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ORIGINAL PAPER

# An Integrative Overview of Non-Amyloid and Non-Tau Pathologies in Alzheimer's Disease

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## Abstract

Alzheimer's disease (AD) is a neurodegenerative disease that devastates the lives of its victims, and challenges the family members and health care infrastructures that care for them. Clinically, attempts to understand AD have focused on trying to predict the presence of, and more recently demonstrate the presence of, its characteristic amyloid plaque and neurofibrillary tangle pathologies. Fundamental research has also traditionally focused on understanding the generation, content, and pathogenicity of plaques and tangles, but in addition to this there is now an emerging independent interest in other molecular phenomena including apolipoprotein E, lipid metabolism, neuroinflammation, and mitochondrial function. While studies emphasizing the role of these phenomena have provided valuable AD insights, it is interesting that at the molecular level these entities extensively intertwine and interact. In this review, we provide a brief overview of why apolipoprotein E, lipid metabolism, neuroinflammation, and mitochondrial research have become increasingly ascendant in the AD research field, and present the case for studying these phenomena from an integrated perspective.

**Keywords** Alzheimer's · Apolipoprotein E · Lipids · Mitochondria · Neuroinflammation

## Introduction

Alzheimer's disease (AD) is a neurodegenerative disorder that, over time, degrades an individual's memory and other cognitive abilities [1]. AD directly afflicts millions around the world, additionally affects family members who become de facto care-providers, and has devastating personal and national financial consequences [2, 3]. AD manifests in two forms, a rare autosomal dominant familial form and the more common sporadic form; in this review we focus on the later.

Symptoms typically begin slowly, most frequently beginning after the age of 65, although in a considerable minority it arises some or potentially many years earlier [4]. Further, when considering the actual start-point, it is well-recognized that AD pathologies predate the onset of clinical symptoms for periods that can exceed decades [5].

The majority of AD pathology studies emphasize the plaques and tangles of the disease, which were described in Alois Alzheimer's initial reports [6, 7]. More recently, an enhanced interest in non-plaque, non-tangle pathologies has emerged. This review considers four well-recognized non-plaque, non-tangle AD-relevant phenomena: apolipoprotein E, neuroinflammation, mitochondrial dysfunction, and lipid homeostasis. Whether these phenomena primarily function as mediators of plaque and tangle-induced damage, or exist as independent or perhaps even driving events is not entirely clear at this time. An improved appreciation of these four entities could provide insight into how AD arises and, consequently, how to treat it.

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## Apolipoprotein E

Apolipoproteins are proteins that possess the ability to bind lipids. The protein-lipid complexes that subsequently arise from these associations are called lipoproteins [8]. The classically recognized function of apolipoproteins is to facilitate the movement of hydrophobic lipids within hydrophilic plasma and cerebrospinal fluid (CSF) compartments. Lipoproteins passing within aqueous environments enable the delivery of the lipid components to cells, which are internalized in conjunction with their apolipoprotein chaperones via receptor-mediated endocytosis.

Apolipoprotein E (ApoE) serves as the brain's major apolipoprotein [9–11]. As the brain contains approximately 25% of an individual's total cholesterol, ApoE is presumably crucial to maintaining brain function and structure. ApoE-cholesterol complexes trigger endocytosis upon binding the low-density lipoprotein receptor (LDLR), low density lipoprotein receptor-related protein 1 (LRP1), apolipoprotein E receptor 2 (Apoer2), or very low density lipoprotein receptor (VLDLR), which collectively comprise the low density lipoprotein (LDL) receptor family [12]. The apolipoprotein E-mediated delivery of lipids to cells comprises a crucial component of neuron repair following brain injury [13].

The gene for ApoE is located at chromosome 19q13.32, and contains four exons and three introns [14]. Two polymorphisms, one at rs429358 and the other at rs7412, define three different *APOE* alleles: ε2, ε3, and ε4. The ε4 allele is considered the ancestral form, and most closely resembles the chimpanzee gene. The ε2 and ε3 versions, on the other hand, have increased in frequency over the last 200,000 years [15]. The general frequencies of the different *APOE* alleles are approximately 6–7% for ε2, 78–79% for ε3, & 14–15% for ε4, although the e4 allele is seen with higher frequency in populations closer to the poles and equator [16].

