been reported that the BBB dysfunction reduces Aβ clearance from AD brain. BBB damage creates devastating consequences in the affected brain, such as neuroinflammation, plasma protein leakage, and reduced brain glucose uptake.[414] BBB dysfunction in AD can be initiated by the presence and absence of Aβ pathology.[415] BBB dysfunction occurs due to the presence of Aβ oligomers, truncated Tau, oxidative stress, inflammation, diabetes, vascular disease, and pathogenic ApoE4 allele. Furthermore, decreased GLUT-1 levels in the AD-affected BBB result in the decreased transport of glucose, essentially leading to the brain starvation.[415] Finally, Aβ accumulation in CNS represents the most common consequence of BBB dysfunction.[415] Here, altered Aβ transport is associated with the reduced LRP-1activity, dysfunction of P-glycoprotein (Pgp, which is an efflux transporter involved in transport of several compounds through BBB),[415] and increased activity of the receptor for advanced glycation end products (RAGE) that serves as one of the mediators of Aβ transport across the BBB.[416] Therefore, BBB impairment leads to the neuroinflammation and oxidative stress, enhances the activity of β-secretase and γ-secretase, and promotes Aβ generation.[415] Additionally, it causes failure of Aβ transport from brain to periphery due to decreased levels of LRP-1 and increased levels of RAGE at the BBB, which consequently gives rise to cognitive impairment.[417] Aβ putative receptor at BBB controls the level of soluble isoforms of Aβ in the brain by influx of circulating Aβ into brain via specific RAGE and gp330/megalin-mediated transcytosis and efflux of brain-derived Aβ into the circulation across the vascular system via BBB is occur by LRP-1.[418]

During aging and in AD, many other alterations, such as losing tight junction, increase barrier permeability, increase pinocytic vesicle, and ROS accumulation are observed in the endothelial cells of the BBB.[419] Interestingly, Wnt/β-catenin signaling is associated with the formation, induction, and maturation of BBB function, whereas dysfunctional Wnt/β-catenin signaling leads to the BBB damages.[420]

2.20. Gut microbiota and nutrients in AD

The human microbiota is made up of trillions of complex communities of commensal, symbiotic, and pathogenic microorganisms that reside in the human body and include various bacteria, archaea, protists, fungi, and viruses. The microbiome is the collective genomes of all these microorganisms. Fascinatingly, the largest populations of microbes are located in the gut, where they play various important roles in nutrition and immunity, and also have numerous effects on the brain and behaviour in human.[421–423] The alterations in gut microbiota are associated not only with several gut disorders but are also related to

various neurological disorders.[421] Zhuang *et al.* reported that gut microbiota composition is disturbed in AD patients and may be involved in the AD pathogenesis, suggesting that brain health is closely associated with the gut microbiota.[424] The altered composition of the gut microbiota leads to the onset of aggregation and accumulation of Aβ in AD.[61] Furthermore, aging and AD pathogenesis may occur due to the increased permeability of the gut and BBB, which is induced by microbiota dysbiosis.[421] These observations reflect the existence of the microbiota-gut-brain axis, which includes multiple immune, endocrine, neural, and metabolic pathways.[421] The disturbance in gut microbiota associated with inhibition of autophagy-mediated protein degradation, change in neurotransmitter levels of the brain, and bacterial amyloid mediated inflammation of CNS.[425] Interestingly, gut microbiota can release proteins, peptides, and lipopolysaccharides that might play a role in the production of proinflammatory cytokines and modulation of signaling pathways associated with the AD pathogenesis.[61] Indeed, alterations in the gut microbiome may activate pro-inflammatory cytokines, increase intestinal permeability, and affect the occurrence of insulin resistance, which is strongly associated with AD pathology.[61] Additionally, bacteria from gut microbiota might excrete components, such as lipopolysaccharides (LPSs), immunogenic mixtures of proteins/peptides, bacterial amyloids, and other microbial exudates into their neighboring milieu. Excretion of these components induces signaling pathways and produces pro-inflammatory cytokines linked with the AD pathogenesis.[421,426,427] Activation of inflammatory responses by gut microbiome might leads to cerebral accumulation of Aβ.[428] Furthermore, bacterial amyloids might cross-seed formation of cerebral amyloids (such as Aβ, Tau protein, and α-synuclein) and also can activate signaling pathways that lead to the nerve cell death and progression of AD.[428] Human gut microbiota is involved in the structural integrity of intestinal mucosa by producing short-chain fatty acids (SCFAs), such as acetate, butyrate, and propionate, which are the end products of fermentation of dietary fibers by the anaerobic intestinal microbiota.[429] The disturbances in microbiota lead to the production of immunogenic endotoxins, increases intestinal permeability, and triggers an inflammatory response.[430–432] The diet and some nutrients can disturb the composition of the gut microbiota that induces production and aggregation of cerebral amyloid proteins.[61] In addition to that, the use of antibiotics, probiotics intervention, diet alterations, and fecal microbiota transplantation (FMT) were shown to bring modifications in the gut physiology and gut microbiota that increased the risks of AD.[433] Therefore, modulation of the gut microbiome using specific nutritional interventions such as prebiotics and probiotics might be an effective strategy to reduce chronic inflammation and amyloid load in AD.[61] Further studies of the interaction between the microbial exudates, such as lipopolysaccharides (LPSs), immunogenic mixtures of proteins/peptides, bacterial amyloids and their host environments are needed for the complete understanding of the complex relationships between the gut microbiota and AD. Personalized diet or utilization of beneficial microbiota may provide a great strategy for the management of AD.

2.21. Targeting autophagy: The finest therapeutic target for AD

As aforementioned, autophagy is the evolutionarily conserved major cellular pathway that degrades damaged organelles and unnecessary misfolded proteins and maintains correct cellular balance.[331,434] Today, autophagy is one of the most rapidly growing fields in biomedical research. Belgian biochemist Christian de Duve has introduced term autophagy

in 1963,[435] and then Japanese cell biologist Yoshinori Ohsumi has worked on the discovery of the mechanisms of autophagy and identification of autophagy-related genes. For this revolutionary work, Yoshinori Ohsumi was awarded Nobel Prize in 2016 in Physiology and Medicine [https://www.nobelprize.org/nobel_prizes/medicine/laureates/2016/].

