Apolipoprotein E metabolism and functions in brain and its role in Alzheimer's disease

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Purpose of review

APOE4 genotype is the strongest genetic risk factor for Alzheimer's disease. Prevailing evidence suggests that amyloid β plays a critical role in Alzheimer's disease. The objective of this article is to review the recent findings about the metabolism of apolipoprotein E (ApoE) and amyloid β and other possible mechanisms by which ApoE contributes to the pathogenesis of Alzheimer's disease.

Recent findings

ApoE isoforms have differential effects on amyloid β metabolism. Recent studies demonstrated that ApoE-interacting proteins, such as ATP-binding cassette A1 (ABCA1) and LDL receptor, may be promising therapeutic targets for Alzheimer's disease treatment. Activation of liver X receptor and retinoid X receptor pathway induces ABCA1 and other genes, leading to amyloid β clearance. Inhibition of the negative regulators of ABCA1, such as microRNA-33, also induces ABCA1 and decreases the levels of ApoE and amyloid β. In addition, genetic inactivation of an E3 ubiquitin ligase, myosin regulatory light chain interacting protein, increases LDL receptor levels and inhibits amyloid accumulation. Although amyloid β-dependent pathways have been extensively investigated, there have been several recent studies linking ApoE with vascular function, neuroinflammation, metabolism, synaptic plasticity, and transcriptional regulation. For example, ApoE was identified as a ligand for a microglial receptor, TREM2, and studies suggested that ApoE may affect the TREM2-mediated microglial phagocytosis.

Summary

Emerging data suggest that ApoE affects several amyloid β-independent pathways. These underexplored pathways may provide new insights into Alzheimer's disease pathogenesis. However, it will be important to determine to what extent each mechanism contributes to the pathogenesis of Alzheimer's disease.

Keywords

Alzheimer's disease, amyloid β, apolipoprotein E, lipid metabolism

INTRODUCTION

Alzheimer's disease is the leading cause of dementia. Its pathological hallmarks include the accumulation of amyloid β and tau as well as neuroinflammation. Prevailing evidence suggests that these pathological alterations initiate or mediate pathogenic cascades, leading to Alzheimer's disease [1]. Amyloid β peptide is produced by proteolytic processing of amyloid precursor protein (APP) by β-secretase and γ-secretase. Importantly, multiple mutations responsible for early-onset familial Alzheimer's disease are found in APP and presenilin genes, essential components of γ-secretase complex. In addition, a protective mutation in *APP* gene is known to decrease amyloid β production, leading to a lower risk of Alzheimer's disease. Although it is still a preliminary finding, anti-amyloid β antibody treatment dramatically decreased amyloid β accumulation and slowed cognitive decline in a clinical trial [2]. Collectively, these genetic, biochemical, and clinical data strongly suggest that amyloid β plays a critical role in the pathogenesis of Alzheimer's disease.

Apolipoprotein E (*APOE*) genotype is the strongest genetic risk factor, with the ε4 allele being an

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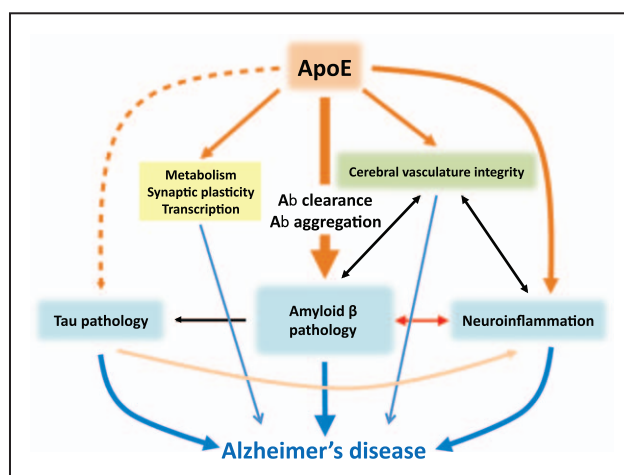Tel: +1 904 953 2652; e-mail: kim.jungsu@mayo.edu

KEY POINTS

- ApoE4, the strongest genetic risk factor for Alzheimer's disease, impairs amyloid β clearance and increases amyloid formation.

