Apolipoprotein E and Alzheimer disease: risk, mechanisms and therapy

Chia-Chen Liu, Takahisa Kanekiyo, Huaxi Xu and Guojun Bu

Abstract | Apolipoprotein E (Apo-E) is a major cholesterol carrier that supports lipid transport and injury repair in the brain. *APOE* polymorphic alleles are the main genetic determinants of Alzheimer disease (AD) risk: individuals carrying the ε4 allele are at increased risk of AD compared with those carrying the more common ε3 allele, whereas the ε2 allele decreases risk. Presence of the *APOE* ε4 allele is also associated with increased risk of cerebral amyloid angiopathy and age-related cognitive decline during normal ageing. Apo-E–lipoproteins bind to several cell-surface receptors to deliver lipids, and also to hydrophobic amyloid-β (Aβ) peptide, which is thought to initiate toxic events that lead to synaptic dysfunction and neurodegeneration in AD. Apo-E isoforms differentially regulate Aβ aggregation and clearance in the brain, and have distinct functions in regulating brain lipid transport, glucose metabolism, neuronal signalling, neuroinflammation, and mitochondrial function. In this Review, we describe current knowledge on Apo-E in the CNS, with a particular emphasis on the clinical and pathological features associated with carriers of different Apo-E isoforms. We also discuss Aβ-dependent and Aβ-independent mechanisms that link Apo-E4 status with AD risk, and consider how to design effective strategies for AD therapy by targeting Apo-E.

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Introduction

Alzheimer disease (AD) is a progressive neurodegenerative disease associated with cognitive decline, and is the most common form of dementia in the elderly. Approximately 13% of people over the age of 65 years and 45% over the age of 85 years are estimated to have AD.[1] Mounting evidence from genetic, pathological, and functional studies has shown that an imbalance between production and clearance of amyloid-β (Aβ) peptides in the brain results in accumulation and aggregation of Aβ. Aggregates of toxic Aβ in the form of soluble Aβ oligomers, intraneuronal Aβ, and amyloid plaques injure synapses and ultimately cause neurodegeneration and dementia.[2,3] The toxicity of Aβ seems to depend on the presence of microtubule-associated protein tau,[4] the hyperphosphorylated forms of which aggregate and deposit in AD brains as neurofibrillary tangles. Aβ is composed of 40 or 42 amino acids and is generated through proteolytic cleavage of amyloid precursor protein (APP).[5]

Early-onset, familial AD—which typically develops before the age of 65 years and accounts for only a small proportion (<1%) of AD cases[2,3]—is primarily caused by overproduction of Aβ owing to mutations in either the *APP* gene or in genes encoding presenilin 1 (*PSEN1*) or presenilin 2 (*PSEN2*), which are essential components of the γ-secretase complexes responsible for cleavage and release of Aβ. The majority of AD cases occur late in life (>65 years) and are commonly referred to as late-onset AD (LOAD). Although multiple genetic and environmental risk factors are involved in LOAD pathogenesis, overall impairment in Aβ clearance is probably a major contributor to disease development.[6] Genetically, the ε4 allele of the apolipoprotein E (*APOE*) gene is the strongest risk factor for LOAD.[7–9] The human *APOE* gene exists as three polymorphic alleles—ε2, ε3 and ε4—which have a worldwide frequency of 8.4%, 77.9% and 13.7%, respectively.[10] However, the frequency of the ε4 allele is dramatically increased, to ~40%, in patients with AD.[10]

Apo-E regulates lipid homeostasis by mediating lipid transport from one tissue or cell type to another.[11] In peripheral tissues, Apo-E is primarily produced by the liver and macrophages, and mediates cholesterol metabolism in an isoform-dependent manner. Apo-E4 is associated with hyperlipidaemia and hypercholesterolaemia, which lead to atherosclerosis, coronary heart disease and stroke.[11,12] In the CNS, Apo-E is mainly produced by astrocytes, and transports cholesterol to neurons via Apo-E receptors, which are members of the low-density lipoprotein receptor (LDLR) family.[8]

Apo-E is composed of 299 amino acids and has a molecular mass of ~34 kDa.[11] Differences between the three Apo-E isoforms are limited to amino acid residues 112 and 158, where either cysteine or arginine is present (Figure 1): Apo-E2 (Cys112, Cys158), Apo-E3 (Cys112, Arg158), and Apo-E4 (Arg112, Arg158).[11] The single amino acid differences at these two positions affect the structure of Apo-E isoforms and influence their ability to bind lipids, receptors and Aβ.[13–15] Human and animal studies clearly

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indicate that Apo-E isoforms differentially affect Aβ aggregation and clearance. Several Aβ-independent functions are also associated with Apo-E isoforms.

In this Review, we provide an overview of clinical evidence for the association between *APOE* genotypes and the risk of cognitive decline in AD, mild cognitive impairment (MCI) and other CNS diseases with a cognitive component, and discuss our current understanding of the mechanisms underlying Apo-E actions and Apo-E-targeted therapies.

APOE genotypes, AD and cognition

APOE ε4 as a strong risk factor for AD

Genome-wide association studies have confirmed that the ε4 allele of *APOE* is the strongest genetic risk factor for AD.[16,17] The presence of this allele is associated with increased risk of both early-onset AD and LOAD.[18,19] A meta-analysis of clinical and autopsy-based studies demonstrated that, in white individuals, risk of AD was increased in individuals with one copy of the ε4 allele (ε2/ε4, OR 2.6; ε3/ε4, OR 3.2) or two copies (ε4/ε4, OR 14.9) compared with those with an ε3/ε3 genotype.[10] Conversely, the ε2 allele of *APOE* has a protective effect against AD: the risk of AD in individuals carrying *APOE* ε2/ε2 (OR 0.6) or ε2/ε3 (OR 0.6) is lower than in those carrying ε3/ε3.[10]

In population-based studies, the *APOE* ε4–AD association was weaker among African American (ε4/ε4, OR 5.7) and Hispanic (ε4/ε4, OR 2.2) populations, and was stronger in Japanese people (ε4/ε4, OR 33.1) compared with white individuals (ε4/ε4, OR 12.5).[10] *APOE* ε4 is associated with increased prevalence of AD and lower age of onset.[7,10,20] The frequency of AD and mean age at clinical onset are 91% and 68 years in ε4 homozygotes, 47% and 76 years in ε4 heterozygotes, and 20% and 84 years in ε4 noncarriers,[7,20] indicating that *APOE* ε4 confers dramatically increased risk of development of AD with an earlier age of onset in a gene dose-dependent manner (Table 1).

