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Review

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Abstract. Brain lipid homeostasis plays an important role in Alzheimer’s disease (AD) and other neurodegenerative disorders. Aggregation of amyloid-β peptide is one of the major events in AD. The complex interplay between lipids and amyloid-β accumulation has been intensively investigated. The proportions of lipid components including phospholipids, sphingolipids, and cholesterol are roughly similar across different brain regions under physiological conditions. However, disruption of brain lipid homeostasis has been described in AD and implicated in disease pathogenesis. Moreover, studies suggest that analysis of lipid composition in plasma and cerebrospinal fluid could improve our understanding of the disease development and progression, which could potentially serve as disease biomarkers and prognostic indicators for AD therapies. Here, we summarize the functional roles of AD risk genes and lipid regulators that modulate brain lipid homeostasis including different lipid species, lipid complexes, and lipid transporters, particularly their effects on amyloid processing, clearance, and aggregation, as well as neuro-toxicities that contribute to AD pathogenesis.

Keywords: Alzheimer’s disease, apolipoproteins, lipids, amyloid, cholesterol, phospholipids

INTRODUCTION

Alzheimer’s disease (AD) is the most prevalent neurodegenerative disease of aging, and affects one in eight older Americans [1]. It affects over 26 million people worldwide, and this number is continuously increasing [2]. In 2012, more than 15 million family members and other unpaid caregivers provided an estimated 17.5 billion hours of care to people with AD, a contribution valued at more than $216 billion. Currently there is no available cure for AD, which makes it a major public health concern.

Late-onset AD, the most common form, affects over 90% of patients, and is sporadic with a complex etiology. In contrast, early-onset AD is a rare form of AD caused by monogenetic defects that follow an autosomal-dominant pattern. The major neuropathological hallmarks of AD are the accumulation of amyloid aggregates due to over-production or impaired clearance of Aβ peptide, the formation and spread of neurofibrillary tangles, as well as the progressive failure of endosomal and lysosomal clearance mechanisms, which lead to loss of synaptic function and ultimately neuronal death [3].

Several lines of evidence indicate that altered brain lipid metabolism may contribute to the pathogenesis of AD [4]. Since lipids are found ubiquitously inside amyloid plaques, the functional roles in Aβ generation, clearance, and deposition have been intensively investigated. For example, lipids can modulate the aggregation of Aβ and hyperphosphorylated tau.
Aβ peptide can interact with numerous lipids and lipid raft components such as gangliosides, phospholipids and cholesterol, thus promoting its aggregation on cell membrane and leading to disruption of membrane integrity. This could subsequently affect intracellular calcium homeostasis, and probably trigger neurotoxic cascades in AD.

One of the strongest genetic risk factors for late-onset AD is the ε4 allele of the ApoE (ApoE4), which is implicated in the transport and delivery of cholesterol in the brain [5–7]. ApoE is known to interact with Aβ, or compete with it for the binding to lipoprotein receptors. It is well-established that ApoE can significantly influence Aβ clearance and aggregation in an isoform-dependent manner and ApoE4 has impaired abilities to clear Aβ in the brain [8]). Recent evidence suggests that ApoE proteins are critical determinants of brain phospholipid homeostasis and ApoE4 isoform is dysfunctional in this process [9].

In the past a few years, several genetic risk factors involved in lipid regulations have been identified in late-onset AD patients. In this review we will discuss the functional roles of brain lipids and their interaction with genetic risk factors of AD that may contribute to disease pathogenesis.