- Induction of ABCA1 by transcriptional and post-transcriptional mechanisms increases the lipidation of ApoE and inhibits amyloid β accumulation.

- ApoE metabolic receptor LDLR facilitates the clearance of ApoE and amyloid β.

- ApoE functions as a ligand for a microglial receptor, TREM2, and regulates the TREM2-mediated microglial phagocytosis.

- Besides its effect on amyloid β, ApoE also affects vascular function, neuroinflammation, metabolism, synaptic plasticity, and transcriptional regulation.


FIGURE 1. ApoE-mediated pathogenic pathways, leading to Alzheimer's disease. ApoE mainly influences the pathogenesis of Alzheimer's disease by affecting amyloid β pathology. The aggregation of amyloid β in parenchymal plaques and CAA triggers neuroinflammation [1]. In addition, ApoE may directly affect neuroinflammation, cerebral vascular integrity, metabolism, synaptic plasticity, and transcription through amyloid β-independent mechanisms [23,35,50]. Some pathways are differentially affected by the isoform, level, and the lipidation status of ApoE [4]. ApoE, apolipoprotein E; CAA, cerebral amyloid angiopathy.

Alzheimer's disease risk factor, whereas the ε2 allele being protective. In the brain, apoE is produced predominantly by astrocytes and to some extent microglia. In addition, neurons express apoE in response to excitotoxic injury [3]. As the major component of HDL-like particles in the brain, ApoE facilitates the transfer of cholesterol and phospholipid between cells. ApoE serves as a ligand in the receptor-mediated endocytosis of HDL-like particles through LDL receptor family. There are three major isoforms (ApoE2, ApoE3, and ApoE4) in humans. Each isoform differs only at one or two positions. ApoE3 has cysteine-112 and arginine-158, whereas apoE4 and apoE2 have arginine and cysteine, respectively at both positions. Importantly, the difference in these positions dramatically changes the structure and function of ApoE. For example, ApoE2 has only 1–2% of binding affinity to LDL receptor (LDLR), compared with ApoE3 and ApoE4. As discussed below, this structural difference between isoforms is also attributed to the differential ApoE cleavage. Given the central role of amyloid β and ApoE in Alzheimer's disease pathogenesis, the mechanistic links between them have been extensively studied. Although in-vitro amyloid β binding and aggregation studies have generated inconsistent data, multiple lines of human and animal data clearly demonstrate that there is an isoform-specific difference in amyloid β clearance and accumulation [4,5]. It is well established that the amyloid β accumulation in human brain follows the pattern of ApoE4 > ApoE3 > ApoE2 [5]. Although the effect of ApoE isoforms on amyloid β metabolism have been considered as its main role in Alzheimer's disease, emerging data suggest that ApoE may also affect Alzheimer's disease

pathogenesis through amyloid β-independent pathways (Fig. 1). In this article, we review recent findings, with particular emphasis on ApoE metabolism, and its roles in vascular function, neuroinflammation, and metabolism.

REGULATION OF APOLIPOPROTEIN E LIPIDATION AND METABOLISM

Because ApoE plays critical roles in Alzheimer's disease pathogenesis, potential roles of ApoE-interacting proteins have been extensively investigated. In this review, we mainly focus on ATP-binding cassette A1 (ABCA1) cholesterol transporter, ApoE receptors, and ApoE proteases because they regulate the lipidation or metabolism of ApoE (Fig. 2).