In contrast to the UPS, autophagy degrades a much more extensive range of substrates, which tend to be bulkier, including whole cellular organelles, protein oligomers, aggregates, and large protein complexes.[26] Importantly, autophagic dysregulation has been strongly associated with many disease manifestations, including neurodegenerative disorders, cancer, inflammation, aging, and metabolic diseases.[331] Based on the mechanisms, by which intracellular components are supplied into lysosome for degradation, autophagy has three types: microautophagy, macroautophagy, and chaperone-mediated autophagy (CMA).[434] Macroautophagy is the primary autophagy type, in which the cytoplasmic material is absorbed by direct invagination of the lysosomal membrane into lysosome. In macroautophagy, cytoplasmic materials are engulfed in double-membrane vesicles called “autophagosomes”. These autophagosomes fuse with lysosomes and transports the cell “waste” inside lysosomes for degradation.[436] In CMA, via coordinated action of chaperones of both sides of the membrane and a dedicated protein translocation complex, cytosolic substrate proteins are selectively targeted and translocated into the lysosomal lumen for their degradation.[437] How autophagy is associated with Aβ-induced neurotoxicity was not completely known. However, recent studies reported that the defects in autophagic regulation may disturb the clearance of Aβ and increase death of nerve cells, suggesting that autophagy plays a neuroprotective role against Aβ-induced neurotoxicity.[438]

The protein homeostasis in autophagy is mediated by a complex molecular machinery that consists of more than 30 autophagy proteins (ATGs) and 50 lysosomal hydrolases.[439] The genes which are linked with and common to autophagy and AD are *PSEN1*, *SNCA*, *UBQLN1*, *UCHL1 ATG7*, *CDK5*, *CLU*, *CTSDITPR1*, *MAPT*, *BCL2*, *BECN1*, *FOXO1*, and *GFAP*.[434] The *ATG7* gene is the key to regulate autophagic conjugation systems in mammalians. Interestingly, ATG7 protein is also associated with the memory functions.[440] Furthermore, it regulates the level of Aβ and Tau proteins.[441,442] Therefore, disturbed *ATG7* expression (causing reduction in the cellular ATG7 protein levels) is associated with AD-like pathology.[440] Ohsumi’s group found that the ATG1 protein (also known as ULK1) combines with the products of the genes *ATG13* and *ATG17* (RB1CC1/FIP200) to form autophagic complex, which is the first stage in autophagosome genesis, and the whole process is controlled by the target of rapamycin (TOR) kinase.[434] The anti-apoptotic factor BCL2 interacts with BECN1 protein and regulate autophagic process, and its overexpression protects neuronal cells *in vitro* against Aβ-related death, reduces APP processing and Aβ deposition.[443] The BECN1 protein facilitates the initiation of autophagy and autophagosomes, which are found to be reduced in AD patients. Indeed, reduced levels of BECN1 increase the Aβ levels in brain.[444] CDK5 is an autophagy-regulating kinase, and studies in the AD mouse models reported that enhanced CDK5 activity protects against Aβ accumulation, Tau hyperphosphorylation, neuroinflammation, and memory loss.[445] Clusterin (CLU) is a chaperone protein that contributes to the biogenesis of autophagosome, and mutations in *CLU* gene have been strongly associated with AD pathology.[446] CLU protects brain against Aβ toxic effects by interacting with Aβ protein and reducing its

aggregation.[447] Lee *et al.* has reported that PSEN1 is essential for controlling acidification and proteolysis of lysosome throughout autophagy.[448] α-Synuclein (SNCA) is abundantly found in brain, where it regulates the formation of autophagosome and is negatively regulated by autophagy.[434] Mutation in *SNCA* gene are strongly associated with the risk of AD.[449] SNCA regulates many events in AD pathology, such as induces expression of Aβ peptides and vice versa, stimulates Aβ peptide aggregation, and modulates the activity of BACE1.[434] Interestingly, the interaction of SNCA with Tau and SNCA with Aβ peptides bring each other fibrillation.[450] Ubiquilin 1 (UBQLN1) is strongly linked to the AD pathology, since APP processing, APP intracellular trafficking, and $A\beta_{40}$/ $A\beta_{42}$ secretion have been reported to be increased due to the reduced UBQLN1 expression in frontal and temporal cortices of AD patients.[450] UCHL1 is an ubiquitin-specific hydrolase that modulates autophagosome-lysosome fusion by interaction with LAMP2.[281] Studies in AD mouse model showed that UCHL1 plays crucial role in the memory and synaptic function.[451] Decreased expression and activity of UCHL1 was found in cerebral cortex of AD patients. However, studies in the AD mouse models reported that overexpression of UCHL1 reduces Aβ production and protects AD brain against memory impairment.[452,453]

The CMA is involved in the removal of aberrant proteins. However, it also becomes victim of the toxic effect of these pathogenic proteins. Therefore, it is essential to analyze whether enhancing CMA activity could be of potential value or not.[437] Transcriptional activity also plays crucial role in autophagic processes. For example, Transcription factor E3 (TFE3) and Transcription factor EB (TFEB) are the critical regulators of lysosomal biogenesis and autophagy.[454] Enhanced activity of autophagy suppressers, such as mTORC, and reduced expression of autophagy-inducing molecules, such as beclin 1, Atg, AMPK, and ULK1 complex proteins leads to inhibition of autophagic induction.[455] Inappropriate lysosomal fusion or pH due to increased autophagic vacuoles (AVs) containing inactive cathepsin and undigested content leads to neurodegeneration in AD neurons (Figure 1B **right panel**).[455]

Autophagy can be targeted for the degradation of pathogenic peptide aggregates such as Aβ and Tau protein. Autophagy-stimulating drugs may provide better treatment of AD, and many related drugs have been reported to show protective effects against AD in preclinical studies and clinical trials. These include rapamycin, nicotinamide, protein phosphatase 2A agonists, carbamazepine (CBZ), lithium, memantine, and latrepirdine.[434] Studies performed by Li *et al.* and Zhang *et al.* in the AD mouse models showed that autophagy enhancer carbamazepine was able to protect brain against memory dysfunction and an increase in Aβ content.[456,457] Mechanistic Target of Rapamycin (mTOR) pathway regulates autophagy and is proved to be strongly associated with the pathology of AD. Studies in the AD mouse models reported that mTOR signaling is inhibited in hippocampus and cortex.[458] Spilman and colleagues has reported that blocking the mTOR signaling by rapamycin reduced cognitive deficits and amyloid pathology in mouse model of AD.[459] It has also been reported that mTOR stimulates Tau pathology by facilitating intra- and extra-cellular distribution of Tau, its phosphorylation, and accumulation.[460,461] Rapamycin is a selective inhibitor of target-of-rapamycin complex 1 (TORC1) that was reported to show reduced Aβ and Tau pathology and improved learning and memory in mouse model of AD.[462] Temsirolimus is the prodrug of rapamycin that induces

autophagy-dependent Aβ clearance, shows memory improvement in cellular and animal AD models,[463] and reduces Tau accumulation in Tau mutant mice.[464] The FDA approved drug memantine act by antagonizing NMDA receptors is also reported to stimulate autophagy in either mTOR-dependent or mTOR-independent way.[465] Resveratrol and its derivatives are bioactive polyphenols that reduce Aβ aggregation via AMPK signaling pathway by activating autophagy.[466] Porquet *et al.* has reported that long-term treatment of AD mouse model with resveratrol reduces memory loss and Aβ levels.[467] The randomized, placebo-controlled trials reported that resveratrol penetrated the blood-brain barrier and was safe and well-tolerated.[468] According to US FDA report, resveratrol is now in phase 3 clinical trial for AD treatment, and the outputs of study are not published as of yet [https://www.alzforum.org/therapeutics/resveratrol]. A study by Steele *et al.* in AD mouse model reported that latrepirdine reduces Aβ peptides level by stimulating autophagy in mTOR- and Atg5- dependent manner.[469] Phase II trial in AD patients reported significant improvement over placebo. However, phase III clinical trial showed no effect, and therefore this clinical trial was discontinued by U.S. Food and Drug Administration (USFDA) [https://www.alzforum.org/therapeutics/dimebon]. Also, numerous autophagy-regulating compounds have shown protective effect against Aβ and Tau induced toxicity and improve memory in AD animal models. These studied compounds include Tetrahydrohyperforin, β-Asarone, Arctigenin, GTM-1, Trehalose, and Oleuropein Aglycone.[434]

