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Review

# New insights on Alzheimer's disease

Randa Abdel Kader Mahmoud El-Desouki *

*Department of Biochemistry and Molecular Medicine, Faculty of Medicine, Taibah University, Almadinah Almunawwarah, Saudi Arabia*

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ABSTRACT

Alzheimer's disease (AD), the most common age-associated dementing disorder, is clinicopathologically manifested by progressive cognitive dysfunction concomitant with the accumulation of senile plaques (SP). SP is consisting of amyloid-β (Aβ) peptides and neurofibrillary tangles (NFTs) of hyper-phosphorylated tau (p-tau) protein aggregates in the brain of affected individuals. Lipid rafts promote interaction of the amyloid precursor protein (APP) with the β-secretase enzyme responsible for generation of the Aβ peptides. Fibrillar Aβ oligomers, which have been shown to correlate with the onset and severity of AD, bind preferentially to cells and neurons expressing cellular prion protein ($PrP^C$). The binding of Aβ oligomers to cell surface $PrP^C$, as well as their downstream activation of Fyn kinase, was dependent on the integrity of cholesterol-rich lipid rafts. Rafts also regulate cholinergic signaling as well as acetylcholinesterase and Aβ interaction. Such major lipid raft components as cholesterol and ganglioside (GM1) have been directly implicated in pathogenesis of the disease. Perturbation of lipid raft integrity can also affect various signaling pathways leading to cellular death and AD.

In this review, I will discuss the more recent findings on the biopathological mechanisms, candidate bio-markers, and therapeutic interventions of the elusive AD.



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* Tel.: +966 543676660.
*E-mail address:* randa592003@yahoo.co.uk

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## 1. Introduction

Alzheimer's disease (AD) is a common, progressive and devastating neuro-degeneration of human brain structure and function, from which over 37 million people are suffering worldwide [1] with an estimated cost of $600 billion in 2010 [2]. Globally, 5 million new cases of AD are diagnosed annually, with one new AD case being reported every 7 s [3]. The risk of developing AD correlates strongly with aging, resulting in a deterioration of mood, behavior, functional ability, cognition, and memory [4], therefore, AD is becoming an increasing socio-economic crisis as life expectancy increases. Taking care of AD patients places a tremendous socioeconomic burden not only on unpaid caregivers but on our health care system as a whole [5]. In spite of this, there is no current therapy that can halt or reverse AD [6].

The disease is associated with brain pathology involving accumulation of extracellular amyloid aggregates (also known as senile plaques) (SP) of small, toxic, and highly amyloidogenic 42 amino acid amyloid beta (Aβ42) peptides and intracellular neurofibrillary tangles (NFTs) of hyper-phosphorylated tau (p-tau) protein [7,8]. According to the amyloid cascade hypothesis, it is the Aβ which is principally responsible for many of the pathological features of the disease with Aβ oligomers representing the most toxic species [9]. The accumulation of Aβ42 as diffuse plaques triggers the inflammatory responses due to microglial activation with release of pro-inflammatory cytokines and the most affected brain areas are the neocortex and hippocampus. In addition, perturbations in the equilibrium between kinases and phosphatases resulting in hyperphosphorylation of tau protein that results in neuronal degeneration and neuronal loss [10].

Allam et al. [11] strongly suggested through the results of their bioinformatics study that presenilins (PS-1, PS-2) and amyloid precursor protein (APP) play a dominant role in the pathogenesis of AD by inducing a pro-inflammatory state; raises the possibility that genetic components are more important in AD compared to environmental, metabolic, and age related factors.

Although there are strong genetic links, including APP, PS-1, and PS-2 mutations [12], as well as the apolipoprotein ε4 allele [13], sporadic AD is the dominant form. From this point of view pre-dominance of AD research based on the mechanisms of early onset disease versus the broader spectrum of the factors leading to the sporadic form might be one of the reasons for the failure of the majority of therapeutic trials and lack of any preventive measures 20 years since the amyloid hypothesis has been proposed [14].

In this review, I will elaborate on the current status of research addressing the biopathological mechanisms, candidate bio-markers, and therapeutic interventions of the elusive AD.

## 2. Lipid rafts

The notion of lipid rafts, while not new, has never been far from controversy, their existence frequently questioned. They are small nanodomains (10–200 nm), heterogeneous, highly dynamic of which there are millions in a single cell [15]. They have recently gained considerable attention as these membrane-embedded clusters of phospholipid-sphingolipid- and cholesterol-enriched, integral and peripheral membrane proteins are instrumental in the processing of APP holoprotein and hence the amyloidogenic process itself [16,17]. Small rafts can sometimes be stabilized to form larger platforms through protein–protein and protein–lipid interactions" [15]. The long, saturated acyl chains of sphingolipids allow tight packing hence their juxtaposition with the kinked, unsaturated acyl chains of bulk membrane phospholipids leads to phase separation. The cholesterol molecules can act as "spacers," filling any gaps in sphingolipid packing [18]. Pike [15] showed the importance of lipid rafts in protein sorting and segregation with glycosylphosphatidylinositol (GPI)-anchored proteins, being preferentially localized in lipid rafts. Other lipid modifications of proteins have also been described, such as palmitoylation and myristoylation which may influence raft localization [15]. In describing membrane lipid clusters as moving platforms, or rafts perhaps the most important finding was that proteins could

be segregated being selectively included or excluded from the rafts. In this way, raft localization can serve to facilitate or obstruct protein interactions or act as a protein scaffold while allowing diffusion [19].