The alleles of *APOE* differ from each other by single amino acid substitutions. These occur at amino acids 112 & 158, with ε2 having two cysteines, ε3 having a cysteine and an arginine respectively, and ε4 having two arginines [8]. ApoE has two domains, the N-terminal and C-terminal, which are connected by an intermediate hinge region [17].

This amino acid variation leads to structural differences between the variants. Some researchers have found the ε4 version shows decreased terminal domain stability in both its C-terminal & N-terminal domains, [18] while others report the ε4 version shows decreased stability in only the N-terminal domain [19]. This ε4-associated loss of stability leads to a higher rate of protein turnover, and reduced levels of the protein in plasma [20]. The ε4 variant also shows a higher binding affinity for larger very low density lipoprotein (VLDL) and LDL particles, while ε2 and ε3 variants preferentially bind the smaller high density lipoprotein (HDL) [21].

ApoE is mainly produced in the liver and separately in the CNS [9]. CNS production is necessary given the high concentration of cholesterol in the brain, as well as cholesterol's inability to cross the blood brain barrier (BBB). Specifically, astrocytes and microglia produce ApoE under normal physiological conditions, while stress or injury can induce neuron production [22]. Neuron synthesis may reflect an attempt to repair intracellular damage, perhaps by increasing lipid delivery to the damaged cell.

The different variants of *APOE* can undergo dissimilar processing within neurons. Notably, a chymotrypsin-like serine protease cleaves the ε4 variant more efficiently than the ε3 form [23]. This cleavage generates fragments that may perturb other cell functions, and in particular mitochondrial function. A proportion of the cleaved ε4 fragments bind to subunits of complexes III and IV of the mitochondrial respiratory chain on the inner mitochondrial membrane, with a subsequent inhibition of enzymatic activity [24]. In neurons, the protease-generated fragments also appear to associate with neurofibrillary tangles (NFT) [25, 26]. Thus, preferential cleavage of the ε4 protein may confer neurotoxic qualities, which exist independent of its reduced lipid binding capacity.

*APOE* ε4 alleles strongly associate with an increased lifetime risk of AD, and *APOE* ε4 alleles currently represent the best-recognized genetic risk factor for late onset, sporadic AD [27]. Having one copy of the allele increases an individual's probability of developing AD by 2–3 fold, while having two copies confers an increase of approximately eightfold [28]. The *APOE* ε2 variant, on the other hand, associates with a reduced lifetime risk of AD [29].

Although ε2, ε3, and ε4 have different lipid binding affinities, whether or not ApoE's role in maintaining lipid homeostasis drives its AD associations is not fully understood. It is possible that the different ApoE isoforms could influence AD risk through mechanisms that are independent of its role in lipid homeostasis [30]. ApoeE ε4 has been shown to localize with amyloid-β (Aβ) in plaques, [31] and ApoE forms complexes with Aβ in the brain and facilitates its clearance from the brain. Notably, the ε4 variant redirects these complexes away from LRP1 receptors and will only interact with the VLDLR. This disrupts clearance, and results in brain Aβ accumulation [32].

## Lipid Homeostasis

Lipids are an integral part of the CNS and their homeostasis is vital to the proper functioning of the nervous system. In his original paper describing AD, Alois Alzheimer

noted many glial cells contained adipose saccules [33]. The processes primarily responsible for maintaining lipid homeostasis include uptake, catabolism, storage, and synthesis [34]. The brain itself holds large amounts of cholesterol, especially within neuron plasma cell membranes, glia cell plasma membranes, and oligodendrocyte-generated myelin sheaths [35].