2.22. Interplay between autophagy and other signaling pathways in AD

To maintain cellular homeostasis, protein quality control (PQC) system is controlled through multi-levels of interactions.[470] Autophagy displays cross-talk with other signaling pathways, which are significantly involved in AD pathogenesis. The **Aβ peptide is generated** as a result of the APP processing during autophagic turnover of APP-rich organelles supplied by both endocytosis and autophagy. The enhanced autophagy induction is also reported to create conditions favorable for Aβ accumulation in AD brain.[71] As discussed in **genetic mutation** part of this review, PSEN1 is a component of γ-secretase complex which is involved in APP cleavage[471] and proteolysis via autophagy.[472] **Genetic mutations in PSEN1** lead to alterations in APP processing. However, recent studies suggested that PSEN1 mutation inhibits autophagy by reducing autophagic cargo elimination.[149] Francois *et al.* has reported interplay between autophagy, inflammation, and AD, suggesting the presence of a link connecting these processes.[473] It has also been reported that autophagy is directly regulated by **neurotransmitter** receptor.[170] The link between autophagy and neurotransmitter receptors is essential for the regulation of neuronal function.[170] **Mitochondria and Mitochondrial autophagy** play crucial role in cell health and its dysfunction leads to insufficient clearance of dysfunctional mitochondria by autophagy.[209,474] Nijholt *et al.* reported that **Endoplasmic reticulum stress** activated autophagy in neuronal cells, however UPS was not activated, suggesting that autophagy is the foremost degradational pathway after UPR activation.[220] Studies also reported that UPR signals in ER are linked to autophagy, since both abnormal UPR and impaired autophagy have been observed in AD.[221] **Oxidative stress/ROS** (mainly mitochondrial H_2O_2 and O_2^-) modulate and induces autophagy via mTOR-dependent pathways. Also, autophagy can reduce oxidative stress/ROS-induced nerve cell damage by removing abnormal protein aggregates and improves their survival.[475] Autophagy also plays an

essential role in controlling the Aβ-induced **neuroinflammation** in brain.[476] CDK5, an autophagy-regulating kinase, protects against neuroinflammation, Aβ accumulation, Tau hyperphosphorylation, and memory loss.[445]

Although the autophagy and **UPS** have independent degradation process mechanisms (Figure 1), wide range of studies have reported the presence of cooperation and cross-talk between these two pathways. These pathways share common substrates, such as CTFβ, Aβ, and α-synuclein, which are among the key harmful proteins for neuronal function. In addition, enzymes of the ubiquitylation machinery, such as E3 ligase Parkin, contribute to both degradation pathways.[26] Thus, any disturbances in autophagy and UPS will affect their ability to effectively counteract proteotoxic stressors that provoke the accumulation of aberrant proteins.[477]

Furthermore, evidence also suggests that perturbations in proteasome activity activate autophagic process indicates that these both pathways are depending on each other's effect.[478] The **insulin resistance** (type 2 diabetes) that involves increase in blood sugar level shows strong correlation with autophagy. Autophagy protects pancreatic β-cells from apoptotic cell death, protects the insulin target organs from hyperglycemia-induced oxidative stress, and preserves their structure and function. Therefore, by activating autophagic process, insulin resistance can be avoided along with AD.[331] The **high intracellular cholesterol** augments the Aβ-induced autophagosome formation. However, it affects lysosomal fusion capacity by changing the content and distribution of RAB7A and SNAP receptors (SNAREs). Reducing cellular cholesterol levels may enhance the delivery of Aβ to lysosomes and degradation.[348] Autophagy is also linked to the neurotransmitter-induced **excitotoxicity**. Excessive stimulation of non-NMDA glutamate receptors activates lysosomal enzymes and induces autophagy. Autophagic activation by excitotoxic neuronal injury is crucial in order to prevent neurodegeneration.[378]

The drugs which targets more than one pathway must be tested for AD treatment such as resveratrol not only act via autophagy stimulation but also shows anti-inflammatory, anti-oxidant, and amyloid inhibition activity.[479] Activation of autophagy is a crucial part of the cellular response to oxidative stress induced by ROS and RNS.[475] Therefore, a large number of resveratrol derivatives can be prepared and studied for Aβ aggregation inhibition and synaptic and memory development. The transcription factor EB (TFEB) regulates lysosomal biogenesis and autophagy. The curcumin, a polyphenol antioxidant compound inhibits the mTOR signaling pathway and activates the TFEB, reduces cognitive impairments, and Aβ formation in AD models.[26] mTOR inhibitor rapamycin exerts its neuroprotective actions and inhibition of Aβ and Tau via its autophagy inducing capability along with antioxidant and anti-inflammatory activity.[476]

3. Some Unanswered Questions

The decades of intensive research on various aspects of AD have generated massive knowledge on both the clinical and basic levels. As many with many other neurodegenerative diseases, AD is recognized now as a multifactorial malady in the broadest essence of this word. AD affects the body on multiple levels, hits different systems,

produces various symptoms, and generates diverse biochemical outputs. AD is a disease with a multifactorial etiology, where any of a broad set of intrinsic and extrinsic factors (protein misfolding and aggregation, mutations, genetic predisposition, oxidative damage, impairment of the protein quality control system, environmental toxins, mitochondiapathy, microbiota dysbiosis, etc.), or their various combinations, can trigger the development of pathology. As a result, the AD field is intensively developing in different directions. New factors potentially involved in the AD pathogenesis are frequently found. To some extent, studies on AD resemble peeling of an onion, where removing one layer uncovers another layer, which in turn hides a new level of complexity. We are slowly going through this multilayer problem, trying to reach its core; trying to understand what the primary cause of AD is, if there is one; trying to get closer to the beginning of all the beginnings. Does “many reasons” necessarily mean “no reason at all”? Such a scenario is very unlikely in the case of AD, as this malady is known to be provoked by multiple individual factors, or by their various combinations. However, the current state of our understanding of AD clearly resembles The Never Ending Story, where a new study discovers a new player, the introduction of which initiates a new round of intensive studies, which produce a new “chronicle” culminating in suggesting of a new logical explanation of the “unique” and almost always “crucial” role of this new player in the development of general story. With all these newly discovered players, all these neatly described “chronicles”, and all these intriguing developments, the question is: are we any closer to understanding the AD aetiology today than we were 30, 20 or 10 years ago? The answer is a definite yes, as we now know more and understand some aspects of the disease better. So, just how far are we from the end of this journey? This question is harder to answer, as we are still searching for the beginning of this never-ending story. The hope is that one day all these individual chronicles will merge together and the puzzle will be solved.

This review summarized the current knowledge on the molecular mechanisms of various signaling pathways related to the AD pathogenesis. Although significant information is accumulated in this field, there is still a number of unanswered fundamental questions about the key mechanisms associated with the AD pathogenesis. Even if one focuses just on the major AD-related culprits, Aβ or Tau, many questions are still waiting for their answers. Among these important questions are: What are the exact molecular mechanisms of AD pathology and is there a single mechanism invariantly causing AD? Is amyloid cascade signaling central to all the AD-related pathways? Are misfolded, oligomerized, aggregated, and fibrillated Aβ and Tau always causing neurodegeneration and cognitive impairment? If so, are Aβ or Tau sufficient to be used as targets for AD therapy? Are there other factors in the brain that can enhance Aβ formation? How do we target signaling pathways to resolve problems leading to the neurodegeneration? Does Aβ and Tau aggregation impair other processes in body? Does Aβ aggregation affect the other signaling pathways in the body? Are the Aβ concentration increases or decreases in the organs of the body other than the brain? What are the mechanisms, by which senile plaques and NFT lead to the brain cell death? Whether these aggregates damage cells other than nerve cells? What could be the reason for autophagic failure with age? What are the mechanisms behind autophagic diminishing caused by Aβ aggregates? If the PQC system activated then how long this activation can be effectively maintained?