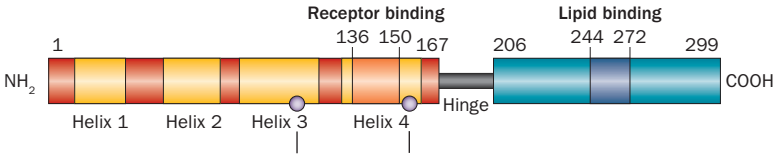
Genetic variants in the *TOMM40* (translocase of outer mitochondrial membrane 40 homologue) gene, which lies adjacent to the *APOE* gene on chromosome 19, have been implicated as a modulator of AD age-of-onset in *APOE* ε3 carriers.[21] A subsequent study, however, cast doubt on the strength of this association.[22] Whether the effects of *APOE* and *TOMM40* on AD risk, both genetically and functionally, are synergistic requires further investigation.

Apo-E and Aβ deposition

Apo-E has an important role in Aβ metabolism (Figure 2). Studies show that *APOE* genotypes strongly affect deposition of Aβ to form senile plaques and cause cerebral amyloid angiopathy (CAA)—two major hallmarks of amyloid pathology in AD brains.[23] Immunohistological evidence demonstrates that Apo-E is co-deposited in senile plaques in the brains of patients with AD.[24] Aβ deposition in the form of senile plaques is more abundant in *APOE* ε4 carriers than in noncarriers.[25–27] The difference was most evident among individuals aged 50–59 years: 40.7% of *APOE* ε4 carriers had senile plaques compared with 8.2% of noncarriers.[25]

Key points

- The ε4 allele of the apolipoprotein E (*APOE*) gene is the main genetic risk factor for Alzheimer disease (AD)
- *APOE* ε4 carriers have enhanced AD pathology, accelerated age-dependent cognitive decline and worse memory performance than do noncarriers
- Numerous structural and functional brain changes associated with AD pathogenesis are detected in *APOE* ε4 carriers before clinical symptoms become evident
- Apo-E affects amyloid-β (Aβ) clearance, aggregation and deposition in an isoform-dependent manner
- Apo-E4 also contributes to AD pathogenesis by Aβ-independent mechanisms that involve synaptic plasticity, cholesterol homeostasis, neurovascular functions, and neuroinflammation
- Apo-E-targeted AD therapy should focus on restoration of the physiological function of Apo-E through increased expression and lipidation, and inhibition of the detrimental effects of Apo-E4



	Isoform-specific amino acid difference		Allele frequency (%)	
	112	158	General	AD
Apo-E2	Cys	Cys	8.4	3.9
Apo-E3	Cys	Arg	77.9	59.4
Apo-E4	Arg	Arg	13.7	36.7

Figure 1 | *APOE* ε4 is a major genetic risk factor for AD. The Apo-E2, E3, and E4 isoforms, which are encoded by the ε2, ε3 and ε4 alleles of the *APOE* gene, respectively, differ from one another at amino acid residues 112 and/or 158 (grey circles). Apo-E has two structural domains: the N-terminal domain, which contains the receptor-binding region (residues 136–150), and the C-terminal domain, which contains the lipid-binding region (residues 244–272); the two domains are joined by a hinge region. A meta-analysis demonstrated a significant association between the ε4 allele of *APOE* and AD.[10] Abbreviations: AD, Alzheimer disease; Apo-E, apolipoprotein E.

In individuals with positive Pittsburgh compound B (PiB)-PET images, which indicate fibrillar aggregates of Aβ,[28] *APOE* ε4 was more common than in those with negative scans (65% versus 22%) in patients with AD.[29]

Fibrillar Aβ deposition is often detected in the brains of elderly, cognitively normal individuals in a manner that depends on the presence of *APOE* ε4, although such an association is weaker than that in patients with AD.[30] In addition, *APOE* ε4 carriers have lower cerebrospinal fluid (CSF) $A\beta_{42}$ levels and show more PiB binding on PET than do noncarriers, which reflect the presence of cerebral amyloid deposition and serve as potential biomarkers for AD.[31,32] PiB-positivity can be detected in cognitively normal *APOE* ε4 carriers at about 56 years of age, compared with around 76 years of age in noncarriers.[33] This difference suggests that *APOE* ε4 probably increases the risk of AD by initiating and accelerating Aβ accumulation, aggregation and deposition in the brain. Although *APOE* ε2 reduces the risk of dementia,[34] both the ε2 and ε4 alleles of *APOE* increase amyloid burden compared with *APOE* ε3 in individuals older than 90 years, suggesting that the protective effects of *APOE* ε2 against AD might not be associated with Aβ deposition.

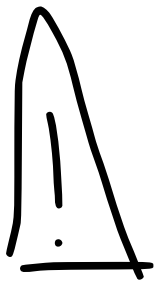


Table 1 | The effect of *APOE* ε4 on AD frequency and age at onset[7]

Characteristic	*APOE* ε4 noncarrier	*APOE* ε4 heterozygous	*APOE* ε4 homozygous
AD frequency (%)	20	47	91
Mean age of clinical onset (years)	84	76	68

Abbreviations: AD, Alzheimer disease; *APOE* ε4, ε4 allele of the apolipoprotein E gene.

APOE ε4 also shows an association with CAA and CAA-related haemorrhages.[35,36] CAA refers to the pathological condition in which amyloid spreads and deposits throughout the cerebral blood vessel walls,[37] and is frequently detected in AD.[23] Interestingly, although *APOE* ε2 is protective against AD, it is a risk factor for CAA-related haemorrhage, independently of AD, possibly by predisposing vessels to vasculopathic complications of CAA.[36]

Prediction of AD in MCI

MCI is a transitional stage between normal ageing and dementia, and is associated with increased risk of AD.[38] The rate at which patients with amnesic MCI (aMCI) progress to clinically diagnosable AD is 10–15% per year, in contrast to a rate of 1–2% per year among healthy elderly individuals.[39] The prevalence of *APOE* ε4 is substantially higher in both aMCI and dys-executive MCI than in control individuals.[40] Patients with MCI who harbour *APOE* ε4 exhibit distinct cognitive profiles, which seem to resemble those of patients in the early stages of AD.[41] A case–control study reported poorer memory performance among patients with MCI who were carriers of *APOE* ε4 compared with noncarriers.[42] *APOE* ε4 is associated with impaired memory performance and increased risk of memory decline in middle-aged (40–59 years) and elderly (60–85 years) people with MCI.[43,44] Furthermore, patients with MCI who are carriers of *APOE* ε4 experience more-rapid decline in several cognitive and functional domains, and severity of the deficits is strongly associated with the *APOE* ε4 gene dose.[41,45,46] Importantly, the presence of *APOE* ε4 is associated with increased risk of progression from MCI to AD-type dementia.[47–49] Among individuals with aMCI, *APOE* ε4 carriers tend to be younger than noncarriers, consistent with younger age of AD onset in individuals with *APOE* ε4.[50] These findings indicate that the *APOE* ε4 genotype in patients with MCI can serve as a predictive factor for determination of clinical outcome and the risk of conversion to AD.