## 3. Lipid raft components and their changes in AD

### 3.1. Raft localization of APP and secretases

Interestingly, all of the enzymatic machinery responsible for the generation of Aβ42, and subsequent SP formation, are plasma membrane-resident secretases with modifier/accelerator/accessory proteins that are involved in the catabolic processing of the membrane-bound beta-APP. Beside the β-secretase; presenilins are transmembrane proteins localized predominantly in the endoplasmic reticulum (ER) and Golgi apparatus. The accelerator proteins include nicastrin, aph-1, pen-2, sortilin, TSPAN membrane proteins, and others [5] interact with PS-1 and PS-2 to form a large enzymatic complex known as γ-secretase that cleaves APP to generate Aβ [20]. In addition, they interact with antiapoptotic Bcl-2 through human FK506-binding protein 38, thus it may regulate the apoptotic cell death [21].

### 3.2. Generation of Aβ42

Aβ is cleaved out of the APP through the sequential action of the β-secretase and the PS-containing γ-secretase complex "amyloidogenic pathway". In the alternative, "non-amyloidogenic pathway", APP is first cleaved by the α-secretase, members of the ADAM (a disintegrin and metalloprotease) family of zinc metalloproteases, within the Aβ sequence thus precluding production of intact Aβ peptides [22].

### 3.3. Cellular mechanisms of Aβ oligomer-mediated neurotoxicity

#### 3.3.1. Cellular prion protein ($PrP^C$) signaling in AD

The key event driving AD pathogenesis is the accumulation of the 40–43 residue Aβ peptides in the brain [23]. The peptides, particularly Aβ1–42, are aggregation prone, self-assembling to form a heterogeneous mixture of soluble oligomers, protofibrils and fibrils. Only levels of the soluble, fibrillar oligomers were found to be elevated significantly in AD brains, where their levels correlate strongly with AD onset-severity, and are therefore proposed to be the major neurotoxic species in AD [24]. Consequent deleterious effects include neurotoxicity, memory impairments, inhibition of long-term potentiation (LTP), loss of dendritic spines and synaptic dysfunction [25]. The cellular mechanisms of Aβ oligomer-mediated neurotoxicity are, however, poorly defined [26].

The cellular prion protein ($PrP^C$) was identified as a high-affinity receptor for Aβ oligomers [27]. $PrP^C$ is a GPI anchored cell surface glycoprotein. It is a neuroprotective and plays important roles in limitation of excessive N-methyl-D-aspartate (NMDA) receptor activity which might cause neuronal damage, neuronal oxidative stress defense, and metal ion homeostasis in the brain [28]. It also lowered Aβ production through the inhibition of β-secretase [29].

However, fibrillar Aβ oligomers, but not monomers or fibrils, bound tightly to $PrP^C$ [27,30] and the presence of $PrP^C$ in hippocampal slices was shown to be responsible for the fibrillar Aβ oligomer-mediated inhibition of LTP [27] and the manifestation of memory impairments in an AD mouse model [25]. Recent studies have identified $PrP^C$ as a critical modulator of the AD-related synaptic dysfunction and cognitive impairments caused by Aβ oligomers [31]. Rushworth et al. [26] revealed details of the molecular and cellular mechanisms underpinning the $PrP^C$-fibrillar Aβ oligomer interaction and the resulting downstream cellular events.