Although it is reported that metabolic syndrome, type 2 diabetes, and AD might be interconnected,[61] it is also possible that other pathways are also linked with this. Autophagic pathway shows cross-link with many other pathways of AD. So, is targeting only autophagy represents an effective way to fight against AD? Do we know all signaling pathways that can lead to AD? Is linking of all the pathogenic signaling pathways to each is required for the pathogenesis of AD? If so, in which order and by what means? How do different pathogenic signaling pathways affect neuronal cell damage and memory loss? Are there new signaling pathways that can be associated with nerve cell death? Are all these pathological pathways always linked to the Aβ aggregation? How do aberrant signaling pathways increase the risk of dementia? What are the clinical links between AD and pathogenic signaling pathways? Answering these questions may provide the platform for the effective development of drugs against AD. This review represents the major signaling pathways associated with the AD pathobiology and emphasizes that consideration of these signaling pathways may help to solve several unanswered questions of AD pathology.

4. Current advances and therapeutic strategies against AD

Till now, there is no any mechanism-based therapy available for the AD. In this review, we have discussed key therapeutic strategies independently at each molecular signaling pathway of AD. USFDA approved five drugs that are able to maintain neurotransmitter levels in the brain but are not able to cure AD. Furthermore, to date, no treatment is available to reverse the symptoms of the AD. For significant breakthroughs in the treatment of any malady, precise knowledge of the underlying pathophysiology is important. For a better understanding of AD pathogenesis, all the related pathways must be checked for interlink between them.

There is still a question of whether targeting Aβ or Tau alone is sufficient for effective AD therapy. Currently, researchers are mainly focusing on developing strategies for the efficient elimination of Aβ. However, targeting only one component for AD therapy may not be sufficient, since numerous drugs targeting Aβ pathway failed in a clinical trial. Therefore, new insights into AD mechanisms and new therapeutic strategies can be helpful. It is very likely that targeting multiple pathways may be more effective than targeting a single pathway and that this complex approach might be beneficial for AD patients. Complete success in AD treatment requires an understanding of the exact molecular mechanisms of this disease. Multi-target therapy aiming at multiple common nodes from various signaling pathways, such as Aβ, Tau, GSK3β, acetylcholinesterase, as well as players related to inflammation, insulin signaling, controlling Ca^{2+} levels, cellular protein quality control systems, and oxidative stress could be more successful than any monotherapy. For example, promising strategies for the design of the effective therapeutics against AD might include various combinations of means for 1) regulating the APP processing by increasing α-secretase activity or blocking the β- or γ-secretase pathways; 2) utilizing various anti-aggregation molecules; 3) increasing Aβ and Tau clearance with antibodies or by activating ApoE, IDE, autophagy/ELS, and UPS; 4) improving Aβ and Tau proteostasis with chaperones, such as HSP70; 5) blocking signaling pathways, such as GSK3β and glutamate; 6) regulating APP processing by modulating cholesterol and lipid metabolism; 7) using anti-oxidant and anti-inflammatory agents; 8) maintaining neurotransmitter balance by reducing

their degradation; 9) Enhance the activity/expression of autophagy-inducing molecules such as ATG proteins and beclin 1; 10) Inhibit the activity of autophagy suppressor such as mTOR; 11) Activating proteasomal degradation of Aβ and Tau; 12) improving neuronal growth by activating NGF and BDNF; and 13) modulating the gut microbiota with specific nutritional interventions. The agents acting through multiple pathways that may show potential in AD therapy. Thus, clinical trial must be undertaken on the drugs that are having multiple targets.

5. Concluding Remarks

Intensive research proposed the existence of numerous signaling pathways that can be related to the pathobiology of AD. Since currently, results of clinical trials for anti-AD drugs are mostly unsatisfactory; there is a strong demand for new drugs that can show some promise in the cure of this devastating disorder. In fact, a detailed mechanism of the pathogenesis needs to know key players associated with AD pathogenesis in order to tackle this pathological event. Therefore, the better understanding of the key cellular signaling pathways related to the propagation of neurodegeneration and various interconnections between them can provide new insights for the evaluation and development of new therapeutic strategies for cure of AD in near future. Indeed, looking at multiple signaling pathways provides valuable information and important insights into the novel pathological mechanisms. Systematic investigation, comparative analysis of individual pathway, finding correlations between them, and how all these pathways are causatively associated with AD could provide a novel perspective for understanding the pathogenesis, successful diagnosis, and management of AD. Identifying common nodes in multiple pathways might offer new opportunities for the designing of specific treatment strategies for AD. Considering cross talk of autophagy with many other pathways, it should be the focus of attention for AD research in the near future. Autophagic upregulation may be a promising therapeutic strategy for AD due to approachability of druggable targets described in this review. Finally, we expect that the next decade will generate additional information on the molecular mechanisms and common nodes of various signaling pathways associated with the AD pathophysiology, which will open new grounds for drug targeting.

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Abbreviations

Aβ	amyloid beta
ABACA1	ATP-binding cassette, sub-family A, member1
ACAT	Acyl CoA: Cholesterol O-acyl transferase
AD	Alzheimer's disease
AGE	advanced glycation end product
AICD	APP intracellular C-terminal domain
AMPK	AMP-activated protein kinase
APOE4	ε4 variant of the apolipoprotein E
APP	amyloid precursor protein
ATF6	AMP-dependent transcription factor ATF-6 alpha
ATG1	autophagy related 1
AV	autophagy vacuole
BACE1	β-secretase
BBB	blood-brain barrier
BDNF	brain-derived neurotrophic factor
BIN1	bridging integrator 1
BVR-A	biliverdin reductase-A
CAT	choline acetyltransferase
CBD	cannabidiol
CD2AP	CD2-associated protein
CLU	clusterin
CMA	chaperone-mediated autophagy
CNS	central nervous system
CR1	complement receptor 1
CREB	cAMP response element binding

CRP	C-reactive protein
CSF	cerebrospinal fluid
DM	diabetes mellitus
DUB	deubiquitinating enzyme
eIF2α	eukaryotic translation initiation factor 2 subunit 1
EOAD	early-onset AD
ER	endoplasmic reticulum
ETC	electron transport chain
FAD	familial AD
FMT	fecal microbiota transplantation
Fz	frizzled
GAD	glutamic acid decarboxylase
GLP-1R	glucagon-like peptide-1 receptor
GLUT	glucose transporter
GPCR	G protein coupled receptor
GSK-3β	glycogen synthase kinase three beta
GWAS	genome wide association studies
HDL	high-density lipoprotein
HSP	heat shock protein
IDE	insulin-degrading enzyme
IGF	insulin-like growth factor
IKK	IκB kinase
IGF1R	tyrosine kinase receptor type 1 receptor (IGF receptor)
InsP3	inositol trisphosphate
InsP3R	InsP3 receptor
INI	intranasal insulin
IR	insulin receptor
IRE1α	serine/threonine-protein kinase/endoribonuclease inositol-requiring enzyme 1 α