In patients with MCI, the adverse effects of *APOE* ε4 on cognitive functions correlate with the severity of neuronal pathology. Those who are carriers of *APOE* ε4 have lower CSF $A\beta_{42}$ levels, higher tau levels and greater brain atrophy than do noncarriers.[50] Furthermore, patients with MCI who are PiB-positive are more likely to be *APOE* ε4 carriers and exhibit worse memory performance than are PiB-negative patients.[51] Other finding suggest, although not without controversy,[52] that *APOE* ε4 has considerable deleterious effects on memory performance[42] and might be used to predict disease progression in combination with AD biomarkers and neuroimaging approaches.[53]

Predicting cognitive decline in healthy cases

Healthy *APOE* ε4 carriers not diagnosed with MCI or AD show accelerated longitudinal decline in memory tests, which starts around the age of 55–60 years, revealing a possible pre-MCI state in this genetic subset of individuals.[54,55] This memory decline, despite ongoing normal clinical status, suggests that pathological changes in AD might manifest in the brain as early as the sixth decade of life.[56,57] Thus, *APOE* ε4 is associated with cognitive decline many years before cognitive impairment becomes clinically apparent.[56,58] Interestingly, *APOE* ε4 has differential effects on memory performance depending on age. Some studies in young adults and children have found evidence of better cognitive performance in *APOE* ε4 carriers than in noncarriers, which could suggest antagonistic pleiotropy,[59–61] in which *APOE* ε4 might offer benefits during development and early adulthood at the expense of more-rapid decline in cognitive function with ageing.[62]

Similar to the situation in patients with MCI, *APOE* ε4 is associated with enhanced amyloid pathology in cognitively normal people. The proportion of PiB-positive individuals follows a strong *APOE* allele-dependent pattern (ε4 > ε3 > ε2),[25,63,64] and *APOE* ε4 increases the amount of amyloid deposition in a gene-dose-dependent manner.[30]

APOE ε4 and other AD risk factors

The *APOE* ε4 genotype combines synergistically with atherosclerosis, peripheral vascular disease, and type 2 diabetes in contributing to an increased risk of AD.[65,66] *APOE* ε4 is a risk factor for cardiovascular disease, suggesting that this allele and cerebrovascular disease might have compounding effects on cognitive decline in AD.[67] Diabetes also increases the risk of AD, and the association is particularly strong among *APOE* ε4 carriers.[66,68,69] Patients with diabetes who are carriers of *APOE* ε4 have more neuritic plaques, neurofibrillary tangles and CAA than do noncarriers.[66] The combination of a diabetes-related factor—that is, hyperglycaemia, hyperinsulinaemia, and insulin resistance—and the *APOE* ε4 allele promotes neuritic plaque formation.[69] *APOE* ε4 seems to modify the risk of AD in patients with diabetes—a disease that directly or indirectly causes vascular and neuronal damage and further exacerbates AD pathology. Furthermore, recent research demonstrated that, independently of Aβ, Apo-E4 triggers inflammatory cascades that cause neurovascular dysfunction, including blood–brain barrier breakdown, leakage of blood-derived toxic proteins into the brain and reduction in the length of small vessels.[70] This result suggests that Apo-E4-associated damage to vascular systems in the brain could have a key role in AD pathogenesis.

APOE and traumatic brain injury

Increasing evidence has shown that *APOE* ε4 is associated with poorer outcomes following traumatic brain injury (TBI) compared with *APOE* ε2 and ε3 alleles, regardless

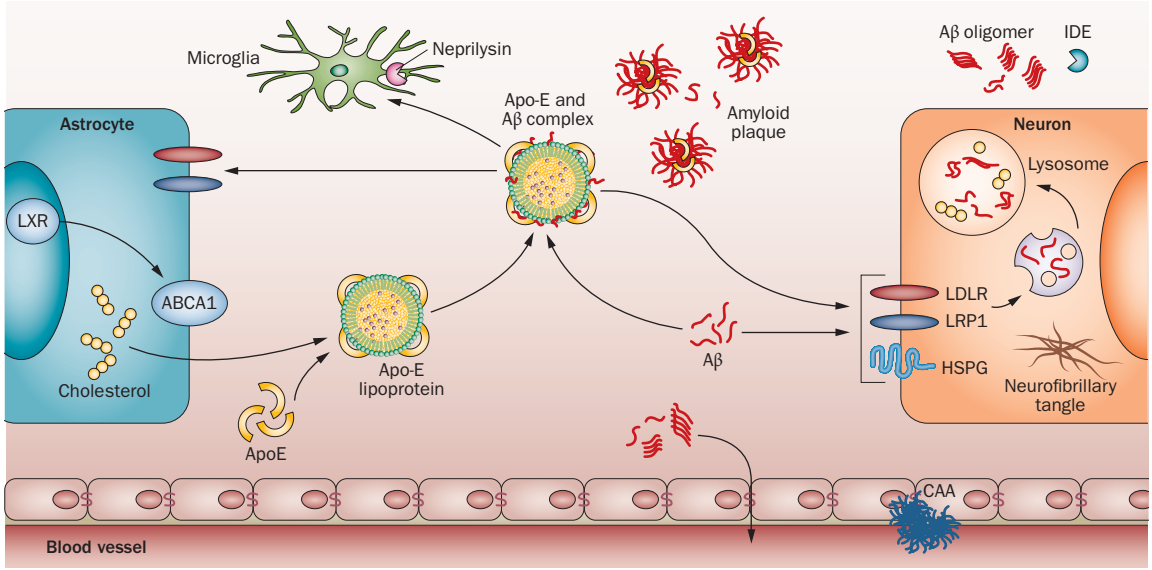


Figure 2 | Apolipoprotein E and amyloid-β metabolism in the brain. Major Aβ clearance pathways include receptor-mediated uptake by neurons and glia, drainage into interstitial fluid or through the BBB, and proteolytic degradation by IDE and neprilysin. Impaired Aβ clearance can cause accumulation in brain parenchyma, triggering formation of Aβ oligomers and amyloid plaques. Perivascular Aβ accumulation leads to CAA, which disrupts blood vessel function. Apo-E is primarily synthesized by astrocytes and microglia, and is lipidated by the ABCA1 transporter, forming lipoprotein particles. Lipidated Apo-E binds soluble Aβ and facilitates Aβ uptake through cell-surface receptors, including LRP1, LDLR, and HSPG.[175,177] Apo-E facilitates binding and internalization of soluble Aβ by glial cells, disrupts Aβ clearance at the BBB in an isoform-dependent manner (Apo-E4 > Apo-E3 > Apo-E2) and influences CAA pathogenesis. Abbreviations: Aβ, amyloid-β; ABCA1, ATP-binding cassette A1; Apo-E, apolipoprotein E; BBB, blood–brain barrier; CAA, cerebral amyloid angiopathy; HSPG, heparan sulphate proteoglycan; IDE, insulin-degrading enzyme; LDLR, low-density lipoprotein receptor; LRP1, low-density lipoprotein receptor-related protein 1; LXR, liver X receptor.