ABCA1 mediates cholesterol efflux to the nascent ApoE particle in the brain. After sufficient amount of cholesterol and phospholipids bind to ABCA1, ABCA1 undergoes conformational changes, leading to dimerization and transfer of lipids to ApoE. In addition to its role in lipid transport, ABCA1 also indirectly facilitates amyloid β clearance through ApoE lipidation in brain [6]. Previous animal studies demonstrated that improvement of ApoE lipidation inhibits amyloid deposition in APP mouse models. Deletion of *ABCA1* gene increases amyloid β accumulation, whereas its overexpression prevents amyloid β aggregation in amyloid mouse
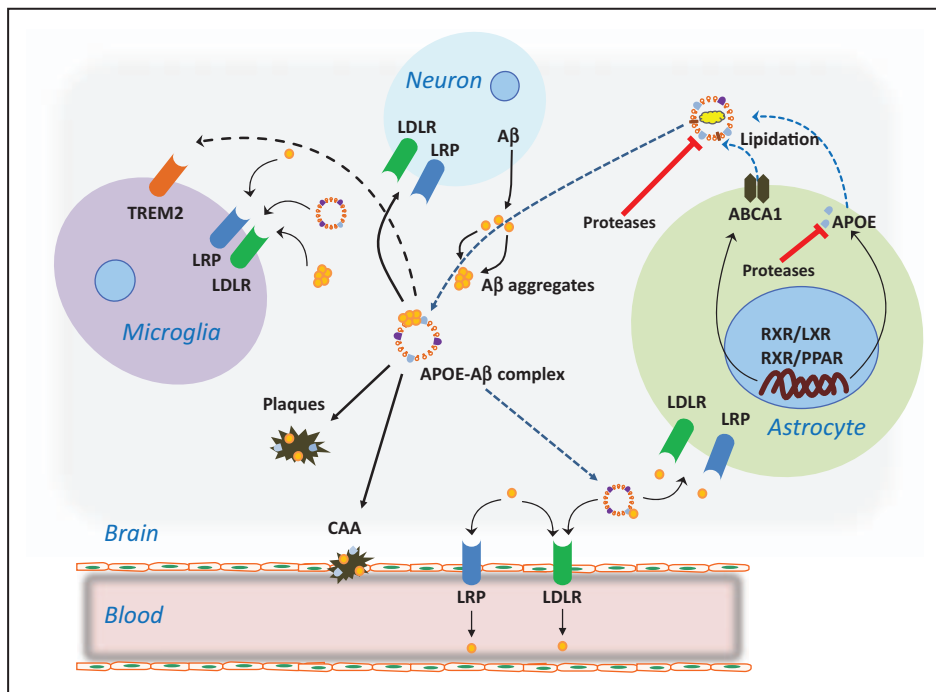
FIGURE 2. Metabolism of ApoE and amyloid β. ApoE is predominantly expressed in astrocytes. The transcription of ApoE is regulated by the heterodimers formed by RXR with PPAR or LXR. After being lipidated by ABCA1, ApoE is secreted into the interstitial fluid and transports lipids to other cells via ApoE receptor-mediated uptake mechanism [6]. LRP1 and LDLR are the major metabolic receptors for ApoE [4]. Recently, a microglial receptor TREM2 is also found to bind ApoE [40■■–42■■]. The level of ApoE can also be down-regulated by various proteases. Amyloid β is synthesized in neurons and released into interstitial fluid [1]. ApoE binds to amyloid β aggregates and colocalizes with amyloid β in plaques and CAA [4]. The interaction between ApoE and amyloid β may affect amyloid β fibrillization. ApoE affects amyloid β clearance by multiple pathways, including enzymatic degradation, receptor-mediated BBB transport, and endocytosis of amyloid β by glial cells [4,23]. ABCA1, ATP-binding cassette A1; ApoE, apolipoprotein E; BBB, blood-brain barrier; CAA, cerebral amyloid angiopathy; LDLR, low-density lipoprotein receptor; LRP1, lipoprotein receptor-related protein 1; LXR, liver X receptor; PPAR, peroxisome proliferator-activated receptor; RXR, retinoid X receptor; TREM2, triggering receptor expressed on myeloid cells 2.