IRS-1	insulin receptor substrate 1
IVIg	intravenous immunoglobulins
JNK	c-Jun N-terminal kinase
KPI	Kunitz-type proteinase inhibitor
LDL	low-density lipoprotein
LOAD	late-onset AD
LPS	lipopolysaccharide
LRP	LDL receptor-related protein
LTP	long-term potentiation
mTOR	mammalian target of rapamycin
NCT	nicastrin
NEO	neutral endopeptidase neprilysin
NFT	neurofibrillary tangle
NF-κB	nuclear factor kappa B
NGF	nerve growth factor
NT-3	neurotrophin-3
NTF	neurotrophic factor
NMDA	N-methyl-D-aspartate
NMDAR	NMDA receptor
NSAID	non-steroidal anti-inflammatory drug
NVU	neurovascular unit
OBR	(or LEPR) leptin receptor
OXPHOS	oxidative phosphorylation
PEN-2	presenilin enhancer protein 2
PERK	PRKR-like endoplasmic reticulum kinase
PET	positron emission tomography
Pgp	P-glycoprotein
PHF	paired helical filament
PICALM	phosphatidylinositol binding clathrin assembly protein

PKR	protein kinase R
PSEN	presenilin
PTK2B	protein tyrosine kinase 2β
RAGE	receptor for advanced glycation end products
RIN3	Ras and Rab interactor 3
RNS	reactive nitrogen species
ROS	reactive oxygen species
RYK	receptor tyrosine kinases
SAD	sporadic AD
SCFA	short-chain fatty acid
SIRT	sirtuin
SLC24A4	solute carrier family 24 (sodium/potassium/calcium exchanger), member 4
SNAREs	soluble NSF attachment protein receptors
SNPs	single nucleotide polymorphisms
SORL1	sortilin-related receptor1
TFEB	transcription factor EB
TGFβ	transforming growth factor beta
TJ	tight junction
TNFR	tumor necrosis factor receptor
TREM2	triggering receptor expressed on myeloid cells 2
Trk	tyrosine kinase
UCHL1	ubiquitin C-terminal hydrolase L1
UPR	unfolded protein response
UPS	ubiquitin-proteasome system
VLDL	very-low-density lipoprotein
VTA	ventral tegmental area

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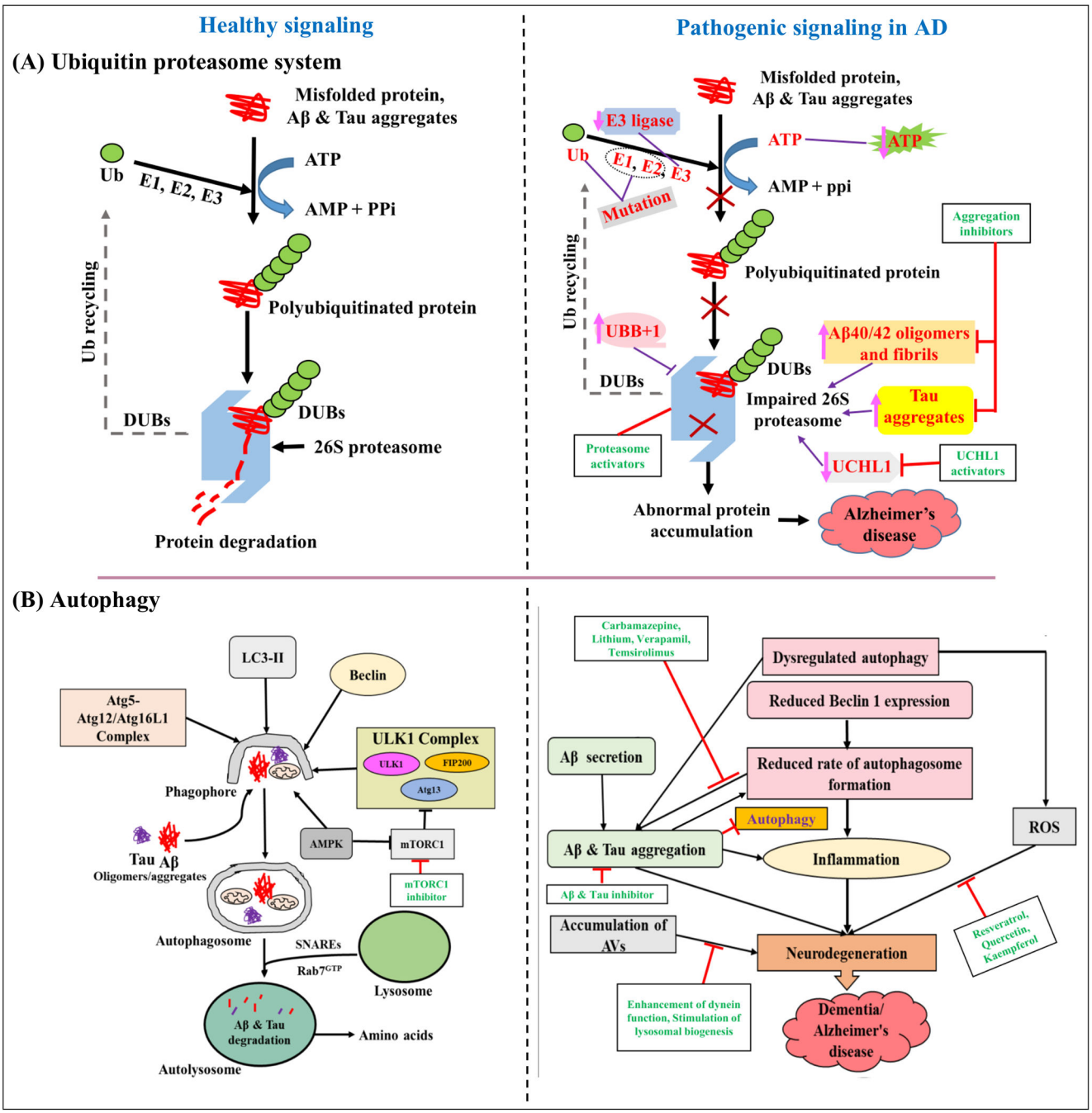

Figure 1: As an example, schematic representation of healthy and pathogenic signaling in AD;