of the severity of initial injury.[71] A meta-analysis demonstrated that the outcome of TBI at 6 months after injury is worse in *APOE* ε4 carriers than in noncarriers.[72] TBI is associated with increased risk of AD,[73] and such a risk is more evident in patients with *APOE* ε4.[74] Only 10% of *APOE* ε4 noncarriers with TBI have Aβ plaque pathology, whereas 35% and 100% of TBI patients with one or two *APOE* ε4 alleles, respectively, possess Aβ pathology.[75] The poorer outcomes associated with Apo-E4 might relate to the reduced ability of this isoform to repair and remodel synapses and protect neurons upon injury compared with Apo-E3.[8] These possibilities are currently under investigation.

APOE and vascular diseases

Vascular cognitive impairment, which comprises clinical conditions with cerebrovasculature-derived cognitive disturbances including vascular dementia, is observed in approximately 8–15% of aged individuals with cognitive dysfunction in Western clinic-based series.[76] A recent meta-analysis has shown evidence of increased risk of vascular dementia in individuals with *APOE* ε4 compared with *APOE* ε3 (OR 1.72).[77] Several studies suggest that the contribution of *APOE* ε4 to risk of vascular cognitive impairment is independent of other vascular risk factors including hypertension, dyslipidaemia and atherogenesis,[78] whereas another report shows that age-related cognitive decline among *APOE* ε4 carriers is induced by brain damage owing to increased blood pressure.[79] In addition, *APOE* ε4 is associated with poor outcome after subarachnoid haemorrhage,[80] and is a strong risk factor for CAA-related intracranial haemorrhage.[81] These results suggest that *APOE* ε4 is closely associated with neurovascular dysfunctions.

APOE and other types of dementia

Lewy body disease is thought to be the second most common form of dementia, and comprises a spectrum of diseases that includes Parkinson disease (PD), PD-associated dementia, and dementia with Lewy bodies (DLB). Clinical and pathological features of PD and AD frequently overlap. Most studies, however, have failed to report associations between *APOE* ε4 and susceptibility to PD and PD-associated dementia.[82,83]

DLB also shares clinical and pathological characteristics with AD and PD,[84] and several reports have shown that *APOE* ε4 increases risk of DLB.[85] Immunohistochemical analysis showed that deposition of Lewy bodies in patients with DLB who are *APOE* ε4 carriers is substantially more abundant than in those who are noncarriers.[86] As Lewy bodies are considerably increased in the cerebral cortex of DLB patients with Aβ deposition,[87] the strong association between amyloid pathology and the pathology of Lewy body disease could explain why *APOE* ε4 increases risk of DLB. *APOE* ε4 might also be a risk factor for frontotemporal dementia,[88] although the pathophysiological role of Apo-E in this disease requires further investigation. The *APOE* genotypes do not seem to influence the risks of Huntington disease[89] nor amyotrophic lateral sclerosis.[90]

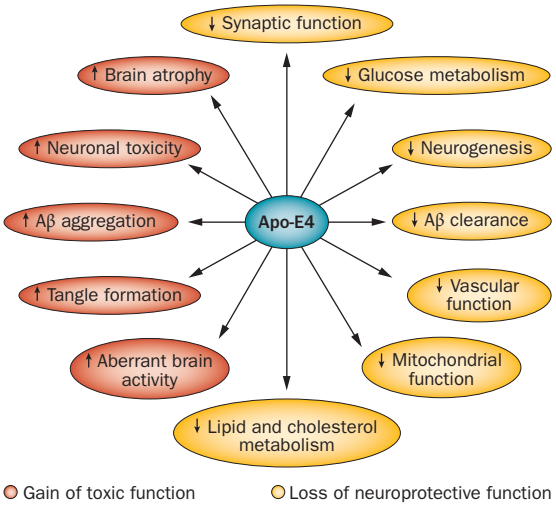


Figure 3 | The role of apolipoprotein E4 in Alzheimer disease pathogenesis. Apo-E4 confers toxic gain of function, loss of neuroprotective function, or both, in the pathogenesis of Alzheimer disease. Key functional differences between Apo-E4 and Apo-E3 are illustrated. Abbreviations: Aβ, amyloid-β; Apo-E, apolipoprotein E.

Mechanisms of Apo-E isoforms in AD

APOE ε4 confers a gain of toxic functions, a loss of neuroprotective functions or both in the pathogenesis of AD (Figure 3).

Aβ metabolism and aggregation

Studies in humans and transgenic mice showed that brain Aβ levels and amyloid plaque loads are Apo-E isoform-dependent (ε4 > ε3 > ε2),[30,63,91] suggesting an important role for Apo-E in modulating Aβ metabolism, aggregation, and deposition. Apo-E4 is less efficient in Aβ clearance than is Apo-E3 in young and old amyloid mouse models that express human Apo-E isoforms.[63] Additionally, Apo-E isoforms differentially regulate cholesterol levels, which have been shown to modulate γ-secretase activity and Aβ production.[92] Several studies reported an *APOE* genotype-dependent effect on CSF and brain Apo-E levels (ε4 < ε3 < ε2) in Apo-E-targeted-replacement (Apo-E-TR) mice, in which the mouse *Apoe* gene is replaced with human *APOE* isoforms.[91,93,94] This result suggests that lower levels of total Apo-E exhibited by *APOE* ε4 carriers might contribute to disease progression. However, whether human Apo-E isoform status affects CSF and brain Apo-E protein levels in healthy individuals and patients with AD remains to be established.[95,96]