**LIPID MEMBRANES**

Lipid rafts are dynamic assemblies of cholesterol and sphingolipids mainly in the cellular membrane, with an important role in signal transduction [10]. Many AD-associated proteins such as amyloid-β protein precursor (βAPP), γ-secretase, β-secretase, and neprilysin, have been found in lipid rafts where these proteins are thought to associate with each other in a functionally meaningful way. For example, lipid rafts can provide platforms where Aβ, ApoE, and tau interact to promote aggregation of Aβ oligomers and hyperphosphorylated tau [11]. A few studies showed that in the absence of ApoE, Aβ fibrils failed to form, and the amount of Aβ in lipid raft was decreased [12, 13], whereas in the presence of ApoE4, the formation of Aβ fibrils was accelerated [14]. Gangliosides are membrane glycolipids preferentially clustered in lipid rafts. It has been reported that gangliosides can modulate Aβ aggregation and cytotoxicity [15–19]. Under physiological conditions, soluble Aβ displays a high affinity binding to lipid rafts containing gangliosides [20, 21], and the specificity of Aβ-GM1 ganglioside complex formation inside lipid rafts is determined by local concentrations of cholesterol and GM1 [18, 22]. Aβ aggregates induce cytotoxicity, partially through altering membrane structure and permeability [23–25]. This toxicity is greatly increased with lipid rafts containing GM1, sphingomyelin and cholesterol [26]. The extent to which Aβ interacts with lipid membranes depends upon its aggregation state [27]. Oligomeric Aβ can bind to liposomes irreversibly, while monomeric Aβ exerts a rapid reversible adsorption [28, 29]. There is also a significant correlation between Aβ peptide formation and lipid composition within rafts, suggesting that changes in lipid composition are of importance in amyloid formation associated with AD pathology [30–32].

Finally, lipid rafts may provide novel therapeutic platforms for drug targets. One study reported that targeting BACE1 inhibitors to lipid rafts led to a decrease in hippocampal Aβ levels in an AD mouse model [33]. Moreover, docosahexaenoic acid (DHA), which is known to promote the non-amyloidogenic pathway and to influence cholesterol homeostasis [34, 35], was decreased in lipid rafts of neuronal membrane in AD brains compared to controls [36]. Restoring DHA levels in lipid rafts may alleviate amyloid pathology in AD.

**CHOLESTEROL IN AD**

Cholesterol is a sterol lipid important in structure and functions of cellular membrane, in particular, of plasma membrane. It also plays a key role in cell growth, viability, and synaptic plasticity [37]. Brain cholesterol represents 25% of the total amount of cholesterol in the human body. It is enriched in myelin and cell membrane of neuronal and glial cells. Cholesterol homeostasis in brain is balanced between cholesterol influx through internalization of ApoE-rich lipoprotein complexes and intracellular cholesterol synthesis.

Cholesterol levels and cholesterol turnover are affected in many neurodegenerative diseases. *In vitro* and *in vivo* studies implicate an essential role for cholesterol in AD pathogenesis [38, 39]. Lack of cholesterol supply to neurons impaired neurotransmission and synaptic plasticity [40], as well as induced neurodegeneration and tau pathology [41, 42]. Decreased levels of free cholesterol and cholesteryl esters induced an increase of cellular Aβ production [43]. Loss of neuronal membrane
cholesterol may also contribute to excessive amyloidogenesis in AD [44].

Conversely, elevated levels of cholesterol are suggested in early amyloidogenesis and development of AD [45]. Some studies showed increased cholesterol levels in human brains at early stages of AD [46–48]. One study [49] found that an increase in CNS cholesterol retention was responsible for an increased formation of Aβ peptide due to an excessive βAPP processing by β- and γ-secretases, leading to cholesterol enrichment around senile plaques, and extracellular deposits of amyloid Aβ. Another study demonstrated that cholesterol loading did not affect BACE1 activity directly [48], but induced βAPP redistribution and clustering in lipid rafts where BACE1 is present and internalized to endosomes where βAPP cleavage occurs, resulting in an increase in Aβ production [50]. Increased BACE1-mediated βAPP cleavage also led to an increased release of βAPP intracellular fragment AICD, which down-regulated low-density lipoprotein-related protein 1 (LRP-1) transcription and decreased the amount of LRPI receptor responsible for exogenous cholesterol capture at the plasma membrane [51]. It was shown that lowering cholesterol levels by statins and methyl-β-cyclodextrine (MβCD), respectively, reduced intracellular and extracellular levels of Aβ40 and Aβ42 in cultured neurons [49, 52, 53], suggesting that amyloidogenesis process is affected by cholesterol composition in lipid rafts [54].