(A) Ubiquitin proteasome system. Left panel shows healthy UPS. Misfolded proteins and protein (Aβ and Tau) aggregates are degraded by 26S proteasome with the help of ubiquitinating (E1, E2, and E3) and deubiquitinating enzymes (DUBs) in ATP-dependent manner. Right panel shows pathogenic UPS in AD. Impaired proteasomal function leads to inhibition of the misfolded proteins and aggregated Aβ and Tau degradation. This leads to accumulation of Aβ and Tau aggregates in neurons, nerve cell death, and finally AD pathogenesis. Enhanced level of mutant UBB+1, Aβ40/42 oligomers and/fibrils, Tau

aggregates, mutation in E1 and E2 enzymes, reduced E3 ligase/CHIP and UCHL1 are responsible for aberrant UPS. Use of proteasome activators, aggregation inhibitors, and UCHL1 activators may provide management of AD. **(B)** Autophagy. Left panel shows healthy autophagy. Beclin 1, LC3-II, ULK1 complex, and Atg5-Atg12/Atg16L1 complex are involved in the formation of autophagosomes. Cytoplasmic contents such as protein aggregates (Aβ and Tau) and defective organelles are sequestered into a double-membrane-bound autophagosome. Further, these are transported and fuse with lysosomes in a Rab7- and SNARE-dependent manner. Aβ and Tau aggregates are then degraded by lysosomal hydrolases. Right panel shows defective autophagy in AD. Failure in autophagic process can be caused by protein aggregates, reduced expression of Beclin1, presenilin 1 dysfunction, disturbed lysosomal pH. Further, autophagic failure leads to accumulation of toxic proteins that subsequently affect cell health and survival. Finally, neurodegeneration affects cognitive function that leads to AD. Various drug targets and agents acting at different stages are shown in green color. The "→" refers to induction/activation and the "⊢" refers to inhibition. "↑" refers to increase and "↓" refers to decrease. Ub: Ubiquitin, DUBs: deubiquitinating enzymes, E1: Ub-activating enzyme, E2: Ub-conjugating enzyme, E3: Ub-ligase enzyme. mTOR: mammalian target of rapamycin; AMPK: AMP-dependent protein kinase; ROS: Reactive oxygen species; AVs: Autophagic vacuoles; ULK1: Unc-51 like autophagy activating kinase; Atg: Autophagy-related protein; SNAREs: Soluble NSF attachment protein receptor.

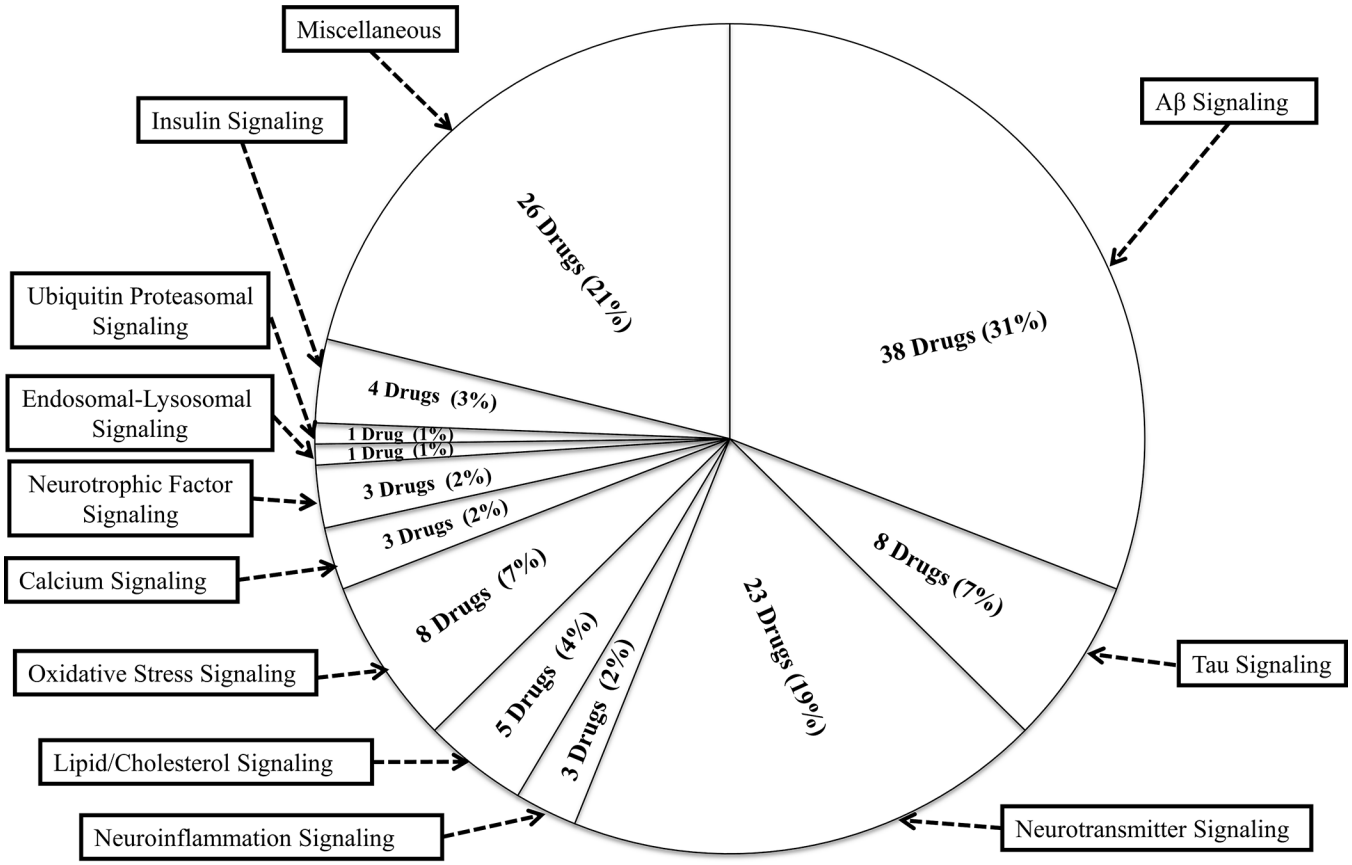

Figure 2: Distribution of drugs in clinical trials by signaling pathways in AD;

Numerous drugs are in different phases of clinical trials that targeting different signaling pathways. Few drugs have targets in more than one pathway. Most of the drugs (38 drugs) have been targeted against Aβ signaling. In addition, some drugs are in the miscellaneous category with an unknown mechanism of action/undisclosed information.

Table 1:

Therapeutic targets for AD based on molecular signaling pathways

Sr. No.	Molecular Signaling Pathways	Therapeutic targets	References
1	Amyloid cascade signaling	Aβ, APP, BACE1, PSEN1, PSEN2, ApoE	480
2	Tau and Neurofibrillary tangles	Tau protein, kinases	29
3	Genetic mutation	APP, PSEN1, PSEN2, ApoE4	2
4	Neurotransmitter signaling	NMDA receptor, acetyl-cholinesterase (AchE), Glutamatergic and GABAergic receptors	162,181
5	Mitochondrial dysfunction	Mitochondrial respiratory enzymes, mitochondrial ROS	201,202
6	Endoplasmic reticulum stress	Unfolded Protein Response (UPR), Stress sensors (IREI, PERK, and ATFE6)	481
7	Oxidative stress	Reactive oxygen species (ROS), Mitochondrial dysfunction, Advanced glycation end products (AGEs)	224,226
8	Neuroinflammatory signaling	Proinflammatory elements such as chemokines, IL-2β, IL-6, IL-12, INF-γ, TNF-α, NO, ROS, IL-1β	39,40,251
9	Ubiquitin-Proteasomal System	Ubiquitin activating enzyme (E1), Ubiquitin conjugating enzyme (E2), UCHL1, 26 S Proteasome	42
10	Autophagy/Endosomal-lysosomal system	Mammalian target of rapamycin (mTOR), AMP-activated protein kinase (AMPK), PSEN1, SNCA, UBQLN1, UCHL1 ATG7, CDK5, CLU, CTSDITPR1, MAPT, BCL2, BECN1, FOXO1, and GFAP	282,291,294,434
11	Protein misfolding and molecular chaperones	Heat Shock Proteins (HSPs), HSP60 and HSP70	296
12	Insulin Signaling	Insulin Receptors (IRs), Insulin degrading Enzymes (IDE), Akt, GSK-3β	305
13	Lipid/Cholesterol metabolism	ApoE, HMG-CoA reductase, Acyl CoA-Cholesterol O-acyl transferases (ACAT)	52,74,482
14	Calcium (Ca^{2+}) signaling	Ca^{2+} homeostasis	365
15	Excitotoxicity	Glutamate, N-methyl-D-aspartate (NMDA) receptors,	59
16	Neurotrophic factors signaling	Brain-Derived Neurotrophic Factor (BDNF), Nerve Growth Factor (NGF), Neurotrophin-3 (NT-3), Neurotrophin-4/5, Trk receptors (TrkA, TrkB, TrkC)	51
17	Wnt/β-catenin signaling	β-catenin, GSK-3β	391
18	Leptin signaling	Leptin, Leptin receptor (ObR)	58,399
19	Blood-Brain Barrier (BBB) dysfunction	Receptor for advanced glycation end products (RAGE), Low-density lipoprotein receptor-related protein 1 (LRP-1)	419
20	Gut Microbiota and Nutrients	Diet and Nutritional interventions (prebiotics and probiotics), Gut microbes	61