models [6]. In support of the previous cell-based and animal studies, cerebrospinal fluid (CSF) from patients with mild cognitive impairment and Alzheimer's disease showed 30% less efficiency in the ABCA1-mediated cholesterol efflux, compared with cognitively normal participants [7■]. Although earlier human genetic analyses provided inconsistent results [4], a recent large-scale study involving more than 92 000 individuals clearly indicated that a well established loss-of-function mutation Asp1800His (N1800H) in ABCA1, is strongly associated with a higher risk of Alzheimer's disease [8■■]. Substitution of an uncharged amino acid, asparagine, with a positively charged histidine is responsible for the loss of function. The N1800H variant was observed at 0.2% frequency and significantly increased the hazard ratio to 4.13. In the same population, the hazard ratio for *APOE* genotype ε4/4 versus ε3/3 was 7.70. Although an association between lower plasma ApoE level and increased risk of Alzheimer's disease was observed in this study, it is unclear whether there is any mechanistic link between them. Because peripheral ApoE cannot penetrate the blood-brain barrier (BBB) [9], there is no or very low correlation between plasma and CSF ApoE levels [10,11]. In another study, higher CSF ApoE levels were associated with higher CSF tau levels and cognitive decline in human [12]. If CSF ApoE level and amyloid positron emission tomography scan data are available in the future study, they will greatly help in determining how the ABCA1 loss-of-function variant affects the risk of Alzheimer's disease.

Several therapeutic approaches were tested to increase ABCA1 level. Most studies focused on the transcriptional regulation of ABCA1 by targeting transcription factors. Nuclear receptors, liver X receptors (LXRs), retinoid X receptor (RXR), and peroxisome proliferator-activated receptor (PPAR), have been studied extensively in this regard. Agonists of these nuclear receptors increased the levels of ABCA1 and decreased amyloid β accumulation in APP mouse models [6]. Although an initial study suggested that ApoE may be directly responsible for

the beneficial effects of agonist, it is important to consider other indirect mechanisms as well. Because LXR and RXR regulate both levels and lipidation of ApoE, it is difficult to distinguish the effect of ApoE levels and lipidation on amyloid β. Subsequent animal studies proposed that ABCA1 and an ApoE receptor may be necessary for the beneficial effects of agonists. However, there are several confounding factors for the proper interpretation. For example, RXR alters the transcription and epigenetic status of numerous genes in mouse brains [13■■]. Therefore, it is hard to pinpoint one particular gene as the major mechanism. Furthermore, a recent study also provided an unexpected mechanism. An RXR agonist directly inhibited the initial step of amyloid β aggregation by directly binding to amyloid β [14■■]. An increase in the production of CSF may be yet another mechanism that mediates the beneficial effects of nuclear receptors [15]. Along with the positive transcriptional regulation, the negative post-transcriptional regulation by microRNAs has been studied recently. ABCA1 expression is suppressed by multiple microRNAs, such as miR-106b, miR-758, and miR-33 [9]. In one study, pharmacological and genetic inhibition of miR-33 significantly increased ABCA1 level and decreased amyloid β levels in the brain [16]. Given the supportive data from animal and human studies, targeting ABCA1 is a promising therapeutic avenue for Alzheimer's disease.

Metabolism of ApoE and amyloid β can be also regulated by endocytic receptors. Because ApoE regulates amyloid β clearance, endocytic receptors for ApoE have been extensively studied. LDLR and lipoprotein receptor-related protein 1 (LRP1) are major cell surface receptors for ApoE. Interestingly, both receptors also directly interact with amyloid β even in the absence of ApoE [17]. Although ApoE and amyloid β are the only known ligands for LDLR in the brain, more than 30 proteins are known to bind LRP1 [4]. Although overexpression of ApoE receptors are expected to increase ApoE-amyloid β clearance and decrease amyloid β level, transgenic mouse model studies provided unexpected findings. Overexpression of LRP minireceptor increased toxic amyloid β levels and caused the deficits in learning and memory, whereas LDLR overexpression decreased amyloid β accumulation [18]. To regulate the expression of endogenous LDLR, one study investigated whether an inactivation of LDLR degradation pathway will increase the clearance of ApoE and amyloid β [19]. Deletion of an E3 ubiquitin ligase increased LDLR and decreased ApoE and amyloid β in the brain. This study suggests that LDLR may be targeted for the development of Alzheimer's disease therapy.