Cholesterol is also proposed to mediate Aβ peptide insertion into phospholipids [55] and ion channels [56] in the cell membranes, causing pore formation and disruption of membrane integrity [57]. Moreover, chronic elevation in serum total cholesterol levels increases brain ApoE mRNA levels and secreted ApoE levels from glial cells [58]. In a rabbit hypercholesterolemic model, a cholesterol-rich diet increased Aβ and ApoE concentrations in temporal and frontal cortices, which paralleled with amyloid pathology observed in these brain regions [59–61]. On the other hand, ApoE contributes to normal cholesterol variability [62]. ApoE2 decreases total cholesterol levels while ApoE4 increases them. It is proposed that the pathogenic effect of the ApoE4 allele on the development of AD may be mediated through high serum cholesterol [63], which could result in an increased transport of iron across the blood-brain barrier [64], and subsequently induce neuronal vulnerability to oxidative stress. The involvements of ApoE in AD pathogenesis are discussed in details in the following section.

**PHOSPHOLIPIDS IN AD**

Growing evidence suggests that phospholipids can mediate and modulate key pathological processes associated with AD [65–67]. Lipid analysis of postmortem brain tissue from AD individuals suggested that anterior temporal cortex of brains from AD patients had significantly lower levels of phosphoinositol (PI) and trends for lower levels of PI phosphate (PIP) and PI-4,5-bisphosphate [PI(4,5)P2] [68]. Another study reported that AD patient brains had decreased levels of phosphatidylcholine and phosphatidylethanolamine, suggesting that AD may be associated with increased membrane phospholipid degradation [69]. A decade later, the list of phospholipids affected in AD is still growing. Reduction in levels of phosphatidic acid and cardiolipin, as well as elevation in levels of sphingomyelin and plasmalogon derivative of phosphatidylethanolamine were reported in AD brains [70]. Familial AD mutations of presenilins were shown to cause an imbalance in the metabolism of PI(4,5)P2 and correcting this imbalance decreased amyloid generation [65].

Further evidence suggests that specific phospholipid homeostasis may play an important role in the pathogenesis of AD [9, 71]. For example, a recent study reported that a recently identified AD risk factor TREM2 (Triggering Receptor Expressed on Myeloid cells 2) acts as a regulator of the microglial response through lipid sensing around senile plaques in an AD mouse model [72]. Our group recently investigated whether ApoE proteins play a critical function in brain phospholipid homeostasis [9]. We have found that brain PIP2 levels were lower in ApoE4 carriers as well as in animal brains, neurons and astrocytes expressing the human ApoE4 allele. While there were no changes in PI at early stages of AD, at advanced disease stages PI levels were significantly decreased. The changes in PIP2 were secondary to increased expression of a PIP2 degrading enzyme, synaptotagmin 1 (Synj1) [73], which is highly expressed in the brain. Interestingly, genetic knockdown of Synj1 expression in ApoE4 KI mice restored brain PIP2 homeostasis and rescued cognitive deficits in these mice [9].

**ROLE OF APOLIPOPROTEIN E IN AD**

ApoE is the main lipid transporter in the CNS where it mainly circulates along with high-density lipoprotein (HDL). Brain ApoE mediates the transport,
delivery, and clearance of cholesterol and phospholipids. It is an important regulator of synapse formation and neuronal signaling critical for learning and memory formation [74, 75]. Human ApoE is a 299 amino acid, 35 kDa glycoprotein that has three major isoforms differing by two residues: E2, E3, and E4. ApoE3 is the most commonly represented isoform, while ApoE4 and ApoE2 isoforms are found in a small portion of human population (with frequencies of 77–78%, 14–15%, and 7–8%, respectively) [76–78]. Epidemiological studies have shown that the presence ApoE4 allele confers an increased risk and decreased age of onset in AD in a gene dose-dependent manner, whereas ApoE2 might play a protective role against AD [79]. While the ApoE4 allele is associated with a more rapid rate of cognitive decline [80], the ApoE2 allele may slow the progression of neurodegeneration [81].