Fibrillar Aβ oligomers cointernalised with $PrP^C$ from the cell surface and then trafficked to endosomes and lysosomes through low-density lipoprotein receptor-1 (LRP1) which is highly expressed in neuronal cells. It is a transmembrane protein that facilitates the clathrin-mediated endocytosis of $PrP^C$ [32] and has also been implicated in the neuronal uptake of Aβ oligomers [33]. Rushworth et al. [26] indicated that LRP1 functions as a transmembrane co-receptor that is involved in the Aβ oligomers-$PrP^C$ interaction and is required for their internalization, and cytotoxicity of the Aβ oligomers. Um et al. [34] revealed that $PrP^C$ also mediates the transcytosis of monomeric Aβ40 across the blood-brain barrier (BBB). The ability of fibrillar Aβ oligomers to stimulate the endocytosis of $PrP^C$, thus lowering its cell surface expression, impaired the ability of $PrP^C$ to inhibit β-secretase, hence increasing the amyloidogenic processing of APP [26]. Thus, $PrP^C$ is no longer protective but contributes to Aβ oligomer neurotoxicity and further Aβ production in a toxic, positive feedback loop. In addition, $PrP^C$ was required for the downstream cytotoxicity of the fibrillar Aβ oligomers through the activation of a member of the Src family kinases (SFK), Fyn kinase. The latter is implicated in multiple pathways that underlie AD [35], including mediating the toxicity of Aβ oligomers and linking Aβ to tau toxicity [36], NMDA receptor phosphorylation and cell surface distribution, dendritic spine loss and lactate dehydrogenase [34]. $PrP^c$ together with the data on β-secretase regulation provides a unifying molecular mechanism explaining the interplay between toxic Aβ species, NMDA receptor-mediated toxicity and copper homeostasis in pathogenesis of AD [37]. Interestingly, the interaction of $PrP^C$ with β-secretase [29] and the interaction of $PrP^C$ with LRP1 [32] are both dependent upon the polybasic N-terminal sequence (KKRP) of $PrP^C$. This same region is also the crucial determinant of $PrP^C$-mediated Aβ oligomer binding and toxicity. Surface plasmon resonance studies showed that deletion of the N-terminus blocked the toxicity of natural Aβ oligomers [38]. Thus, this region appears to be critical to a number of functions of $PrP^C$, although its role in protective functions raises questions, would be a viable approach for the treatment of AD? [26].

Rushworth et al. [26] found that not only the binding of the oligomers to $PrP^C$ but also the downstream signaling mechanisms is dependent on the integrity of the raft microdomains, disruption of the rafts caused a significant (80%) reduction in Aβ oligomer binding to the cells and prevented the activation of Fyn kinase.

The importance of using well-defined oligomer conformations for biological activity potentially explain the discrepancies in results showing a lack of $PrP^C$-dependence of Aβ oligomer toxicity, as different studies have employed distinct, often poorly characterized Aβ oligomer preparations or unnatural APP constructs which may not lead to the generation of biologically relevant Aβ oligomers [23]. As the conformation of fibrillar Aβ oligomers is a critical determinant of their $PrP^C$-mediated binding and subsequent toxicity so, disrupting the conformation of Aβ oligomers could also be a potential therapeutic approach for AD [22].

Tau is a microtubule-associated protein that stabilizes neuronal microtubules under normal physiological conditions, however in AD, Aβ induces tau phosphorylation that can result in the generation of aberrant aggregates that are toxic to neurons [39]. Mutations in tau give rise to NFTs but not plaques and mutations in APP or in the probable APP proteases give rise to both plaques and tangles indicates that amyloid pathology occurs upstream of tau pathology [11].

Aβ accumulation can be affected by numerous factors including increased rates of its production and/or impaired clearance. There are numerous proteases in the brain that participate in Aβ degradation and clearance including cathepsins, gelatinases, endopeptidases, aminopeptidase, neprilysin, serine protease, and insulin-degrading enzyme (IDE) [40]. Genetic linkage studies have also linked AD and plasma Aβ42 levels to chromosome 10q, which harbors the IDE gene. IDE has been observed in human cerebrospinal fluid (CSF); and its activity levels and m-RNA are decreased in AD brain tissue and is associated with increased Aβ levels [41].

### 3.4. APP sorting, transport, trafficking and processing

Although the function of APP remains to be fully elucidated, understanding APP trafficking and processing would also provide new insights into the regulatory mechanism of the amyloidogenic pathway. The processing of APP involves numerous steps, including APP sorting, transport, internalization and sequential proteolysis [42]. Newly synthesized APP in ER is sorted through the trans-Golgi-network (TGN), trafficked to the cell surface membrane, and internalized via its NPTY motif near the C terminus of APP into endosome/TGN for recycling or into lysosome for degradation [43]. Altered routing of APP trafficking and distribution in neurons might lead to the amyloidogenic pathway, which is implicated in the pathology of AD. Hence, the intracellular distribution and transport of APP are critical for Aβ production [44]. Sortilin is important in neuronal functions and shares genetic similarity with other Vps10p family members, such as SorLA, SORCS1 and SORCS2 [45]. SorLA is down-regulated but sortilin is up-regulated in AD [46]. SorLA is reported to retain APP in Golgi, this can lead to decreasing Ab production. Meanwhile, sortilin is associated with APP via head-to-head (the extracellular domain) and tail-to-tail (the intracellular domain) interactions; it regulates APP lysosomal and lipid raft trafficking through FLVHRY motif, and may promote lysosome-dependent degradation of APP [44]. They found that lack of the FLVHRY motif reduces APP lysosomal targeting and increases APP distribution in lipid rafts in cotransfected HEK293 cells, and in sortilin knockout mice [44]. Other, membrane-integral or -peripheral associated modulators of Aβ42 peptide generation such as TSPAN 12 further contributes to the kinetics of formation, cleavage, processing, and speciation of APP [47]. Recently, the participation of a membrane-spanning triggering receptor expressed in myeloid cells 2 protein supports a role for yet another plasma membrane-integral glycoprotein in phagocytosis and the clearance of Aβ42 peptides before they aggregate into SP [48]. Hence, depending on the processing pathways and biological signals utilized, the plasma membrane can be the source of both beneficial and detrimental signals to further modulate amyloidogenic, inflammatory or neurotrophic aspects of the AD process [5].