Structural difference among ApoE isoforms also accounts for the differential ApoE degradation. In neuron, ApoE4 undergoes preferential proteolytic cleavage, generating neurotoxic fragments [20]. Initially, it was demonstrated that the proteolysis of ApoE could be inhibited only by a cysteine protease inhibitor, suggesting that cysteine proteases may play a major role in ApoE degradation. However, subsequent studies demonstrated that aspartic and chymotrypsin-like serine proteases may also mediate the degradation of ApoE. The apparent discrepancy between reports might be attributed to the differences in cell types and the concentrations of protease inhibitors used in each study. Unlike neurons, in monocytes and a microglial cell line, elastase-like proteases mediate the degradation of ApoE4 [21]. A recent study implicated high-temperature requirement serine peptidase A1 (HtrA1) as one of ApoE protease [22■]. Interestingly, HtrA1 degrades ApoE4 more efficiently than ApoE3. Preliminary data suggest that ApoE4 may inhibit HtrA1-mediated tau degradation *in vitro*. Although this is an interesting new hypothesis that may explain the effect of ApoE isoform on Alzheimer's disease pathogenesis, its implication to *in vivo* condition is still unclear. Most previous studies used recombinant ApoE with no or little lipidation under *in vitro* condition. Because the exact identity of the protease that degrades ApoE *in vivo* is still elusive, further investigations under physiological conditions are warranted.

APOLIPOPROTEIN E IN CEREBRAL VASCULAR FUNCTION

ApoE affects cerebral vasculature by affecting cerebral blood flow, neuronal-vascular coupling, and BBB integrity [23]. Its influence on these outcomes stems from the effects of ApoE on cerebral vasculature from both peripheral side and the brain side. In the periphery, ApoE has important implications in atherosclerosis and hyperlipoproteinemia [3,23], which also affect cerebral vasculature. Within the central nervous system, ApoE affects the onset and amount of cerebral amyloid angiopathy (CAA). CAA is amyloid β deposition on the blood vessels in the brain and it is often associated with hemorrhagic lesions, ischemic lesions, encephalopathy, and dementia. Although the peripheral and central nervous system mechanisms both affect cerebral vascular dysfunction, their contributions could be different under different circumstances. For example, although both ApoE2 and ApoE4 are risk factors for microhemorrhage, ApoE2 likely contributes to microhemorrhage via hyperlipidemia-associated blood vessel changes. It is unclear

whether ApoE2 exacerbates CAA, given the conflicting data [24–26]. In contrast, ApoE4 causes micro-hemorrhage largely by increasing CAA. Whether ApoE4 disrupts BBB integrity independent of amyloid β is still under debate. Although some studies have shown that ApoE4 disrupts BBB integrity in non-APP mice, it was recently reported that non-APP ApoE4 knock-in mice do not have any widespread BBB disruption [27].

Some amyloid β antibodies triggered amyloid-related imaging abnormalities (ARIAs) in clinical trials and ARIAs tend to be more frequent in APOE4 carriers [28]. The exacerbation of CAA and CAA-associated vasculopathy may be responsible for ARIAs. Recently, it was found that amyloid β antibody treatment redistributes ApoE from brain parenchyma to blood vessels in humans, mirroring the shift of amyloid β [29]. However, it is unknown whether ApoE actively transports amyloid β from parenchyma to blood vessels or it was later cotranslocated to CAA simply by binding to the preformed amyloid β aggregates in vessels. Many studies demonstrated that ApoE coaggregates with both parenchymal plaques and CAA [30,31]. However, it is unclear whether ApoE coaggregates with amyloid β in these two distinct compartments in a similar or different mechanism. In APP transgenic mouse models, murine ApoE is associated with increased amyloid β plaques while ApoE4 is associated with increased CAA [32,33]. In 5XFAD mice that express one copy of murine ApoE and one copy of ApoE4, ApoE4 colocalized more with CAA while murine ApoE colocalized more with plaques [34]. This suggests that different forms of ApoE can affect the location of amyloid β deposition via a coaggregation mechanism. The degree to which apoE colocalizes with amyloid β in plaques or CAA was associated with its ability to facilitate the corresponding lesions [34].