Brain ApoE is produced mainly by astrocytes and to a much less extent by oligodendrocytes and microglia [82]. It plays an essential role in secretion of glial lipoproteins under physiological conditions. ApoE binds to HDL and forms complexes that function as the major carriers of cholesterol in the brain, supporting synaptic formation and plasticity, as well as maintaining integrity of myelin and neuronal membrane [83, 84]. ApoE-containing lipoproteins are internalized via receptor-mediated endocytosis by low density lipoprotein receptor and LRP family members [85]. The amino acid differences between the ApoE isoforms may result in functional differences, especially their binding affinities to different ApoE receptors and lipoprotein subtypes [85, 86]. For example, ApoE4 binds preferentially to large, triglyceride-rich very low density lipoprotein, whereas ApoE2 and ApoE3 will bind preferentially to small, phospholipid-rich HDLs. In brains of individuals with AD, de novo synthesis of cholesterol and lipid molecules was reduced in cortical and hippocampal areas, and neurons were dependent upon the internalization of exogenous ApoE-rich lipoprotein complexes as a source for such lipids. The ApoE4-induced cognitive decline in AD seemed to be exacerbated in patients with concurrent cerebrovascular disease [87], hypertension, diabetes, hypercholesterolemia, or atherosclerosis [88–91], partially due to dysregulation of intracellular lipid trafficking [92–94].

Several lines of evidence suggest that ApoE isoforms differentially regulate Aβ aggregation and uptake, degradation, and phagocytic clearance in the brain [95, 96]. In addition, ApoE may have a protective role against Aβ-induced oxidative stress, with ApoE2 and ApoE3 being more efficient than ApoE4 [97].

Aβ is a soluble monomeric amphipathic molecule that has diverse functions in the brain [98]. Aβ can self-aggregate (oligomerization) which leads to fibril formation in pathological conditions, whereas under physiological conditions Aβ is associated with lipoproteins [99]. A study suggested that Aβ is a functional constituent of ApoE in ApoE-HDL lipoprotein complexes in the brain and peripheral circulation [100]. Aβ when not associated with lipoproteins may induce neurotoxicity or glial activation. Evidence suggests that ApoE4 enhances the nucleation and aggregation of Aβ deposits [101], which contribute to an increased Aβ-mediated oxidative damage [102].

Furthermore, ApoE can affect Aβ clearance through ApoE receptor-mediated endocytosis by neurons and glial cells [95, 103, 104], or through the efflux of Aβ across the blood-brain barrier. In vitro studies demonstrated a functional role of ApoE in the internalization and degradation of Aβ by microglia and astrocytes [95, 105, 106]. Other studies suggested that Aβ clearance was greatly decreased upon complex formation between Aβ and ApoE [107, 108]. The rate of endocytosis became much slower when transporting Aβ bound to ApoE-HDL complexes than internalizing Aβ alone [109]. The efflux of Aβ across the blood-brain barrier is shown to be mediated by LRP1 receptors [108, 110, 111]. One proposed mechanism in AD pathogenesis is the competition between ApoE and Aβ for binding to LRP1 could affect Aβ clearance from CNS [14, 112].

In addition, the lipidated state of ApoE may play an important role in AD pathogenesis. It has been suggested that lipidation of ApoE might influence the ability of ApoE-containing lipoproteins to interact with Aβ and subsequently influence Aβ aggregation. Non-lipidated ApoE3 and ApoE4 form similar amounts of SDS-stable complexes with Aβ, while lipidated ApoE2 and ApoE3 interact with Aβ and form SDS-stable complex more efficiently than ApoE4 does [103, 113, 114]. Lipidated ApoE4 appears less effective in removing extracellular Aβ, and more effective at promoting Aβ fibril formation and zinc- and copper-induced Aβ aggregation [103, 115, 116].

ABC-TRANSPORTERS IN AD

ATP-binding cassette (ABC)-transporters play an important role in trafficking lipids and other lipophilic
molecules across membranes, as well as regulation of lipid homeostasis [117]. ABCA1, a member of the ATP binding cassette superfamily, is a transmembrane cholesterol and phospholipid transporter. In the brain, ABCA1 is required for cholesterol efflux to apolipoproteins such as ApoE [118, 119]. It has been reported that AD is associated with a polymorphism in ABCA1 (ATP-binding cassette, subfamily A, member 1) [120].

ABCA1 deficiency decreased lipid efflux to secreted ApoE, increases intracellular glial lipid accumulation, reduced ApoE lipidation, and decreased ApoE levels in whole brain, particularly in the striatum and hippocampus [118]. The decreased ApoE levels were not related in ApoE gene expression, but likely resulted from an increased metabolism of abnormally lipitated ApoE-containing lipoprotein particles [121]. Mice lacking ABCA1 had dramatically lower ApoE levels in the plasma, cerebrospinal fluid (CSF) and brain [121, 122].