Apo-E-knockout mice clear Aβ from the brain faster than do control mice.[97] Stimulation of liver X receptors (LXRs)[98,99] or the retinoid X receptor (RXR)[100] facilitates Aβ clearance, probably by increasing Apo-E levels and lipidation. Further investigation is needed to determine whether Apo-E levels are directly associated with Aβ clearance. In addition, a recent study showed that lack of one copy of ATP-binding cassette transporter A1 (ABCA1), which shuttles lipids to Apo-E, impairs Aβ clearance and exacerbates amyloid deposition and memory deficits in Apo-E4-TR mice, but not in Apo-E3-TR mice.[101] This result suggests that Apo-E isoforms exhibit differential lipidation status, which affects Aβ clearance in an isoform-dependent manner. Alternatively, Apo-E–lipoprotein particles may sequester Aβ and promote cellular uptake and degradation of Apo-E–Aβ complexes.[102]

Apo-E4–lipoproteins bind Aβ with lower affinity than do Apo-E3–lipoproteins,[103] suggesting that Apo-E4 might be less efficient in mediating Aβ clearance. In addition, Apo-E might modulate Aβ removal from the brain to the systemic circulation by transporting Aβ across the blood–brain barrier. In this respect, Apo-E impedes Aβ clearance at the blood–brain barrier in an isoform-specific fashion (Apo-E4 > Apo-E3 and Apo-E2).[104] Finally, studies in microglia have shown that Apo-E3 promotes enzyme-mediated degradation of Aβ more efficiently than does Apo-E4.[105] Together, these studies suggest that Apo-E4 inhibits Aβ clearance and/or is less efficient in mediating Aβ clearance compared with Apo-E3 and Apo-E2.

Apo-E also seems to regulate Aβ aggregation and deposition. An important study showed that deletion of the mouse *Apoe* gene essentially eliminates deposition of fibrillar Aβ in amyloid mouse models.[106] Given that Apo-E is co-deposited with Aβ in human AD brains,[24] it is possible that Apo-E promotes Aβ aggregation and deposition in an isoform-dependent manner. The exact mechanisms by which Apo-E isoforms differentially regulate Aβ aggregation and deposition require further investigation.

Brain activity and atrophy

AD is associated with both functional abnormalities of the hippocampus and cortical atrophy in the memory network.[107,108] Patients with AD or MCI who are *APOE* ε4 carriers exhibit greater medial temporal lobe atrophy, particularly in the hippocampal area.[41,109,110] Structural MRI studies found that, compared with noncarriers, *APOE* ε4 carriers have accelerated age-related reduction in cortical thickness and hippocampal volume that are tightly coupled to decline in cognitive performance.[111–113]

Functional MRI (fMRI) studies reported that Apo-E4 disrupts resting-state fMRI connectivity and the balance between brain networks, in the absence of amyloid pathology.[114,115] Furthermore, cognitively normal *APOE* ε4 carriers have elevated resting-state activity in the default mode network—a network that is preferentially affected early in AD—and higher hippocampal activation during memory tasks.[116–118] Such changes have been hypothesized to represent a compensatory response by *APOE* ε4 carriers in which increased cognitive effort is required to achieve an equivalent level of performance to that of noncarriers.[116,118]

Elevated baseline activity in brain networks of *APOE* ε4 carriers could potentially contribute to increased Aβ production, as Aβ levels are regulated by neuronal activity.[119,120] Interestingly, in adults who do not have dementia, increased hippocampal activity was associated with reduced cortical thickness in the medial temporal lobe and brain regions that are vulnerable to AD pathology.[121] Studies suggested that hippocampal hyperactivity might represent impending synaptic dysfunction and incipient cognitive decline.[122] Interestingly, another study showed

a reduction of posterior default mode network connectivity in *APOE* ε4 carriers in cognitively normal elderly people, implying that *APOE* ε4 carriers exhibit more-rapid decline in connectivity of this network than do noncarriers as they age.[115]

^{18}F-fluorodeoxyglucose PET imaging, which measures cerebral metabolic rates of glucose as a proxy for neuronal activity, correlates with disease progression and predicts histopathological diagnosis in AD.[123] Mounting evidence suggests that *APOE* ε4 carriers exhibit lower cerebral glucose metabolism.[124–126] Healthy adults with *APOE* ε4 show altered patterns of brain metabolism both at rest and during cognitive challenges compared with noncarriers.[126,127] Representative studies illustrating the association of Apo-E4 isoform with altered brain metabolism and activity, memory decline, and amyloid pathology in cognitively normal people are shown in Figure 4. Improved understanding of the mechanisms of Apo-E4-related brain activity changes, brain atrophy and reduced metabolism should help to explain why Apo-E4 is a risk factor for cognitive decline and AD.

Tau phosphorylation and neurotoxicity

Apo-E is produced primarily by astrocytes and microglia. Neuronal Apo-E expression can, however, be induced in response to stress or injury, probably for the purpose of neuronal repair and remodelling.[128,129] A truncated fragment of Apo-E4, resulting from proteolytic cleavage of Apo-E following stress or injury, increases tau hyperphosphorylation, cytoskeletal disruption and mitochondrial dysfunction.[128,130,131] Apo-E4 also exacerbates neurotoxicity triggered by Aβ and other insults.[128,131]

A recent study showed that neurons in patients with temporal lobe epilepsy who harbour *APOE* ε4 are less resilient to the damaging hyperexcitability and more susceptible to Aβ toxicity than are those in *APOE* ε3 carriers,[132] suggesting that Apo-E3 might confer a neuroprotective advantage over Apo-E4 against neuronal stress. Interestingly, astrocyte-derived Apo-E4 has neuroprotective effects against excitotoxic injuries, whereas neuronal expression of Apo-E4 promotes excitotoxic cell death. This result suggests that Apo-E derived from various cellular sources might exhibit different physiological and pathological activity.[133]

Lipid metabolism

Abnormal lipid metabolism is strongly related to the pathogenesis of AD. In the CNS, Apo-E mediates neuronal delivery of cholesterol, which is an essential component for axonal growth, synaptic formation and remodelling—events that are crucial for learning, memory formation and neuronal repair.[134,135] Brain cholesterol levels are substantially reduced in hippocampal and cortical areas in patients with AD compared with age-matched controls.[136] Preferential degradation of Apo-E4 relative to Apo-E3 in astrocytes in transgenic animals has been proposed to result in low levels of Apo-E in the brain and CSF and reduced capacity for neuronal delivery of cholesterol, suggesting that low levels of total Apo-E exhibited by *APOE* ε4 carriers may directly contribute to disease progression.[93] Apo-E4 is also less efficient than Apo-E3 in transporting brain cholesterol.[137] Moreover, Apo-E4-TR mice have abnormal cholesterol levels and impaired lipid metabolism.[138] Insufficient levels of Apo-E and/or impaired Apo-E function in carriers of the ε4 allele might, therefore, lead to aberrant CNS cholesterol homeostasis and neuronal health, which contribute to AD risk.