Genes involved in lipid homeostasis influence AD risk. Two early genome wide association studies (GWAS) identified a contribution for two such genes, *CLU* and *PICALM* [36, 37]. The *CLU* gene produces the protein clusterin, also known as apolipoprotein J, which participates in membrane recycling [38, 39]. The phosphatidylinositol binding clathrin assembly protein expressed by *PICALM* plays a role in clathrin-mediated endocytosis.

In addition to *CLU* and *PICALM*, the bridging integrator-1 (*BIN1*) gene also associates with AD. Similar to *PICALM, BIN1* is relevant to endocytosis [40]. Although it reportedly influences Aβ levels, neither *BIN1* knockdown nor over-expression alter APP processing [40].This suggests *BIN1* may influence AD through its effects on lipid biology. Finally, a subsequent GWAS revealed an association between AD and the gene that encodes the ATP-binding cassette sub-family A member 7 (*ABCA7)* [41]. The ATP-binding cassette family is involved in lipid trafficking [42].

A component of the plasma membrane is lipid rafts, which are composed of proteins, glycosphingolipids, and cholesterol that transit as a group independently along the cytoplasmic leaflet of the membrane [43]. In individuals with AD these rafts contain altered lipid profiles, which are characterized by low levels of long chain polyunsaturated fatty acids (LC-PUFA) and perturbed interactions between phospholipids and fatty acids [43]. Differences in lipid composition between individuals with AD and healthy individuals are seen both at the general cellular level, as well as by brain region. For example, the prefrontal cortex of AD patients exhibits altered levels of diacylglycerol and sphingolipids when compared to brains from healthy, age-matched individuals [43].

Higher serum cholesterol levels during midlife reportedly associate with an increased risk of late-onset AD [44]. Observational studies of individuals taking cholesterol-lowering statin drugs suggested this intervention might reduce the risk of developing AD or other dementias, [45] although clinical trials of statin drugs performed in AD participants showed no benefit [46].

Sterols used to generate myelin are produced via local synthesis, and not through the input of cholesterol into the brain [47]. The CNS is highly enriched in LC-PUFAs, the most important of which is docosahexaenoic acid (DHA), an omega-3 fatty acid [48]. Epidemiologic studies have reported that individuals with a reduced intake of omega-3 fatty acids have an increased risk of developing cognitive deficits [49].

Under baseline conditions, neurons are believed to utilize glucose to produce energy. They appear unable to perform fatty acid beta-oxidation, although astrocytes can successfully execute this biochemical pathway [50, 51]. Potential advantages of avoiding neuron beta-oxidation include preserving fatty acids for use in membrane expansion or maintenance, and also limiting beta-oxidation associated reactive oxygen species (ROS) production [52]. Advantages of pursuing astrocyte fatty acid beta-oxidation include the production of ketone bodies, which are potentially shuttled to neurons and used there to support energy production [53].

Cells use lipids for a number of functions during normal conditions, and when there is a change in the environment they can adapt to meet the new needs. The lipidome is a dynamic part of cells that will actively respond to changes in physiologic conditions [54, 55]. The downstream effects of an altered lipidome, though, are complex and could potentially result in dysfunction or disease, or simply reflect a downstream effect of dysfunction or disease.

## Neuroinflammation

Inflammation represents the response of the immune system to endogenous or exogenous-induced tissue damage. When this response occurs in the central nervous system (CNS) it is referred to as neuroinflammation [56, 57]. In the short term, such reactions can minimize tissue damage or initiate repair, while chronic activation can conversely cause harm. Neuroinflammation is frequently present in neurodegenerative conditions, where it may reflect a byproduct of an upstream neurodegenerative pathology, or alternatively potentially instigate neurodegenerative pathology [58]. Neuroinflammation is observed in the early stages of AD, and may actually precede Aβ aggregation and tau neurofibrillary tangles [59].

Recent research identifies links between AD and variants within genes that influence inflammation, including *TREM2, CR1, HLA-DRB5/DRB1, INPPD5, MEFC2*, and *PTK2B* [37, 60, 61]. The triggering receptor expressed on myeloid cells 2 (*TREM2)* gene expresses a protein that is highly expressed on microglia, and which regulates cytokine release [62]. Complement receptor type 1 (*CR1*) is involved in the innate immune system's regulation of complement [63]. Human Leukocyte Antigen–antigen D Related beta chain (*HLA-DRB)* is implicated in Multiple Sclerosis, a degenerative-autoimmune disease that is characterized by inflammation [64].