Besides regulating ApoE metabolism, ABCA1 also influences ApoE lipidation and recycling [123, 124]. Previous studies showed that in ABCA1-deficient mice, levels of astrocyte-secreted ApoE were decreased and the secreted ApoE was poorly lipitated [118, 121, 122], which may contribute to impaired clearance of Aβ in the brain [121, 125]. As a result, a deficiency of ABCA1 increased Aβ deposition in human βAPP transgenic mice [118, 121, 122]. Interestingly, ABCA1 deficiency only increased Aβ deposition in ApoE4 mice with an APP Swedish/PS1ΔE9 transgenic background, but not in ApoE3 mice [126], suggesting that the effects of ABCA1 on Aβ clearance are mediated through ApoE isoforms.

Another ABCA family member ABCA7 has also been described as a genetic risk factor for late-onset AD [127]. Similar to ABCA1 (with 54% sequence homology), ABCA7 is involved in regulating lipid homeostasis [128], phospholipids and cholesterol transport across cell membranes to ApoA and ApoE, as well as lipidation of ApoE. ABCA7 is highly expressed in the brain [129–131]. Overexpression of ABCA7 in cell lines expressing human βAPP resulted in decreased Aβ levels, whereas deletion of ABCA7 impaired Aβ uptake in vitro [117, 131, 132]. A recent study also showed that overexpression of ABCA7 was neuroprotective against AD [132], whereas deletion of ABCA7 increased amyloid plaque burden in the brain of βAPP transgenic mice due to reduced phagocytic clearance of Aβ [132].

Finally, another less known member of ABCA protein family, ABCA5 has been recently associated to AD [133]. ABCA5 is highly expressed in hippocampal and cortical neurons in both human and mouse brains. Interestingly, ABCA5 may act on Aβ production rather than its clearance. Overexpression of ABCA5 reduced levels of secreted Aβ peptides, possibly due to modulation of AβPP processing [133].

**PHOSPHOLIPASE D**

Phospholipase D (PLDs) are ubiquitous enzymes which catalyze the hydrolysis of phosphatidylcholine to phosphatic acid and choline. Phosphatic acid is a lipid second messenger which regulates cytoskeletal organization, vesicular trafficking, and cell proliferation. Choline, on the other hand is the precursor for acetylcholine synthesis. Interestingly in AD, early pathological changes are characterized by cholinergic dysfunction with neuronal loss, starting with cholinergic neurons.

A few lines of investigation link PLD to AD. In cells that exhibit AD-like mutations PLD activity was reduced, but overexpression of PLD1 in these cells corrected impaired intracellular trafficking of βAPP and reduced Aβ production [134]. In contrast, PLD2 was found to promote Aβ toxicity in cell cultures [135]. Overexpression of human wild type βAPP in P19 mouse embryonic cells caused an increase in PLD activity [136]. Aβ also induced an increase in PLD activity in rat hippocampal primary cultures. This increase in PLD activities was correlated with an enhanced release of cytosolic protein lactate dehydrogenase, suggesting a potential association with Aβ-induced toxicities [137]. These studies implicate a potential crosstalk between PLD1, βAPP and PS1 contributing to amyloidogenesis and amyloid-induced toxicities [134, 138, 139]. However, it is unclear whether this crosstalk occurs in vivo. It should be noted that PLD1 and PLD2 seem to play distinct roles in AD pathogenesis, probably due to their differential subcellular localizations, expression levels in different brain cells, as well as distinct regulation in disease processes.

A third PLD isoform, PLD3, has been recently associated with AD through identification of PLD3 risk variants by whole-exome sequencing and functional studies [140]. Overexpression of PLD3 decreased levels of βAPP, Aβ42, and Aβ40, whereas PLD3 knockdown increased extracellular Aβ42 and Aβ40 [140]. Another study reported that PLD3 was
expressed at significantly lower levels in neurons from AD brains compared with non-AD brains [141]. However, several follow up genomic studies failed to replicate the impact of PLD3 risk variants in sporadic AD cases [142, 143]. More validation studies are needed to clarify functional relevance of PLD3 in AD pathogenesis.