Synaptic plasticity and spine integrity

Synaptic failure is an early pathological feature of AD.[139,140] Increasing evidence demonstrates that Apo-E isoforms differentially regulate synaptic plasticity and repair.[141,142] In AD and healthy aged controls, *APOE* ε4 gene dosage correlates inversely with dendritic spine density in the hippocampus.[143] Apo-E4-TR mice also have lower dendritic spine density and length compared with Apo-E3-TR mice.[144,145] Apo-E3, but not Apo-E4, prevents loss of synaptic networks induced by Aβ oligomers.[146] Apo-E isoforms also differentially regulate dendritic spines during ageing.[143,147] The age-dependence of these differences implies that the effects of Apo-E isoforms on neuronal integrity might relate to increased risk of dementia in aged *APOE* ε4 carriers.

Reduced synaptic transmission was observed in 1-month-old Apo-E4-TR mice compared with Apo-E3-TR mice, suggesting that Apo-E4 may also contribute to functional deficits early in development, which could account for alteration of neuronal circuitry that eventually results in cognitive disorders later in life.[147] In addition, Apo-E4 selectively impairs Apo-E receptor trafficking and signalling, as well as glutamate receptor function and synaptic plasticity.[141] Together, these findings suggest that the effect of *APOE* ε4 genotype on risk of AD might be mediated, at least in part, through direct effects on synaptic function.

Neuroinflammation

Neuroinflammation contributes to neuronal damage in the brain and is implicated in AD pathogenesis.[148] Apo-E colocalizes with plaque-associated amyloid and microglia, suggesting a role for Apo-E in the innate immune response in AD. Lack of Apo-E in mice is associated with increased inflammation in response to Aβ,[149,150] but Apo-E isoforms might differently regulate the innate immune response.[151] Apo-E4 seems to have pro-inflammatory and/or reduced anti-inflammatory functions, which could further exacerbate AD pathology. For example, Apo-E4-TR mice exhibit greater inflammatory responses to lipopolysaccharide compared with Apo-E3-TR mice.[152] In addition, young *APOE* ε4 carriers show an increased inflammatory response that may relate to AD risk later in life.[153] Consistent with this notion, non-steroidal anti-inflammatory drugs were shown to reduce AD risk only in *APOE* ε4 carriers,[154] suggesting that *APOE* genotype might determine the effect of anti-inflammatory medications for AD.

Neurogenesis

Hippocampal neurogenesis has an important role in structural plasticity and maintenance of brain networks.

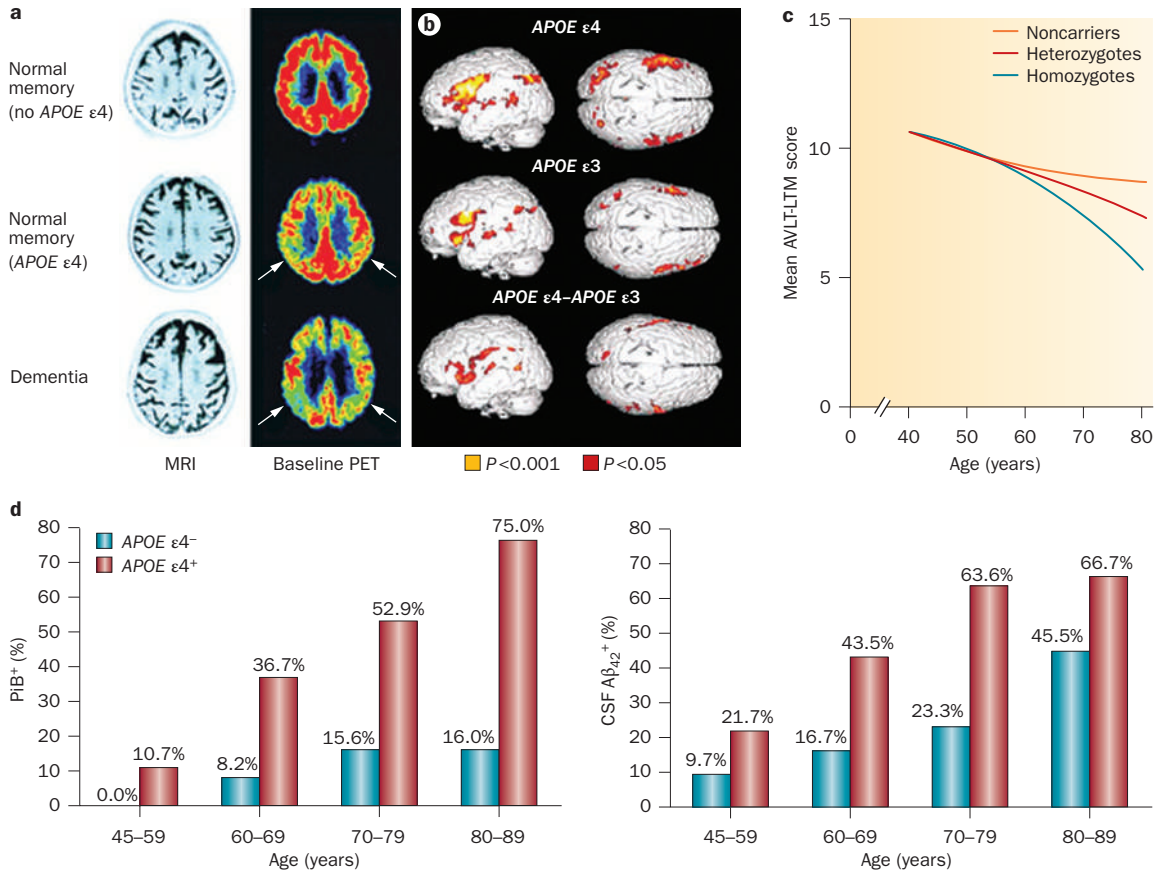


Figure 4 | Brain function, neuropathology and memory in cognitively normal *APOE* ε4 carriers. **a** | On ^{18}F-FDG PET imaging, cognitively normal *APOE* ε4 carriers have lower glucose metabolism than do noncarriers. **b** | *APOE* ε4 carriers exhibit greater increase in functional MRI signal in brain regions associated with task performance, and increases in additional regions compared with *APOE* ε3 carriers. **c** | Age-related memory decline occurs more rapidly in *APOE* ε4 carriers than noncarriers, starting from age 55–60 years. **d** | *APOE* ε4 carriers show increased cerebral Aβ deposition, becoming more pronounced with age. Increased PiB binding and reduced CSF $A\beta_{42}$ levels reflect cerebral amyloid deposition. Abbreviations: Aβ, amyloid-β; APOE, apolipoprotein E; AVLT-LTM, long-term memory score of the Auditory Verbal Learning Test; CSF, cerebrospinal fluid; PiB, Pittsburgh compound B. Part a is modified, with permission from the National Academy of Science, USA © Small, G. W. *et al. Proc. Natl Acad. Sci. USA* **97**, 6037–6042 (2000). Part b is modified, with permission, from the Massachusetts Medical Society © Bookheimer, S. Y. *et al. N. Engl. J. Med.* **343**, 450–456 (2000). Part c is modified, with permission from the Massachusetts Medical Society © Caselli, R. J. *et al. N. Engl. J. Med.* **361**, 255–263 (2009). Part d is modified, with permission, from John Wiley and Sons © Morris, J. C. *et al. Ann. Neurol.* **67**, 122–131 (2010).