## 4. Genetic studies/bioinformatics analysis

The bioinformatics analysis revealed 3 important proteins “PS-1, PS-2, and APP” out of 74 proteins to be the key pathological proteins in the evolution of AD [11].

### 4.1. Familial Alzheimer’s disease (FAD)

Missense mutations in the genes of APP, PS-1, and PS-2 that are located on chromosomes 21, 14, and 1, respectively share the common feature of altering the γ-secretase cleavage of APP to increase the production of the amyloidogenic Aβ42, the primary component of amyloid plaques in both familial and sporadic AD [11,49]. The mutated compounds, apart from increasing the ratio of Aβ42 to Aβ40, may down-regulate the calcium buffering activity of the ER. Decrease in the ER calcium pool would cause compensatory increases in other calcium pools, particularly in mitochondria with the consequent of enhanced formation of superoxide radical formation, and damage to the neurons and their senility [49].

Intriguingly, glucosylceramide (GlcCer) synthase expression, an enzyme needed for the production of GlcCer, is reduced in mutant PS1-transfected neuronal cells without any effect on its mRNA expression [50]. Correspondingly, the amount of GlcCer and neuroprotective gangliosides which is synthesized from GlcCer, is significantly reduced in these cells. This reduction may affect the functions of lipid rafts and therefore make these cells vulnerable to cellular stress. In the same mutant cells, the high affinity nerve growth factor receptor “Trk” which is resident in lipid rafts, became also insensitive to its ligand, NGF. So, these cells became more sensitive to oxidative stress than those of their parental cells [51].

## 5. Lipids and Alzheimer’s disease connection

### 5.1. Phospholipids

Phospholipid alterations could lead to membrane instability and synaptic loss, in that way, contribute to AD pathology [52]. Plasma membrane-derived phospholipids and esterified dococahexaenoicacid (DHA) are the substrate for phospholipases, and hence the precursors for arachidonic acid cycle metabolites and cyclooxygenase

conversion, that supports inflammatory signaling in the CNS [53]. Plasma membranes can also provide free DHA for conversion via a 15-lipoxygenase into neuroprotectin D1, a potent neurotrophic docosanoid [54].

The availability of APP to α- or β-secretase determines how much of the pathogenic Aβ peptides will be produced. Since these two secretases/pathways are likely to be spatially separated within the cell, it is possible that alterations of APP trafficking, caused by lipid changes, may be the primary cause of the disease process [55]. Under normal conditions, only a small portion of β-secretase is localized in lipid rafts. Targeting of β-secretase to lipid rafts by adding an GPI anchor at the place of transmembrane and C-terminal domain increased the production of Aβ. In contrast, α-secretase is under normal conditions exclusively present in non-raft fractions. Replacing its transmembrane and cytosolic domain with GPI anchor caused retargeting it to lipid rafts and hence reduced amyloidogenic APP processing. Overall, these results imply that regulation of lipid rafts protein targeting could be a good approach for controlling APP amyloidogenic processing [56].

However, another signal for β-secretase targeting to lipid rafts is S-palmitoylation of Cys 474, 478, 482 and 485. Mutations of these Cys residues to Ala relocated β-secretase out of lipid rafts, but without affecting APP amyloidogenic processing [57]. Meanwhile, S-palmitoylation of γ-secretase complex subunits nicastrin and aph-1 is important for their stability and raft localization, but not for γ-secretase processing of APP [58].

Another interesting approach was the synthesis of the membrane-anchored version of β-secretase inhibitor, which was targeted to endosomes and lipid rafts, where its local concentration was increased. In that way, this inhibitor was more potent and focused on active β-secretase [59].

### 5.2. Gangliosides (GM)

The link of GM with AD pathology has been mostly related to their localization in lipid rafts which act as a platform for GM1-induced aggregation of Aβ peptide [60]. The N-terminal region of Aβ interacts with GM1 clusters through hydrogen bonding and electrostatic interactions, and cholesterol may facilitate GM1 clustering [59]. Extraction of cortical lipid rafts from human AD brains showed an increase in both GM1 and GM2 despite an overall reduction of GM [60], indicating that they accumulate in SP and may be involved in the conversion of Aβ to a neurotoxic oligomeric form [14].

### 5.3. Cholesterol

Cholesterol has long been clinically associated with AD pathogenesis and this connection attracted many research groups to explore the underlying causal role of cholesterol on APP processing for therapeutic intervention [60].