The BBB ideally restricts the access of systemic immune cells to the CNS, thereby conferring an "immune privileged" status to the brain [65]. Accordingly, the brain

has its own resident cells that fill the role of an immune system, the microglia. Under baseline conditions they typically show phenotypic conformity, but in the context of homeostatic changes or frank damage morphologic and gene expression changes occur [66]. Neuron damage activates local microglia, and activation of local microglia in turn stimulates more remote microglia and amplifies the overall neuroinflammation state [67].

Activated microglia can produce a number of potentially neurotoxic pro-inflammatory cytokines, including interleukins (IL-1, IL-6), and tumor necrosis factor (TNF-α) [68]. Microglia further act as the macrophages of the nervous system, and remove debris, pathogens, and unwanted cells. It is well recognized that microglia actively disassemble synapses formed by damaged neurons [69]. Interestingly, in AD, microglia can be seen in the vicinity of otherwise intact neurons whose synapses are separating [70]. This raises the possibility that microglia-mediated synaptic stripping might represent an early pathologic event that, in its most extreme form, independently contributes to neurodegeneration. In AD, synapse degradation correlates reasonably well with cognitive function [71].

Microglia constitute only one neuroinflammation component. Astrocytes, oligodendrocytes, and the BBB also play a role in neuroinflammatory responses. The different components mediate specific effects that arise at different time-points in the course of a neuroinflammatory response. For this reason, inflammation that occurs within acute settings, such as a traumatic brain injury or a stroke, can dramatically differ from more chronic neuroinflammatory responses that arise during the course of multiple sclerosis or AD [57].

BBB disruption is a frequent component of neuroinflammation, to the point that myeloid cells transit from the circulation to the CNS parenchyma. In fact, myeloid cells only cross the BBB when there is a breakdown in its integrity [72]. During normal ageing the BBB becomes less restrictive, which allows for a more extensive interaction of blood immune cells with the brain parenchyma [73]. This upsets CNS homeostasis and further amplifies the inflammatory response, to the point that cells with immune-response potential that would normally remain quiescent become active. For example, astrocytes can be induced to release relatively large volumes of chemokines, which further perpetuates the pro-inflammatory cytokine response [74].

Due to the multitude of response amplifications that can occur, acute activation can potentially evolve into a chronic response that fuels its own perpetuation. In diseases such as AD, it is still not clear why neuroinflammation arises, or if it is initiated through an acute insult.

## Mitochondrial Dysfunction

Mitochondria are considered the "powerhouse" of the cell because they produce most of the ATP used by cells. Mitochondria are dynamic, mobile organelles that can divide or fuse to form branching complex structures [75]. Such adaptations help cells meet their overall energy demands, address local energy stresses at specific cell regions, and repair or remove damaged mitochondria. To increase mitochondrial mass, cells can undergo a process called mitochondrial biogenesis. Mitochondrial biogenesis primarily occurs within neuron cell bodies, although it can also occur in axons as well [76]. Similarly, while most lysosome-mediated elimination of cell waste takes place in the soma, axons can also perform localized mitophagy via the PINK1 & Parkin pathway [77]. The flexible nature of the mitochondrial pool helps cells more efficiently meet their energy needs, and the loss of this flexibility can result in dysfunction or disease.

Mitochondrial dysfunction is seen in a number of neurodegenerative conditions including AD, Leber's hereditary optic neuropathy(LHON), Parkinson's disease, and amyotrophic lateral sclerosis (ALS) [78]. Mitochondria may account for observed relationships between advancing age and an age-related increase in the incidence of various neurodegenerative diseases, as mitochondrial function declines with advancing age [79]. In various tissues, including the nervous system, somatic mutations accumulate within mitochondrial DNA (mtDNA), which may contribute to or compound age-related changes in mitochondrial function [80, 81]. Some have proposed declines in mitochondrial function that exceed a threshold can contribute to the onset or progression of neurodegenerative diseases [82, 83]. According to one scheme, an individual's genetic inheritance helps to define a baseline level of mitochondrial function, and the rate at which that individual's mitochondria decline over decades further determines how rapidly the individual approaches a functional threshold that allows for the manifestation of an age related disease such as AD [84].