APOLIPOPROTEIN E IN NEUROINFLAMMATION

Besides amyloid plaques and neurofibrillary tangles, Alzheimer's disease is also characterized by the activation of astrocytes and microglia. Neuroinflammation is believed to contribute to Alzheimer's disease pathogenesis, although the exact mechanism is complex and not fully understood. ApoE modulates neuroinflammation through several pathways, including the alteration of cytokine levels in response to various stimulus, microglial migration, or microglia-mediated amyloid β phagocytosis [35]. On the other hand, cytokines also influence ApoE and further affect amyloid β uptake. A recent study found that an anti-inflammatory cytokine interleukin-10 (IL-10) increases ApoE and exacerbates amyloid β deposition in an APP mouse model. The same group also reported that ApoE binds amyloid β and attenuates the uptake of amyloid β by cultured microglia [36].

Recent studies indicate that ApoE binds a microglial receptor, triggering receptor expressed on myeloid cells 2 (TREM2). TREM2 is a member of the Ig superfamily of receptors. Rare missense variants in TREM2 are associated with an approximately two-fold to four-fold increase in risk of Alzheimer's disease. In several studies using APP mice, TREM2 deficiency consistently decreased the number of plaque-associated microglia and inflammatory cytokines. However, the effects of TREM2 deficiency on amyloid plaque load are not consistent across these studies [37]. Interestingly, when the morphology of individual plaques was analyzed, it was found that TREM2 deficiency results in the decreased ratio of compact region versus diffused region of plaques [38,39]. Similar observation was also made in human Alzheimer's disease brain with TREM2 R47H mutation [38]. TREM2 recognizes a variety of ligands, including ApoJ and ApoE [40■■–42■■]. In a series of in-vitro experiments, ApoE has been shown to facilitate the TREM2-mediated microglial phagocytosis [40■■,41■■]. The TREM2 disease variants reduced the affinity between ApoE and TREM2, which led to an impairment of phagocytosis. It was proposed that the lower affinity between ApoE and TREM2 disease variants may decrease the uptake of amyloid β-ApoE complex [40■■–42■■]. Interestingly, there is no difference in binding affinity between TREM2 and different ApoE isoforms [40■■–42■■]. Therefore, it appears that the physical interaction between TREM2 and ApoE may not explain the differential effects of ApoE isoforms on Alzheimer's disease pathogenesis. Further studies are warranted to determine whether TREM2 could indirectly affect downstream phenotypes in an ApoE isoform-dependent manner. ApoE is also found to affect TREM2 expression in primary microglia cultured from apoE knock-in mice in response to various microglia activation reagents. ApoE4 led to a lower TREM2 expression as compared to ApoE3 [43], which might impair the TREM2-mediated amyloid β clearance. In summary, the new connection between ApoE and TREM2 provides new insight into Alzheimer's disease.

APOLIPOPROTEIN E IN METABOLISM OF LIPID AND GLUCOSE

ApoE plays a key role in the lipid metabolism in the brain via ApoE receptor-mediated uptake of lipoprotein particles [3]. In the plasma, ApoE4 associates

preferentially with large, triglyceride-rich VLDL particles while ApoE2 and ApoE3 have a preference for small, phospholipid-rich HDL [3]. In brain, the only lipoprotein particle is HDL-like in size. Recently, it has been shown that the sizes of ApoE particles in the CSF of middle-aged nondemented humans follow the pattern of ApoE 2/3 > ApoE3/ 3 > ApoE3/4 > ApoE 4/4 [44■■]. In older adults, the sizes of CSF ApoE complexes follow the pattern of ApoE4-negative > ApoE4-positive. However, there is no difference between nondemented and those with mildest dementia in the sizes of CSF ApoE lipoprotein particles.

To investigate the effects of ApoE in the brain metabolome, Lee *et al.* [45] analyzed metabolites of young ApoE knockout and LDLR knockout mice. The absence of LDLR or ApoE elevated the serum cholesterol dramatically while having very subtle effects on the fatty acids or lipids metabolism in the brain [45]. The authors concluded that ApoE and LDLR alone may not play a significant role in these mouse models at an early age, but instead require the cumulative effect from different pathways that lead to dysfunction at a much later stage of life. Besides the broad range of lipid metabolites, how a specific type of lipids is influenced by ApoE was also investigated. ApoE participates in the brain phospholipid homeostasis in an isoform-dependent manner. In a set of experiments in humans, ApoE knock-in mice, and primary neurons, ApoE3 regulates brain phosphoinositol biphosphate (PIP_2) via suppressing the level of phosphoinositol phosphatase synaptojanin 1, a PIP_2-degrading enzyme, while ApoE4 is dysfunctional in this process [46].