The role of cholesterol has been especially clarified by the findings of genetic, epidemiological, and biochemical studies [36]. Several genes involved in cholesterol metabolism or transport are AD susceptibility genes, including apolipoprotein E (ApoE), ApoJ, ATP-binding cassette subfamily member 7 and sortilin-related receptor [36]. Cholesterol dyshomeostasis has a close association with the progression of Alzheimer's cognitive impairment [37], the synaptic loss [20], Aβ [37], and NFTs pathology [22,39,61]. Individuals with elevated cholesterol levels during mid-life tend to develop AD pathology. The levels of total cholesterol and LDL in serum correlate with Aβ load in the AD brains [62]. If cholesterol increases do elevate lipid raft abundance, then it would increase Aβ formation and, on the contrary, low cholesterol levels will lead to up-regulation of the activity of the α-secretase [14,62].

However, quantification of global cholesterol levels are not necessarily reflective of the number or distribution of lipid rafts [63]. Formation of the Aβ "seed" and initiation of Aβ aggregation was shown to be cholesterol dependent. It facilitated the insertion of Aβ into the plasma membrane. In so doing, Aβ then destroys the cells' membrane integrity [64]. Aβ peptides also modulate the metabolism of cholesterol, in particular its esterification rate, alter vesicle trafficking and cholesterol homeostasis and prevent its interaction with low-density lipoprotein. It might also act as a component of lipoprotein complexes affecting reverse cholesterol transport from neuronal tissue to the periphery [65].

However, APP intracellular domain (AICD) was found to regulate cholesterol levels via lipoprotein receptor apoE/LRP1. There are data reporting that cholesterol in physiological concentrations can protect neuronal cells against Aβ-induced toxicity and slow down the process of formation of toxic aggregates of Aβ with metal ions, in particular with aluminum [14,66]. Cholesterol depletion disrupts lipid rafts with GPI-anchored $PrP^C$ being redistributed into non-raft regions of the membrane. However, depletion was also shown to affect formation of functionally active AICD resulting in reduced levels of expression of the amyloid-degrading enzyme, neprilysin [67].

### 5.4. Statins

In retrospective studies patients treated with statin, the inhibitor of hydroxymethyl glutaryl coenzyme A (HMG CoA) reductase, and the key enzyme in the biosynthesis of cholesterol, showed significantly reduced prevalence and incidence of AD. Statin may reinforce α-secretase activity via modifying the biophysical properties of plasma membranes or modulating the function of unidentified protein kinases via the Rho/ROCK1 protein phosphorylation pathway [68] thus impeding Aβ generation. It limits the amyloidogenic pathway via inhibiting the dimerization of β secretase (the active form) and indirectly inhibits γ-secretase activity [69]. It has also a role in limiting the hyperphosphorylation of tau [68]. Sabbagh et al. [70] indicated that AD carriers of the KIF6 719Arg allele (Arg/Arg homozygotes and Arg/Trp heterozygotes) is associated with the effects of statin on cholesterol levels. In particular, fluvastatin modifies the trafficking of APP and increase lysosomal degradation of APP and hence facilitates Aβ clearance [71–73]. Atorvastatin prevents cognitive impairments via improving hippocampal synaptic function, and restores BBB integrity to enhance the clearance of Aβ by anti-inflammatory lipid-modulating process [71,72].

Statin has also non-lipid neuroprotective role, it attenuates Aβ pathology via anti-inflammation, anti-atherosclerotic, anti-oxidant, and anti-apoptotic actions [73]. It significantly suppressed the Aβ-induced expression of IL-1β, inducible nitric oxide synthase by microglia and monocytes, and rac1-dependent activation of NADPH oxidase and superoxide production [68]. As ApoE has been found necessary for Aβ pathology suppressing ApoE secretion by statin could inhibit the production of Aβ and the formation of amyloid plaques [68,74].

Recently, however, the benefits of statin with respect to the incidence or cognitive decline in patients with AD have been challenged. Some studies evidence beneficial effects, but others show a slight or no clinically demonstrable cognitive benefit [68,72–74]. Statin can induce intracellular accumulation of APP, β-secretase-cleaved fragments, and Aβ via an isoprenoid-dependent mechanism. Simvastatin showed reduced Aβ in treated patients, but no corresponding improvement in cognitive performance. The Cochrane Dementia and Cognitive Improvement Group study reported that statin treatment had no effect on the prevention or treatment of dementia [74]. However, taking into account the highly variable relationship between the initiation of statin therapy and the time and severity of the AD, it is very difficult to get a conclusive assessment, so any epidemiological meta-analysis study should use a defined set of criteria for their patients [75].

Since all enzymes involved in APP processing are transmembrane proteins, as well as APP, it is logical to assume that lipid rafts could be involved in AD pathogenesis.

## 6. Factors influencing the initiation and progression of AD

Among the factors that influences the initiation and progression and thus, have a role in the pathophysiology of AD are Aβ42/Aβ40 ratio and oligomers of these peptides; oxidative stress; proinflammatory cytokines produced by activated glial cells, alterations in cholesterol homeostasis, and alterations in cholinergic nervous system [11].