Dysfunctional mitochondria may produce reactive oxygen species (ROS), which can damage lipids, proteins, and DNA [85]. Multiple markers of oxidative stress are consistently elevated in AD subject autopsy brains, and perhaps other tissues as well [86]. Whether oxidative stress, either as a byproduct of mitochondrial dysfunction or some other generator, mediates pathology or primarily serves as a marker of mitochondrial dysfunction, is unclear.

## Interactions and Integration

ApoE, lipid biology, neuroinflammation, and mitochondria are functionally inter-related. In one study that utilized *APOE* knock-in mice, the expression of two human ε4 transgenes resulted in higher serum cholesterol, lower brain cholesterol, and lower brain phospholipid levels [87]. On the other hand, in another study that featured ε4 knock-in mice, the synapse plasma membrane exofacial leaflets contained increased cholesterol [88, 89]. Therefore, although cholesterol levels in the brains of mice expressing the *APOE* ε4 allele may show an overall decrease, that decrease is not evenly distributed and localized increased levels of cholesterol are possible. ApoE ε4 expression in neurons, but not astrocytes, also reduces mitochondrial respiration [90]. It therefore appears that ApoE affects both lipid composition and mitochondrial respiration; whether these effects occur independently, or are mechanistically linked, is difficult to resolve.

Some note inflammation can influence lipid mobilization, at least in adipose tissue [91, 92]. Others have proposed that in the CNS, lipid mobilization may serve to alleviate energy stress [93]. Potentially relevant data suggest neuroinflammation may also regulate proteins that manage CNS lipid handling. For instance, following treatment with IL-1β, rat glial cell cultures showed a significant increase in extracellular ApoE, while TNF-α treatment reduced extracellular ApoE [94]. This suggests the ability of neuroinflammatory responses to regulate ApoE action can be both precise yet flexible (Fig. 1).

Further research that highlights interactions among ApoE, lipid biology, and neuroinflammation include a study that compared mice expressing *APOE* ε4 versus ε3 transgenes. The ε4-expressing mice showed an increased lipopolysaccharide (LPS) challenge-induced response of their NF-κB signaling pathway, as well as increased microglial activation [95]. These results suggest that the *APOE* ε4 isoform potentiates neuroinflammation responses. To this point, the ε2 and ε3 isoforms can better interact with the low-density lipoprotein receptor family, with a resulting suppression of c-Jun N-terminal kinase (JNK) activation and a reduction in pro-inflammation signaling [96].

ApoE also participates in cerebrovascular regulation. By regulating a CypA-NFκB-matrix metalloproteinase 9 pathway in pericytes, *APOE* ε2 and ε3 isoforms promote BBB integrity, while expression of ε4 promotes BBB permeability [97]. Prior studies, therefore, identify multiple pathways through which ApoE may facilitate, modulate, or otherwise influence neuroinflammation.

Interactions between mitochondria and neuroinflammation are also well recognized. BV2 and SH-SY5Y cells exposed to extracellular mtDNA increased their production