Type 2 diabetes is associated with Alzheimer's disease, although it is still not clear whether it is a cause or consequence of Alzheimer's disease. In humans, ApoE genotype modifies the response to insulin treatment. The relationship between amyloid β and insulin resistance is also modulated by ApoE genotype [47]. The interplay between amyloid β, insulin, and ApoE isoforms were investigated using an APP mouse model expressing human ApoE isoforms [48,49]. ApoE4 enhanced the amyloid β-induced impairment of insulin signaling and accelerated the hippocampal-dependent cognitive deficits, as compared with ApoE3 [49]. There was less insulin receptor coimmunoprecipitated with ApoE in brain lysates of APP/ApoE4 mice as compared with that in APP/ApoE3 mice, suggesting a weaker interaction between insulin receptor and ApoE4 as compared with ApoE3 [48]. Because amyloid plaque burden is higher in the ApoE4 mice compared with ApoE3 mice, it is hard to rule out whether the higher amount of amyloid β in the

APP/ApoE4 mice actually contributes to the insulin resistance.

APOLIPOPROTEIN E IN SYNAPTIC PLASTICITY

Previous studies demonstrated that ApoE isoforms differentially affect synaptic function [50]. Two recent studies provide critical new insights into in-vivo mechanisms. Compared with ApoE3 and ApoE4, ApoE2 strongly enhanced the binding between synaptosomes and astrocytes *in vitro* and enhanced the phagocytic capacity of astrocytes in ApoE knock-in mice [51■■]. ApoE4-mediated synaptic impairment was also attributed to the disruption of slow gamma oscillations in the hippocampus of the apoE knock-in mice [52■■]. Taken together, these data suggest that ApoE isoforms affect astrocyte-mediated synaptic pruning and sharp-wave ripples, leading to synapses network dysfunction.

APOLIPOPROTEIN E IN THE TRANSCRIPTIONAL REGULATION

Recently, it was shown that ApoE can translocate to nucleus, bind DNA, and function as a transcription factor in human glioblastoma cells [53]. Genome-wide mapping of ApoE binding site indicated that ApoE4 binds the promoter regions of ~1700 genes, including genes associated with synaptic function, neuroinflammation, and insulin resistance. In another study, ApoE4 increased the nuclear translocation of histone deacetylases (HDACs) in human neuroblastomas, thereby reducing brain derived neurotrophic factor expression [54]. In contrast, ApoE3 retains HDACs in the cytosol via elevating the expression of protein kinase C ε. In the brains of Alzheimer's disease patients, nuclear translocation of HDA6 was increased as compared with controls. These studies suggested that ApoE may regulate the transcription of certain genes. It will be important to determine the relative contribution of the transcriptional effects of ApoE in Alzheimer's disease pathogenesis, as compared with other well-established effects of ApoE.

CONCLUSION

APOE genotype, the strongest genetic risk factor for Alzheimer's disease, affects the clearance and aggregation of amyloid β. Therefore, several approaches have been devised to target ApoE. Recent studies demonstrated that activation of LXR, RXR, and PPAR pathway increases ABCA1 level, leading to

ApoE lipidation and amyloid β clearance. Along with the transcriptional activation, the post-transcriptional regulation of ABCA1 was also explored by targeting the negative regulators, mainly microRNAs. The most exciting finding comes from the discovery of TREM2 as a novel risk factor for Alzheimer's disease and its direct interaction with ApoE. Although neuroinflammation was initially considered as a consequence of Alzheimer's disease pathology, emerging data clearly indicate that neuroinflammation may play a causal role in the pathogenesis of Alzheimer's disease. The direct involvement of ApoE in neuroinflammation provides new insight into Alzheimer's disease and may potentially lead to the identification of novel therapeutics. Further studies are warranted to determine how other pathways, such as vascular function, metabolism of lipid and glucose, and synaptic plasticity, contribute to the onset and progression of Alzheimer's disease.

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Conflicts of interest

There are no conflicts of interest.

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