### 6.1. Lipid raft redox signaling

Lipid rafts microdomains, are able to form different membrane macrodomains or platforms upon stimulations, including redox signaling platforms, which serve as a critical signaling mechanism to mediate or regulate cellular activities or functions. In particular, assembling of NADPH oxidase subunits and the recruitment of other related receptors, effectors, and regulatory components, resulting, in turn, in the activation of NADPH oxidase and downstream redox regulation of cell functions [76].

### 6.2. Oxidative stress and neuronal death

Increased levels of reactive oxygen species (ROS), one of the major age-related damaging agents, produced by normal mitochondrial activity, inflammation and excess glutamate levels, are proposed to accelerate neurodegenerative processes characteristic of AD [77]. Aβ causes hydrogen peroxide accumulation in cultured hippocampal neurons that results in oxidative damage to cellular phospholipid membranes suggesting a role for lipid peroxidation in the pathogenesis of AD. The loss of membrane integrity due to Aβ-induced free-radical damage leads to cellular dysfunctions, such as inhibition of ion-motive ATPase, loss of calcium homeostasis, inhibition of glial cell $Na^+$-dependent glutamate uptake system that results in NMDA receptors mediated delayed neurodegeneration, loss of protein transporter function, disruption of signaling pathways, and activation of nuclear transcription factors and apoptotic pathways [11].

### 6.3. Inflammation and neuronal death

Significant dose-dependent increase in the production of prointerleukin-1 (IL-1), IL-6, tumor necrosis factor-α (TNF-α), monocyte chemoattractant protein-1, macrophage inflammatory peptide-1, IL-8, mitogen-activated protein kinase pathways, and macrophage colony-stimulating factor were observed after exposure to preaggregated Aβ42 as foreign material, since Aβ assemblies are apparently never observed during the development of brain and in the immature nervous system [11]. The involvement of inflammatory process in the pathogenesis of AD disease is further supported by the observation that inhibition or neutralizing the actions of TNF-α could be of benefit to these patients [11,78].

### 6.4. Cholinergic system and AD

A primary clinical symptom of Alzheimer's dementia is the progressive deterioration in learning and memory ability. There is a profound loss in the cholinergic system of brain, including dramatic loss of choline acetyltransferase level, choline uptake, and acetylcholine (ACh) level in the neocortex and hippocampus and reduced number of the cholinergic neurons in basal forebrain and nucleus basalis of Meynert occurs that are closely associated with cognitive deficits in AD. Pharmacological interventions that enhance or block further fall in ACh levels and thus, improve cholinergic neurotransmission are known to produce improvement in learning and memory in AD [11,79]. Aβ could enhance free radical generation and induce inflammation that could result in profound loss in the cholinergic system of brain [11]. ACh also has anti-inflammatory actions, and hence, a decrease in its level may further aggravate the inflammatory process and progression of AD. This "cholinergic anti-inflammatory pathway" acts by inhibiting the production of early proinflammatory cytokines "TNF-α, IL-1", late proinflammatory mediators "macrophage migration-inhibitory factor, and high mobility group box 1 protein" and suppresses the activation of NF-kB expression. Even more, systemic injection of IL-1 decreased extracellular ACh in the hippocampus. In addition, receptors of IL-1 are on APP mRNA positive cells and its ability to promote APP gene expression suggests that IL-1 plays an important role in AD [80].

Lipid raft localization has recently been linked to acetylcholinesterase (AChE), although the functional implications of this are as yet unclear [81]. AChE inhibition by compounds such as rivastigmine or galantamine represents the

major therapeutic option for treating the cognitive impairment seen in the early stages of AD. AChE exists in a number of different molecular forms (G1, G2, G4) of which the tetrameric G4 form is predominant in brain. In AD, brain G4 AChE levels fall as the disease progresses, while G1 and G2 levels rise somewhat, as compared to normal brains. In some brain regions with AD pathology, virtually all of the AChE is localized in these complexes, leading to the suggestion that AChE may promote Aβ aggregation [82].

A direct interaction between Aβ and AChE has been proposed, with binding occurring at the peripheral anionic site (PAS) of the enzyme. Those AChE inhibitors which occupy the PAS (e.g., propidium) show the most significant reductions in fibril formation since the catalytic site is not required for interaction with Aβ. Furthermore, monoclonal antibodies directed against the PAS inhibit fibril formation, which has led to the development of PAS blockers, such as the DUO compounds, that also occupy the active site. They show inhibitory activity on AChE as well as inhibition of Aβ40 fibril formation and have been suggested as potential novel AD therapeutics targeting two facets of the disease [83].