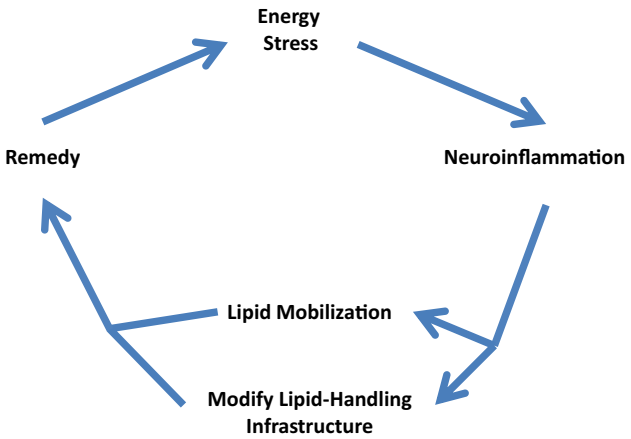


**Fig. 1** Neuroinflammation may help cells respond to energy stress. As depicted, neuroinflammation activates both lipid mobilization and proteins (such as ApoE) that assist in the utilization of those lipids. These actions can serve to alleviate an energy stress, although since energy stress can also initiate neuroinflammation, this process could also potentially compensate for a primary energy deficit

of pro-inflammatory cytokines [98]. Astrocytes exposed to IL-1β, one of the major pro-inflammatory cytokines, exhibited altered mitochondrial cycle dynamics, with an increase in mitochondrial fission [99].

In terms of relationships between mitochondria and lipid homeostasis, it is important to note mitochondria play essential roles in both lipid catabolism and synthesis [100]. Mitochondrial function, therefore, should presumably affect the lipidome.

BV2 microglia cells exposed to LPS showed an increased saturated fatty acid content, as well as a concomitant decrease in monounsaturated fatty acid levels [101]. In the setting of inflammation, macrophage ApoE expression declines due to changes in AP-1 and NF-κB regulation [102]. Consequently, inflammation plays a role in the regulation of both ApoE and lipid levels. Figure 2 schematically illustrates potential connections between ApoE, lipid metabolism, neuroinflammation, and mitochondria.

## Future Directions

ApoE, mitochondrial dysfunction, lipid metabolism, and neuroinflammation are implicated in AD. Strong biological connections functionally link ApoE, mitochondrial dysfunction, lipid metabolism, and neuroinflammation. The extent to which these components act independently to influence AD, or work through interactions to mediate the disease, remains to be seen. Addressing this question could facilitate a deeper understanding of what causes AD, and ideally how to treat it.

After over a century of studying AD, the field is finally reaching the point that it can visualize its classic

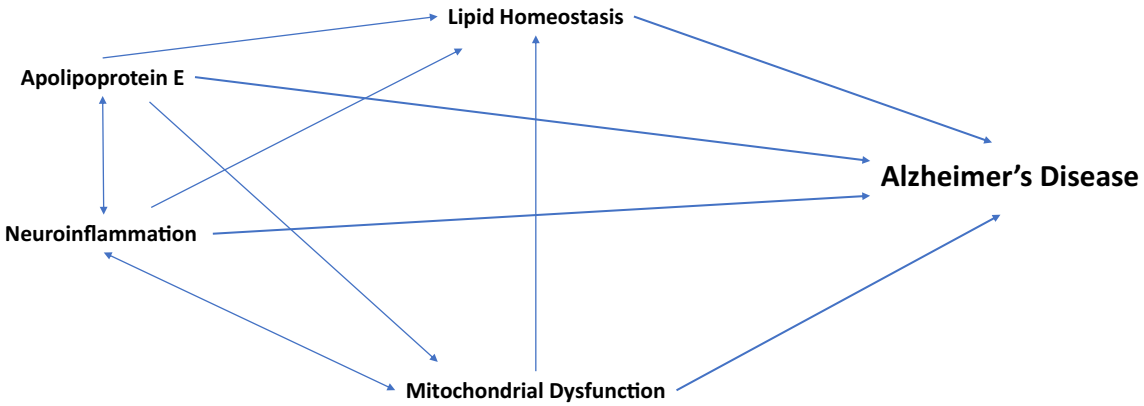


**Fig. 2** Interactions between ApoE, lipid metabolism, neuroinflammation, and mitochondria may cooperatively influence the development of AD

histopathologies, the plaques and tangles, in living patients. Having achieved these milestones, the AD field is hopefully now poised to address the critical question of why plaques and tangles appear. A fuller understanding of ApoE, mitochondrial, lipid metabolism, and neuroinflammation biology could potentially inform this critical challenge.

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