Dysfunctional neurogenesis resulting from early disease manifestations could, therefore, exacerbate neuronal vulnerability to AD and contribute to memory impairment.[155] Apo-E is required for maintenance of the neural stem or progenitor cell pool in the adult dentate gyrus region of the hippocampus.[156] In Apo-E-TR mice, Apo-E4 inhibits hippocampal neurogenesis by impairing maturation of hilar γ-aminobutyric acid-containing interneurons, which contributes to learning and memory deficits.[157,158] These results demonstrate an important pathological role of Apo-E4 in impairment of neurogenesis, which might contribute to AD pathogenesis.

Apo-E as a therapeutic target in AD

Most therapeutic approaches for AD target the Aβ pathway. With the recent failure of clinical trials of drugs targeting solely Aβ, an urgent need exists to define new targets and develop alternative therapeutic strategies to treat AD. As *APOE* genotype determines AD risk, and Apo-E has crucial roles in cognition, Apo-E might offer an attractive alternative target for AD therapy. *APOE* genotype status could be included in clinical trial enrolment criteria, as some therapies might be effective only in specific *APOE* genotypes. Here, we briefly discuss several approaches that are currently being explored (Table 2).

APOE genotype and Aβ immunotherapy

Recent phase III trials of immunotherapy have shown that bapineuzumab, an antibody that targets the N-terminus of Aβ, prevents Aβ deposition in the brains of *APOE* ε4 carriers with mild or moderate AD, but not noncarriers.[159,160] Bapineuzumab also lowers levels of phosphorylated tau in the CSF of both *APOE* ε4 carriers and noncarriers.[159,160] These reports suggest that Aβ immunotherapy is useful to eliminate Aβ from the brains of patients with AD and that its effect is likely to depend on Apo-E isoforms. Major adverse effects of bapineuzumab—namely, vasogenic cerebral oedema and microhaemorrhage—occur more

Table 2 | Apo-E-targeted strategies for treatment of Alzheimer disease

Strategy	Rationale	Examples
Pharmacological approaches		
Modulate Apo-E levels	Promotes Aβ clearance, lipid homeostasis and synaptic function	LXR and RXR agonists, small molecules
Increase ABCA1 expression	Promotes Apo-E lipidation and stabilizes Apo-E, thereby decreasing amyloid deposition	LXR and RXR agonists, small molecules
Disrupt Apo-E–Aβ interaction	Reduces Aβ aggregation and deposition	Aβ12-28P, small molecule inhibitors, Apo-E-specific antibody
Stimulate conversion of Apo-E4 to Apo-E3	Increases Apo-E3-associated protective functions and decreases Apo-E4-related toxic effects	Small molecules (for example, disulphonate and monosulphoalkyl)
Restore Apo-E functions	Increases Apo-E protective functions and decreases neuroinflammation	Apo-E-mimetic peptide
Block Apo-E fragmentation	Decreases tau pathology and prevents toxicity to mitochondria	Inhibitors of specific proteinases involved in Apo-E fragmentation
Increase LRP1 and/or LDLR levels	Enhances Aβ clearance, cholesterol transport and synaptic plasticity	Small molecules
Increase Apo-E receptor 2 and/or VLDLR levels	Increases Apo-E signalling and synaptic plasticity	Small molecules
Restore brain vascular integrity	Eliminates Apo-E4-mediated blood–brain barrier breakdown and leakage of blood-derived toxic molecules	Cyclosporine A
Nonpharmacological approaches		
APOE genotyping prior to immunotherapy	Helps to predict clinical outcome of Aβ-targeted or other therapies	Aβ immunotherapy might be more effective in *APOE* ε4 carriers or noncarriers
Preventive care	Maintains healthy brain vasculature function	Physical exercise, intellectual activities (for example, puzzles), social connections (for example, calling family and friends), healthy diet

Abbreviations: Aβ, amyloid-β; ABCA1, ATP-binding cassette transporter A1; AD, Alzheimer disease; Apo-E, apolipoprotein E; LDLR, low-density lipoprotein receptor; LRP1, low-density lipoprotein receptor-related protein 1; LXR, liver X receptor; RXR, retinoid X receptor; VLDLR, very-low-density lipoprotein receptor.

frequently in *APOE* ε4 carriers than in noncarriers.[159,160] Although bapineuzumab failed to prevent cognitive and functional decline in these clinical trials, a combination of Aβ immunotherapy and an Apo-E-targeted approach might lead to more-effective therapeutic strategies.

Prevention of cognitive decline in ε4 carriers

A prospective study of a cognitively normal cohort showed that risk of dementia in *APOE* ε4 carriers is negatively associated with high education, high level of leisure activities, and absence of vascular risk factors.[161] A recent study demonstrated that physical exercise was strongly associated with reduced PiB-positivity in cognitively normal *APOE* ε4 carriers,[31] indicating that a sedentary lifestyle in *APOE* ε4 carriers might increase the risk of amyloid deposition. Such studies indicate that high education, active leisure activities and exercise, and maintenance of vascular health could be beneficial in reducing the risk of AD and cognitive decline, particularly in *APOE* ε4 carriers.