AChE is not a transmembrane protein, rather it is anchored to the plasma membrane by the proline rich membrane anchor (PriMA) which is a type I transmembrane protein and can be acylated. PriMA contains cholesterol recognition amino acid consensus motif which sequesters PriMA into lipid rafts and hence AChE is also partly associated with rafts [83].

### 6.5. Exosomes and microRNAs

Plasma membrane-derived exosomes are 30–90 nm diameter vesicles secreted into the extracellular milieu [84]. Besides containing various proteins and molecular constituents reflective of their cells of origin, these vesicles contain microRNAs as their most abundant nucleic acids [85]. These organelles may be capable of the paracrine transfer of genetic information between cells, either within the local environment of the brain or throughout the entire cerebrospinal or systemic circulation, at least in part dependent on plasma membrane-mediated biological mechanisms [84,85].

### 6.6. Dietary and environmental factors

Environmental and dietary factors which modulate plasma membrane integrity, flexibility and lipid raft effects might not only be relevant in amyloidogenesis but also in paracrine microRNA trafficking and the intercellular spreading of these soluble and mobile genetic signals. For example, plasma membrane biophysics, dynamics, and lipid raft domain perturbation by cholesterol and statin might not only have effects on cholesterol incorporation into membranes and lipid raft formation but also on the exocytosis of exosomes [16,17,84]. Furthermore, cholesterol can perturb the biophysical structure of the membrane and reorganize lipid raft domains, via protein–lipid and protein–protein interactions, contributing to membrane-mediated dysfunction of homeostatic APP neurobiology [5,16]. Also, the potential involvement of neurotropic viral infection with AD, involving processes that are plasma membrane-mediated, pro-inflammatory, and evasive of the brain's innate immune response [55,85].

## 7. AD-type 2 diabetes (T2DM) co-morbidity

Substantial epidemiological evidence shows an increased risk for developing AD in people with T2DM. Yet the underlying molecular mechanisms still remain to be elucidated. AD patients exhibit cerebral glucose hypometabolism possibly due to impairments of insulin signaling, brain insulin resistance and altered thiamine metabolism. Moreover, AD brains show decreased insulin levels, decreased activity of insulin receptors and signs of compensatory mechanisms such as increased insulin receptor density indicating AD as "type 3 diabetes" [86]. Thence, the contribution of glucose transportation abnormality and intracellular glucose catabolism dysfunction, with the consequent multiple pathogenic cascades induced by impaired cerebral glucose metabolism could result in neuronal degeneration and cognitive deficits in AD patients [87]. Moreover, the induction of multiple pathogenic factors as the result of glucose metabolism abnormality such as oxidative stress, inflammation, mitochondrial dysfunction, advanced glycation end products (AGEs), APOEε 4, cholesterol and so forth appear to be an important mediators that are likely to act synergistically in promoting AD pathology in diabetic subjects [87]. T2DM is also a risk factor for micro- as well as macro-vascular complications. Vascular abnormalities are strongly associated with AD [88] implying further involvement of T2DM in disease onset. Ischemic CVD caused by T2DM is positively associated with AD through the shared pathological mechanisms such as hyperinsulinemia, impaired insulin signaling, oxidative stress, inflammatory mechanisms and AGEs. In vitro insulin-stimulated Akt phosphorylation is decreased in hyperinsulinemic conditions in cortical neurons [89]. All forms of Aβ (monomers, oligomers and Aβ-derived diffusible ligands) can inhibit insulin signaling by directly binding to the insulin receptor and inhibit insulin signal [88]. Even more, aging increases the co-incidence of AD and T2DM. Tau phosphorylation at AD-related epitopes, including Thr212, Thr231, Ser262, and Ser396, increased with age in the soluble brain extracts of chronic T2DM obese rats and were accompanied by synaptic protein loss. There was also a marked age-dependent accumulation of polyubiquitinated tau in neurons of these diabetic rats. In addition, the mRNA and protein levels of p62, a known cargo molecule that transports polyubiquitinated tau to proteasomal and autophagic degradation systems, decreased robustly with age in rats. The impaired degradation of polyubiquitinated p-tau, due to age-T2DM-dependent and decreases in p62 transcription is a primary mechanism underlying increased AD-like pathology in a T2DM rat model as age increases [90].

These finding can guide to some potential possibilities to uncover diagnostic biomarkers for AD from abnormal glucose metabolism and to develop drugs targeting at repairing insulin signaling impairment and correcting thiamine metabolism abnormality [87–89].

## 8. AD diagnosis

Certain diagnosis of AD can be made only post-mortem. However, today in specialized clinics, using a combination of tools that include taking a disease history from patients and their families, and assessing cognitive function by neuropsychological tests, in combination with neuroimaging (CT, MRI and PET) to exclude other causes of dementia [91], AD can be diagnosed with more than 95% accuracy. Neurological tests, which are still the gold standard for the diagnosis of AD, are mostly accurate in identifying individuals with already developed dementia. Structural MRI provides measures of brain atrophy, which reflect loss of dendrites, synapses and neurons [56].