Table 2:

Drugs in clinical trials for AD based on molecular signaling pathways

Sr no.	Agents in clinical trial	Mechanism of action	Company	Trial status	References
1. *Aβ signaling*					
1	ACI-24	Anti-Aβ	AC Immune's Supramolecular Technology	Phase-I	483
2	ALZ-801	Prevent Aβ aggregation	Alzheon	Phase-I	484
3	BI-1181181	BACE-1 inhibitor	Boehringer Inhelneim	Phase-I	485
4	BMS-932481	BACE-1 inhibitor	Bristol-myers Squibb	Phase-I	486
5	Exebryl-1	Modulate α and β secretase activity	Proteo Tech	Phase-I	487
6	KHK-6640	Anti-Aβ	Kyowa Hakko Kirin	Phase-I	488
7	MEDI-1814	Anti-Aβ	Astrazeneca	Phase-I	489
8	Lu-AF-20513	Anti-Aβ	Lundbeck	Phase-I	490
9	SAN-61	Stimulate proliferation of neural stem cell acting simultaneously on Amyloid plaques and aggregates	Diamedica company	Phase-I	491
10	SAR-228810	Anti-Aβ	Sanofi company	Phase-I	492
11	TTP-400	Recombinant proteins affecting Aβ	Trans Tech Pharma	Phase-I	493
12	AD-02	Anti-Aβ	Affiris	Phase-II	494
13	AD-04	Anti-Aβ	Affiris	Phase-II	103
14	BAN-2401	Anti-Aβ	Eisai	Phase-II	495
15	Bexorotene	Anti-Aβ	Eisai	Phase-II	496
16	BLU-8499	Antiamyloidogenic agent	Alzheon	Phase-II	497
17	E-2609	BACE1 inhibitor	Eisai Co	Phase-II	498
18	EVP-0962	BACE1 inhibitor	FORUM Pharma	Phase-II	499
19	Octagam	Anti-Aβ	Octapharma AG	Phase-II	500
20	PN-1219	Anti-Aβ	PFizer	Phase-II	501
21	Posiphen	Antiamyloidogenic agent	QR Pharma	Phase-II	502
22	Ro-63–8695	Anti-human serum Amyloid P (Anti-SAP)	GalaxaSmithKline	Phase-II	503
23	UB-311	Anti-Aβ	United Biomedical	Phase-II	504
24	Aducanumab	Anti-Aβ	Biogen Co.	Phase-III	505
25	ALZT-OP1	Prevent Aβ aggregation	AZ Therapeutics	Phase-III	506
26	AZD-3293	BACE1 inhibitor	AstraZeneca, EliLilly	Phase-III	507
27	Bapineuzumab	Acting on soluble form of Aβ	Oop & Johnson	Phase-III	508
28	Crenezumab	Anti-Aβ	AC Immune & Genetech	Phase-III	509
29	EGCG	Amyloid related	TaiyoInternational	Phase-III	510
30	Gammagard	Anti-Aβ	Baxalta	Phase-III	511
31	Gantenerumab	Anti-Aβ	Hoffman-La Roche	Phase-III	512
32	GV-971	Inhibit Aβ aggregation	Shanghai Green Valley	Phase-III	513

Sr no.	Agents in clinical trial	Mechanism of action	Company	Trial status	References
33	JNJ-54861911	BACE1 inhibitor	Janssen	Phase-III	514
34	MK8931	BACE1 inhibitor	Merck & Co	Phase-III	515
35	ELND005	Inhibit Aβ aggregation	Transition Therapeutics	Phase-III	516
36	Solanezumab	Reduce Aβ burden in brain by peripheral sink hypothesis	Ely Lilly	Phase-III	517
37	Tramiprosate	Anti-Aβ	Neurochem	Phase-III	518
38	TRx-00237	Amyloid-related	Janssen, Pfizer, TauRx Therapeutics	Phase-III	519
2. *Tau Signaling*					
1	ACI-35	Tau-aggregation	ACImmune	Phase-I	520
2	BMS-986168	Tau-aggregation	Bristol-myers squibb	Phase-I	521
3	RG-7345	Tau-aggregation	Genetech, Hoffmann-La Roche	Phase-I	522
4	TPI-287	Tau-aggregation	Cortice Biosciences	Phase-I	523
5	AADvac-1	Tau-aggregation	Axon Neuroscience	Phase-II	524
6	Methylene Blue	Tau-aggregation	TauRx Therapeutics	Phase-II	525
7	TRx-0014	Tau-aggregation	TauRx Therapeutics	Phase-II	526
8	TRx-00237	Tau-aggregation	Janssen, Pfizer, TauRx Therapeutics	Phase-III	519
3. *Neurotransmitter Signaling*					
1	AVN-322	5-HT6 receptor antagonist	Avineuro	Phase-I	527
2	Basmisanil (RG-1662)	GABA (A) receptor agonist	Roche	Phase-I	528
3	Bisnorcymserine	Selective inhibitor of butyryl-cholinesterase (BuChE)	QR Pharma	Phase-I	529
4	Huperzine A, Cerebra	NMDA R Antagonist, AChEI, Signal transduction modulator	NutriHerb	Phase-I	530
5	Memogain	Nonselective inhibitor of butyryl and acetylcholinesterases	Neurodyn Life Sciences	Phase-I	531
6	PQ-912	Glutaminyl cyclise inhibitor	Probiodrug AG	Phase-I	137
7	SUVN-G3031	H3R antagonist	Suven Life Sciences	Phase-I	532
8	AN2/AVex-73	Block sodium channels and act as agonist of sigma-1 receptors and muscarinic (M1) receptors, and AChE inhibitor	Anavex Life Science	Phase-II	533
9	AZD-3480	Agonist of alpha-4-beta-2-nAChR	Targacept	Phase-II	534
10	Ladostigil	Inhibitor of Acetylcholinesterase and monoamine oxidase A nad B	Avraham	Phase-II	535
11	Nelonicline (ABT-126)	Nicotinic alpha-7-nAChR agonist	AbbVie	Phase-II	536
12	ORM-12741	Alpha 2C adrenoceptor antagonist	Orion	Phase-II	537
13	PXT-864	Multitarget: NMDAR and GABA (B) antagonist, modulate metabotropic glutamate receptor	Pharnext	Phase-II	538
14	Rasagiline	Monoamine oxidase type B (MAO-B) inhibitor	Teva	Phase-II	539