Regulation of Apo-E expression

Apo-E levels in CSF and plasma tend to be lower in patients with AD than in healthy individuals, although such findings remain controversial.[162,163] Thus, increasing the expression of Apo-E in all *APOE* genotypes may prevent or slow progression of AD through acceleration of Aβ metabolism and promotion of Apo-E functions in lipid metabolism and synaptic support. Compounds that increase brain Apo-E expression can be identified through comprehensive drug screening. Given that expression of Apo-E is controlled by peroxisome proliferator-activated receptor-γ and LXRs (which form complexes with RXRs),[100,164] agonists or antagonists of these nuclear receptors are potential candidates as Apo-E modulators. Indeed, recent work has demonstrated that oral administration of an RXR agonist, bexarotene, to an amyloid mouse model decreases Aβ plaque deposition and improves cognitive function in an Apo-E-dependent manner.[100] The LXR agonist TO901317 also increases Apo-E levels in the brain, facilitates clearance of $A\beta_{42}$, and reverses contextual memory deficit in amyloid mouse models.[98,99]

In addition to Apo-E, LXRs also regulate ABCA1, which promotes cholesterol efflux.[165] Consequently, reduction of amyloid burden by the LXR agonist GW3965 depends on expression of ABCA1 in amyloid mouse models.[166] These results suggest that upregulation of lipidated Apo-E might be necessary to maximize therapeutic effects in AD. These studies did not, however, assess the effect of increasing human Apo-E3 or Apo-E4 specifically. Because Aβ deposition is greater in *APP*-transgenic mice expressing mouse Apo-E than in those expressing human Apo-E isoforms,[167] further studies are needed to confirm the therapeutic effect of modulating the level of human Apo-E isoforms. In addition, whether increasing Apo-E4 is beneficial or harmful in

AD brains remains unclear, and the effects might depend on age and disease status. Toxic functions associated with Apo-E4 suggest that lowering Apo-E4 expression might be beneficial in *APOE* ε4 carriers with cognitive decline during MCI and AD. Additional preclinical studies are needed to test potential beneficial or harmful effects of increasing or decreasing Apo-E expression, particularly with regard to Apo-E isoforms.

Blockade of Apo-E–Aβ interaction

Apo-E is required for deposition of Aβ fibrils in amyloid mouse models.[106] Recent studies have demonstrated that haploinsufficiency of human *APOE* results in significantly decreased amyloid plaque deposition in amyloid mouse models regardless of *APOE* isoform status.[168,169] Thus, disruption of the interaction between Apo-E and Aβ might reduce Aβ aggregation and deposition, and should be considered as a therapeutic approach. Aβ interacts with Apo-E through amino acid residues 12–28. A synthetic peptide mimicking this sequence, Aβ12-28P, reduces Aβ deposition and ameliorates memory deficits in amyloid mouse models.[170] Blocking the Apo-E–Aβ interaction using Aβ-mimicking peptides could, therefore, be an effective approach for treatment of AD. Screening assays can also be used to identify compounds or Apo-E-specific antibodies that block Apo-E–Aβ interaction. These approaches should be assessed carefully because they could disrupt Apo-E–lipid interactions and the associated beneficial functions of Apo-E.

Other Apo-E-based therapeutic approaches

Apo-E4 is structurally different from Apo-E2 and Apo-E3 owing to different domain interactions,[131] and this difference probably contributes to Apo-E4 isoform-specific harmful effects. Modification of the structure of Apo-E4 to form an Apo-E3-like molecule might, therefore, be an interesting approach to ameliorate these harmful effects. Indeed, several molecules that bind to Apo-E4 and interfere with domain interactions between the N-terminus and C-terminus have been found. GIND-25 (disulphonate) and GIND-105 (monosulphoalkyl) are good candidates because they decrease Aβ production induced by Apo-E4 to a level similar to that induced by Apo-E3.[131] CB9032258 (a phthalazinone analogue) and its derivatives disrupt Apo-E4 domain interaction and restore functional activities of Apo-E4 in neurons.[171]

An Apo-E-mimetic peptide containing the receptor-binding region suppresses neuronal cell death and calcium influx associated with *N*-methyl-D-aspartate exposure *in vitro*.[172] COG112, a chimeric peptide containing the receptor-binding region, is also reported to improve symptoms in mouse models of multiple sclerosis[173] and sciatic nerve crush[174] through modulation of inflammatory responses. The effects of these peptides on AD pathogenesis are unknown, however, because they do not contain Aβ-interacting or lipid-binding regions.[13]

Apo-E receptors are also potential targets for AD therapy. For example, low-density lipoprotein receptor-related protein 1 and low-density lipoprotein receptor have crucial roles in brain lipid metabolism and Aβ clearance (Figure 2).[175–177] Apo-E receptor 2 and very low-density lipoprotein receptor are essential for reelin signalling, which is important for neuronal migration during development and synaptic plasticity in adult brains.[178] Modulation of expression of these Apo-E receptors in AD brains might, therefore, restore lipid homeostasis and synaptic plasticity, and augment Aβ clearance.[8,178] Although Apo-E-based therapies are still in early stages of development, they offer great promise in the fight against AD. Clinical trials to further evaluate therapeutic potential of Apo-E-based strategies are needed, with an eventual goal to develop curative and/or protective treatments for AD.

Conclusions

Work summarized in this Review highlights clinical evidence for the association between *APOE* ε4, AD and cognitive decline. Although the presence of *APOE* ε4 does not necessarily entail disease development, this genetic isoform probably accelerates the rate of disease conversion and progression. In particular, the effects of *APOE* ε4 on brain network connectivity, memory performance, and rate of cognitive decline are age-dependent in patients with AD and cognitively normal individuals. Thus, understanding the potential pathogenic link between *APOE* ε4 and cognitive function might enable earlier identification of people at increased risk of AD. In combination with other putative AD biomarkers—such as MRI scans, PiB-PET, and measurements of CSF Aβ and tau—*APOE* allele status could add predictive value to clinical diagnosis and evaluation of treatment efficacy.

Mechanistically, Apo-E4 seems to increase risk of AD and cognitive decline through both Aβ-dependent and Aβ-independent pathways. Apo-E isoforms differentially regulate Aβ production, aggregation and clearance. Independently of Aβ, Apo-E4 might be less efficient than Apo-E3 and Apo-E2 in delivering cholesterol and essential lipids for maintenance of synaptic integrity and plasticity. In addition, Apo-E is a crucial regulator of the innate immune system, with Apo-E4 promoting proinflammatory responses that could exacerbate AD pathogenesis. Finally, Apo-E isoforms have differential roles in maintaining vascular health—roles that are crucial given that vascular pathology is strongly associated with AD. Elucidation of the contribution of Apo-E4 to AD pathogenesis is a considerable challenge, but one that affords the potential to assist in combating AD.

Review criteria

This Review was based on searches of the PubMed database using the following terms: "apolipoprotein E", "cognitive decline", "Alzheimer disease", "amyloid beta", "synaptic plasticity", "cerebral amyloid angiopathy", "mild cognitive impairment", "cholesterol", "brain activity", "cerebrovascular diseases", "brain metabolism", "neurogenesis", "brain atrophy", "neuroinflammation", "tau" and "traumatic brain injury". Only articles published in English were retrieved. Full-text papers were available for most of the articles that were chosen for review, and the references of these articles were searched for further relevant material.

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CORRECTION

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In the version of this article initially published, in the author list, Chia-Chen Liu's name was misspelt. The error has been corrected for the HTML and PDF versions of the article.