**MITOCHONDRIAL DYSFUNCTION: A ROLE FOR CARDIOLIPINS**

Mitochondrial dysfunction such as alterations in mitochondrial enzyme activities has been associated with AD pathology [144, 145]. Brain mitochondrial dysfunction leads to oxidative stress, loss of cellular Ca\(^{2+}\) homeostasis, and disruption of membrane structure. It should be noted that functional integrity of mitochondrial membrane is highly dependent upon phospholipid composition, mainly cardiolipin content and diversity [146–148].

Cardiolipin is an anionic tetra-acyl phospholipid present in mammalian cells, and is fundamental to membrane assembly of redox complexes in electron transport chain system and phosphorylation apparatus that regulate mitochondrial bioenergetics [149, 150]. Specifically, cardiolipin is required for proper structure and activity of mitochondrial electron transport chain enzymes [150, 151]. Alterations of cardiolipin metabolism have been associated with several pathologies, including neurodegenerative diseases [152]. Lipidomics studies reveal that synaptic deficit is associated with alterations in phospholipid composition of synaptic mitochondrial membranes. In 3xTg-AD mice brains, cardiolipin species were significantly reduced in synaptic mitochondria membranes [153], which could contribute to progressive synaptic loss and neurodegenerative processes in AD.

In mammals, cardiolipins are exclusively confined to the inner membrane of mitochondria [154] and contain polyunsaturated fatty acid residues which make them prone to oxygenation. Cardiolipin peroxidation plays a critical role in the function of numerous mitochondrial enzymes involved in electron transport chain function and other proteins involved in energetic metabolism [155–158]. Aberrant cardiolipin peroxidation seems to be an important pathogenic pathway in acute brain injury. Indeed, the peroxidation process yields a high diversity of oxidized cardiolipin products that are required to activate the neuronal death signaling pathways [159]. Oxidized cardiolipin also induces pro-apoptotic factors release from mitochondria into the cytosol and caspase activation [160]. Evidence suggests that the oxidized cardiolipins were involved in deleterious signaling cascades leading to cellular death after traumatic brain injury [161–163]. However, despite the fact that lipid peroxidation has long been associated with acute brain injury, its specific roles in mediating damaging pathways and signaling cascades are yet to be understood [164, 165].

**ISOPROSTANES IN AD**

Isoprostanes are prostaglandin-like compounds among which the secondary end products of lipid peroxidation F2-isoprostanes (F2-IsoPs) are derived from arachidonic acid through a free radical-mediated mechanism [166, 167]. The release of isoprostanes into the plasma, where they bind to lipoproteins, is mediated through the phospholipase A2 activation [168–170].

In an AD transgenic mouse model (Tg2576), high levels of F2-IsoPs were detected in the brain before the appearance of A\(\beta\) deposits [171, 172]. Interestingly, lowering brain F2-IsoPs formation resulted in a significant decrease in A\(\beta\) levels and deposition in the BAPP/PS1 mice [173] while increasing F2-IsoPs brain levels by supplementing aluminum in mouse diet led to accelerated AD phenotypes [174]. The effect of F2-IsoPs, especially 8-isoPGF\(_{2\alpha}\), on A\(\beta\) pathogenesis seemed to be mediated through thromboxane receptors, by which blockade of the receptors abolished the effects of F2-IsoPs on brain A\(\beta\) level and deposition [175–180].

Similar findings about the effects of F2-IsoPs were reported in a number of studies with human AD brain samples. For example, increased levels of F2-IsoPs were found in AD brain regions [181–184], and in CSF samples of AD patients [185, 186]. Another report also demonstrated that CSF F2-IsoPs level in clinically diagnosed probable AD patients who presented with cognitive deficits, were much higher than those in cognitively normal individuals [187].

Moreover, the link between CSF F2-IsoPs content and the ApoE genotype has been studied. While one study reported no differences in F2-IsoPs levels in ApoE4 carriers versus non-carriers [188], others found higher F2-IsoPs levels in ApoE4 carriers than those in non ApoE4-carriers [189]. Several studies have described changes in CSF F2-IsoPs levels along disease progression in AD patients [190, 191]. A cross-sectional study further demonstrated a corre-
lation of CSF F2-IsoPs level with age of subjects only in ApoE4 carriers but not in non ApoE4-carriers [192]. A recent study also found that F2-IsoPs levels in ApoE4 carriers were increased to much higher extent along disease progression than those in non ApoE4-carriers, and these changes were correlated with the rate of cognitive decline in ApoE4 carriers [193].