Sr no.	Agents in clinical trial	Mechanism of action	Company	Trial status	References
15	Riluzole	Multitarget: group of targets in the glutamatergic system and different types of ion channels	Rockefeller University	Phase-II	540
16	S-38093	Ionic channel modulator, antagonist of H3-histamine receptors (H3R)	Servier	Phase-II	541
17	S-47445	Inotropic glutamate receptor	RespireRx Pharmaceuticals	Phase-II	542,543
18	SUVN-502	5-HT6 receptor antagonist	Suven Life Sciences	Phase-II	544
19	AVP-786	NMDAR antagonist	Avanir Pharmaceuticals	Phase-III	545
20	Encenicline hydrochloride	Acetylcholine (nicotinic) receptors Ligand, nicotinic alpha-7-nAChR agonist	Bayer	Phase-III	546
21	Intepirdine	5-HT6 receptor antagonist	GlaxoSmithKline	Phase-III	544
22	Lu-AE-58054	Serotonin receptors	Lundbeck	Phase-III	547
23	Dexpramipexole	Dopamine receptor agonist	Biogen	Phase-II	528
4. *Neuroinflammation signaling*					
1	AAD-2004	Cytokines inhibitor	GNT Pharma	Phase-I	548
2	Entanercept	Inflammation	Amgen, Inc., Pfizer	Phase-II	549
3	Pioglitazone	Inflammation	Takeda	Phase-III	550
5. *Lipid/Cholesterol Signaling*					
1	GSK-2647544	Inhibitor of phospholipase A2	GSK	Phase-I	551
2	Atorvastatin	Lowers cholesterol level	PFizer	Phase-II	552,553
3	Pitavastatin	Statin	Kowa	Phase-II	553
4	Rilapladib	Inhibitor of phospholipase A2	Glaxo Smith Kline	Phase-II	554
5	Simvastatin	Statin	NTA	Phase-II	555,556
6. *Oxidative stress Signaling*					
1	ARC-031	Antioxidant	Archer Pharmaceuticals	Phase-I	557
2	Curcumin	Antioxidant	Now Foods	Phase-II	558
3	Lu-AF-20513	Antioxidant	Lundbeck	Phase-II	559
4	Quercetin	Antioxidant	Twinlab	Phase-II	558
5	EGCG	Antioxidant	Taiyo International	Phase-III	510
6	HX-106	Antioxidant	VitroMed	Phase-III	558
7	Nilvadipine	Antioxidant	Astellas Pharma	Phase-III	560
8	SK-PC-B70M	Antioxidant	SK Chemicals	Phase-III	561
7. *Ca^{2+} Signaling*					
1	ARC-031	Calcium channel blocker	Archer pharmaceuticals	Phase-I	557
2	Levetiracetam	N-type calcium channel blocker	Agene-Bio	Phase-II	562,563
3	Nilvadipine	Calcium channel blocker	Astellas pharma	Phase-III	560
8. *Neurotrophic-factor Signaling*					
1	FGL-2	Stimulates the secretion of nerve growth factor (NGF)	Enkam	Phase-I	564
2	NSG-0202	Stimulates the secretion NGF	Ns Gene	Phase-I	565

Sr no.	Agents in clinical trial	Mechanism of action	Company	Trial status	References
3	T-817MA	Neurotrophic agent	Toyama, FUJIFILM	Phase-II	566
9. *Endosomal-lysosomal System*					
1	GC-021109	Inducer of phagocytosis	Glia cure	Phase-I	567
10. *Ubiquitin Proteasomal System*					
1	Resveratrol	Restore proteasomal activity	Solgar, Country life, MRM	Phase-III	203,568
11. *Insulin Signaling*					
1	Exenatide	Agonist of human glucagon-like peptide-1 (Amino acids 7–37)	NIH	Phase-II	569
2	Liraglutide	Agonist of human glucagon-like peptide-1 (Amino acids 7–37)	Imperial college	Phase-II	570
3	MSDC-0160	Antidiabetic	Metabolic solutions	Phase-II	571
4	Humulin	Insulin signaling	NIH	Phase-III	524
12. *Miscellaneous*					
1	AUS-131	Non-hormonal selective estrogen receptor beta (ERbeta) agonist	Ausio pharmaceuticals	Phase-I	572
2	BPN14770	Phosphodiesterase inhibitor	Tetra discovery partners	Phase-I	573
3	Copaxone	Immunomodulator	Cedar-sinai medical center	Phase-I	574
4	RP-5063	Multitarget	Reviva Pharma	Phase-I	575
5	Telmisartan	PPARalpha agonist, signal transduction modulator, PPARgamma modulator	Astellas Pharma	Phase-I	576,577
6	AVN-101	Not-disclosed	Avineuro	Phase-II	578
7	AVN-397	Not-disclosed	Avineuro	Phase-II	579
8	Benfotiamine	Neuroprotector	Burke Medical Research Institute	Phase-II	580
9	BI-409306	Phosphodiesterase inhibitor	Boehringer Ingelheim	Phase-II	581
10	Bryostatin-1	Activator of protein kinase C (PKC) isozymes	Blanchette Rockefeller Neuroscience institute	Phase-II	582
11	DAOI-B	Inhibits D-amino acid oxidases	Chang Gung Memorial Hospital	Phase-II	583
12	Davunetide	Glial cell mediator of vasoactive intestinal peptide (VIP) induced neuroprotection	Allon therapeutics Inc., paladin Labs INC.	Phase-II	584,585
13	Isotretinoin	Retinoid receptors	Hexal AG	Phase-II	586
14	LND-101001	Not-disclosed	Lupin	Phase-II	587
15	MK-7622	Not-disclosed	Merk & Co.	Phase-II	588
16	Rph-201	Not-disclosed	Regenera pharma	Phase-II	589
17	Sargramostim	Granulocyte macrophage-stimulating agent	Perrigo	Phase-II	590
18	Tamibarotene	Retinoic acid receptor (RAR) alpha agonist	Osaca City University	Phase-II	591
19	UE-2343	Inhibitor of 11-beta-hydroxysteroid dehydrogenase type-1	Actinogen	Phase-II	592
20	VX-745	MAPK P^{38} inhibitor	EIP pharma	Phase-II	593

Sr no.	Agents in clinical trial	Mechanism of action	Company	Trial status	References
21	Xanamen	Inhibitor of 11-beta-hydroxysteroid dehydrogenase type-1	Actinogen	Phase-II	[592]
22	AC-1202	Undisclosed	Accera	Phase-III	[594]
23	AC-1204	Stimulation of metabolic process	Accera	Phase-III	[595]
24	Insulin detemir	Not-disclosed	Novo Nordisk	Phase-III	[596]
25	Masitinib mesylate	Inhibitor of c-KIT receptor, growth factor receptor (PDGFR), Fibroblast growth factor receptor-3 (FGFR-3) tyrosine kinases	AB Science	Phase-III	[597]
26	Memryte	Durin-leuprolide acetate and GnRH (LHRH) receptor agonist	Durect, Curaxis pharmaceutical	Phase-III	[598]