CSF is the most informative fluid source for neurodegenerative disease diagnosis/research, because of its constant physical contact with brain. CSF biomarkers p-tau, total tau and Aβ42 are useful for AD diagnosis and for identifying individuals with prodromal AD in mild cognitive impairment (MCI) cases [91]. Low CSF levels of Aβ strongly correlate with intracranial amyloid plaques and high concentrations of CSF p-tau correlate with tau-associated NFTs [91]. In humans, structural MRI and CSF biomarkers allow for the indirect assessment of the cellular changes underlying AD in vivo. The biggest challenge for clinicians and for application of novel therapies against AD is to accurately recognize prodromal AD patients and/or individuals with MCI who will develop AD. The multicenter study found that these CSF biomarkers identify incipient AD with good accuracy, but with less accuracy compared to single-center studies. Additional effort is needed for standardization of analytical techniques and clinical procedures to avoid variability between different centers [56].

### 8.1. Lipids as biomarkers for AD diagnosis

Unchanged phosphatidylcholine (PC) levels, but decreased lysoPC/PC ratio with elevation in different PC metabolites, have been reported in the CSF from individuals with AD compared to individuals with memory complaints, but without dementia, suggesting that AD is accompanied with increased PC hydrolysis. Sphingolipid alterations found in AD brain were also observed in the CSF. Increased levels of ceramides have been found in the CSF from individuals with AD compared to age-matched individuals. Han and coworkers found approximately 40% reduction of sulfatides in the CSF in an early stage of AD and unchanged levels of phosphatidylinositol (PI). The authors suggested that CSF sulfatide/PI ratio could be a sensitive and specific biomarker for early AD diagnosis [92]. Recently, Kosicek et al. [93] developed a high-performance liquid chromatography–electrospray/mass spectrometry method for CSF phospholipid screening for AD patients at different stages of the disease, including prodromal AD. They observed a statistically significant increase (around 50%) in sphingomyelin (SM) levels between prodromal AD group and cognitively normal group, while PI, phosphatidylethanolamine (PE) and PC levels were unchanged in all examined groups [56,93].

Recent work suggested that CSF levels of heart fatty acid binding protein (HFABP), a lipid binding protein involved with fatty acid metabolism and lipid transport may have diagnostic and prognostic value in the earliest stages of AD [94]. Desikan et al. [95] suggested that CSF HFABP reflects intra-cranial lipid biology and associates with Aβ-associated neurodegeneration irrespective of p-tau. Clinically, these findings suggested that HFABP may represent an important modifier of progression from amyloid deposition to neurodegeneration [95]. In addition to p-tau, the HFABP/Aβ/neurodegeneration axis may represent an important area for further investigation [96].

Although CSF is the most informative sample for monitoring brain pathological processes, blood/plasma is much easier and less invasive to collect and, thus, is more suitable for routine diagnosis and/or monitoring. Due to BBB and huge influence of diet and other body processes outside the brain on blood lipid levels, it is difficult to make a direct link between blood phospholipid levels and neurodegenerative processes [56]. Mielke et al. [97] found significantly lower ceramide levels in plasma from individuals with MCI, while no difference was observed in plasma ceramide levels between AD and non-demented controls.

Although so far reported CSF/blood phospholipid changes are not specific and sensitive enough to be a diagnostic biomarker, a combination of different sphingolipid CSF and/or blood levels could potentially contribute to more precise AD diagnosis in a very early stage. However, further research is required in order to clearly state that any of those lipids could be used as a biomarker [56].

## 9. Conclusion

AD is an age-related devastating neurodegenerative disorder, which severely impacts on the global economic development and healthcare system. Though AD has been studied for more than 100 years since 1906, the exact cause(s) and pathogenic mechanism(s) remain to be clarified. Also, the efficient disease-modifying treatment and ideal diagnostic method for AD are unavailable. A combination of diet, lifestyle, vascular, genetic, and amyloid related factors, enhance each other's contribution in the onset and course of AD, will be more likely the cause of the disease instead of one sole mechanism. To clarify the causes, pathogeneses and consequences on cerebral hypometabolism in AD will help break the bottleneck of current AD study in finding ideal diagnostic biomarker and disease-modifying therapy. Although the role of lipids rafts in AD pathogenesis is still controversial (as lipid rafts are controversial per se), it is evident that specific membrane platforms are involved in APP, β- and γ-secretase co-localization, APP processing and formation of the pathogenic Aβ peptide. Phospholipids provide an optimal membrane environment for protein interactions, trafficking and function. In terms of future progress, lipid raft research might open new avenues in regulation of the proteolytic and signaling processes involved in AD pathology. However, any therapeutics aimed at manipulation of lipid raft composition should be treated with caution.

## Conflict of interest

The author declares that I have no conflict of interest. I confirm that this manuscript does not infringe any other person's copyright or property rights, the author have contributed substantially to the manuscript, and I have agreed to publication of the work.

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