F4-neuroprostane (F4-NeuroPs) is another isoprostane-like end product from lipid peroxidation, which is generated from the peroxidation of docosahexaenoic acid. One study reported that higher levels of F4-NeuroPs were present in CSF of AD patients when compared to those in normal individuals [194]. However, a recent study showed no significant differences in CSF F2-IsoPs and F4-NeuroPs levels between AD patients and normal aging subjects [195]. The functional relevance of F4-NeuroPs in AD is yet to be validated and characterized.

CONCLUSIONS

In summary, converging lines of evidence indicate a strong relationship between alterations in brain lipid homeostasis and AD pathogenesis.

First of all, cellular membrane lipid composition is of importance in AD pathology because Aβ has a high affinity binding to lipid membrane. Aβ formation is highly correlated to the composition of lipid rafts. In addition, the cytotoxicity of Aβ is regulated by the proportion of ganglioside GM1 inside lipid rafts.

Cholesterol is an important key player in AD, but how it acts precisely in AD development and progression remains elusive. Indeed, at a low level, cholesterol induces an increase of Aβ. It has been described that drugs lowering cholesterol levels decreased intracellular and extracellular levels of Aβ40 and Aβ42. In contrast, elevation in cholesterol levels is a risk factor for amyloidogenesis. Together, these studies suggest that brain cholesterol homeostasis is tightly regulated, and under-production or over-production of cholesterol could lead to AD development.

Phospholipids are affected along the AD pathology. Depending upon the nature of phospholipids, modulation of phospholipids can be differentially affected at different stages of disease progression. For example, levels of PIP2 were reduced whereas PI was not affected at early stages of AD. At later stages, levels of all PI species (PI, PIP, and PIP2) were reduced in AD brains. The reduction of PIP2 can be explained by the increased expression of a PIP2 degrading enzyme synaptojanin 1 (synj1). Genetic knockdown of synj1 expression in ApoE4 KI mice rescued cognitive deficits in these mice, indicating synj1 as a potential drug target for AD therapies.

The transport of cholesterol and phospholipids in the brain is mediated by ApoE. The ε4 allele of ApoE is identified as one of the strongest risk factors for sporadic AD, strongly suggesting that dysfunction of lipid-transport system could be central to AD pathological processes. ApoE isoforms differentially regulate Aβ aggregation, clearance, and degradation. ApoE4 increases aggregation of Aβ deposits which leads to increased oxidative damages mediated by Aβ, whereas ApoE2 and ApoE3 play a protective role against Aβ-induced oxidative stress. The lipidated state of ApoE affects the ability of ApoE-containing lipoproteins to interact with Aβ and subsequently influences Aβ aggregation.

The family of ABC-transporters is involved in regulating lipid homeostasis, transport, and trafficking, and is implicated in neuroprotection. Three members of the ABCA family are associated with AD: ABCA1, 5, and 7 with distinct functions in amyloid pathways. ABCA1 modulates Aβ deposition, which is likely mediated through ApoE. ABCA5 reduces the secretion of Aβ, whereas ABCA7 acts upon Aβ uptake and clearance.

A few players are linked to AD but the functional relevance is yet to be characterized. One PLD family member, PLD1 was reported to regulate intracellular trafficking of βAPP and Aβ generation, while the role of another family member PLD3 in AD pathology remains controversial.

Cardiolipin content in mitochondrial membrane was significantly reduced in AD mouse model. It is well established that cardiolipin plays an important role in the regulation of mitochondrial bioenergetics. However, the mechanisms leading to neurodegenerative processes are still poorly understood, and need to be further investigated.

Finally, studies conducted in human subjects and AD transgenic mouse models suggest that oxidative stress contributes to AD pathogenesis [174], and the end products like F2-IsoPs and F4-NeuroPs may be considered as potential therapeutic targets and disease biomarkers for AD.

Together, several lines of evidence suggest that disruption of brain lipid homeostasis is crucial in AD pathogenesis. However, the question remains whether it is a cause or a consequence of AD. Different lipid species and lipid regulators have distinct
roles in AD pathogenesis. The complex regulation of brain lipid homeostasis makes comprehension and integration of disease mechanisms more difficult, and as a result the development of new therapeutic strategies targeting at lipid dysregulation in AD becomes more challenging.

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