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Review

The Role of APOE and NF-κB in Alzheimer's Disease

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Abstract: Apolipoprotein E (APOE) has three different isoforms, with APOE4 carriers representing a major risk factor for the development of Alzheimer's disease (AD). AD is the most common form of dementia, and is a relentlessly progressive disorder that afflicts the aged, characterized by severe memory loss. Presently, AD does not have a cure, increasing the urgency for the development of novel therapeutics for the prevention/treatment of AD. The APOE4 isoform is associated with many pathological mechanisms, such as increased neuroinflammation and a reduction in β-amyloid (Aβ) clearance. The accumulation of Aβ plaques in the brain is a hallmark of AD. The presence of APOE4 can increase neuroinflammation via overactivation of the nuclear factor kappa B (NF-κB) pathway. The NF-κB pathway is a family of transcription factors involved with regulating over 400 genes involved with inflammation. AD is associated with sustained inflammation and an overactivation of the NF-κB pathway. Therefore, targeting the APOE4 isoform and suppressing the NF-κB pathway using anti-inflammatory compounds may result in the development of novel therapeutics for the prevention/treatment of AD.

Keywords: neurodegeneration; neuroinflammation; APOE4; APOE3; APOE2; pro-inflammatory

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1. Introduction

The global population is reaching unprecedented levels of advanced age, generating a large demographic vulnerable to brain insults, thus creating enormous healthcare, economic and social impacts. Alzheimer's disease (AD) is a relentlessly progressive disorder that afflicts the aged, and is the sixth leading cause of death in the United States (Centers for Disease Control and Prevention). Two hallmarks of AD include β-amyloid (Aβ) peptides that are extracellularly deposited, and neurofibrillary tangles (NFTs), composed of intracellular filamentous aggregates of hyperphosphorylated tau protein [1–4]. In June 2021, Aducanumab was approved as a disease-modifying therapeutic via the removal of Aβ plaques in the brain [5]. However, the presence of Aβ plaques does not always result in AD, which has led to controversy over the use of aducanumab. Other therapeutics used for AD do not alter the course of the disease, which increases the urgency of developing novel therapeutics for AD.

Apolipoprotein E (APOE) has emerged as a therapeutic target for the treatment of AD. APOE is a cholesterol carrier that is involved with lipid transportation and repair in the brain [6]. APOE is a polymorphic protein with three isoforms, APOE4, APOE3, and APOE2, which differ from each other by two amino acid substitutions (arg/arg, cys/arg, and cys/cys, respectively), resulting in different tertiary structures and likely altering APOE function. Despite the similarity among the isoforms, they present major differences in the risk of developing AD, with APOE4 being a strong risk factor for the development of AD. APOE3 is the most common isoform and does not affect risk of developing AD, and APOE2 is associated with a decreased risk of the development of AD. The worldwide frequency of APOE4 is 13.7%, that of APOE3 is 77.9%, and that of APOE2 is 8.4% [7]. The frequency of APOE4 in AD is approximately 40% [7]. Genome-wide association studies have shown that APOE4 is the strongest genetic risk factor for early-onset AD and late-onset AD [8,9].

2. Neuroinflammation and Alzheimer's Disease

Immunological processes in the brain contribute to AD progression and severity [10]. Microglia are the resident macrophages of the central nervous system (CNS) that detect the presence of pathogens and cellular debris while providing tissue maintenance. In addition, microglia contribute to synaptic plasticity through phagocytosis, which removes select synapses [11]. Therefore, sustained inflammation may cause synaptic dysfunction. The depletion of microglia is associated with learning and memory impairments [12]. Microglia become active once exposed to pathogen-associated molecular patterns (PAMPs) or damage-associated molecular patterns (DAMPs). Microglia bind to soluble and fibrillar forms of Aβ in different ways [13]. Microglia bind to soluble forms of Aβ via endocytosis and the low-density lipoprotein (LDL) receptor-related protein pathway. The fibrillar form of Aβ binds to the cell surface of the innate immune receptor complex, which results in phagocytosis. Other reviews have examined the role of microglia in AD in more detail [10].

Nuclear factor kappa B (NF-κB) is a family of transcription factors involved with the regulation of inflammation [14,15]. The NF-κB family includes NF-κBp50/105, NF-κBp52/100 (RelB), NF-κBp65 (RelA), and NF-κBp75 (c-Rel), with dimers bound by the inhibitory protein IκB. The NF-κB proteins are often located in the cytoplasm in an inactive state [16]. The activation of NF-κB results in two signaling pathways, the canonical and nonconical pathways, which are both important for the modulation of inflammatory and immune responses [17,18]. The canonical NF-κB pathway is activated when binding occurs with immune receptors, including tumor necrosis factor receptor (TNFR), interlukin-1 receptor (IL-1R), toll-like receptors (TLR), and lipopolysaccharide (LPS), which activates the IκB kinase (IKK) trimeric complex (IKKα, IKKβ, and IKKγ (NEMO)) and phosphorylates IκBα [19]. The NF-κB p50/RelA dimers translocate from the cytoplasm into the nucleus and bind to IκB, which regulates NF-κB-associated genes [20]. The noncanonical NF-κB pathway is activated by the B-cell activating factor belonging to the TNF family receptor (BAFFR) and the receptor activator for NF-κB (RANK), which involves interactions with IKKα and the phosphorylation of NF-κB p100. Once NF-κB p100 is degraded, NF-κB p52/RelB dimers translocate from the cytoplasm into the nucleus to modulate NF-κB genes [19].

NF-κB dysregulation is associated with various neurological conditions, including ischemic stroke, multiple sclerosis, AD, and other neurodegenerative disorders [21–25]. In AD, the transmembrane aspartic protease beta site amyloid precursor protein cleaving enzyme 1 (BACE1) initiates the production of Aβ with gamma-secretase, which cleaves a portion of the extracellular amyloid precursor protein (APP) [26]. This results in an accumulation of Aβ that can form plaques between neurons, which disrupts the neuronal signaling and leads to dysfunctional synaptic plasticity and neuroinflammation [27]. The NF-κB pathway is involved with the modulation of BACE1 expression, and therefore the production of Aβ. The inhibition of the functional binding site IkappaB kinase of Nf-κB prevents Aβ-induced BACE1 promoter transactivation, suggesting that this pathway could modulate an Aβ-associated phenotype [28]. NF-κB activation upregulates the transcription of BACE1 and increases the expression of Aβ [29,30]. Aβ infusions into mice brains and nonhuman primates increased IKKβ/NF-κB signaling in the hypothalamus [31]. In drosophila, the genetic overexpression of NF-κB in neurons and glial leads to an AD phenotype with increased neurodegeneration [32]. AD is associated with sustained inflammation, which in part may be due to the Receptor for Advanced Glycation End-Products (RAGE)/NF-κB axis, which activates an autoregulatory loop that further amplifies neuroinflammation [33]. The Advanced Glycation End-Products (AGEs)/RAGE complex upregulates BACE1 via the activation of the NF-κB pathway [34]. The immunoreactivity of p65 was increased near Aβ plaques in AD patients, suggesting that NF-κB is active in neurons surrounding Aβ plaques [24]. The regulation of NF-κB by Aβ may result in glial cell activation, as demonstrated by experiments showing that Aβ activated the NF- κB pathway and increased nitric oxide in astrocytes [35]. Tanshinone I inhibits the NF-κB pathway in LPS-induced microglia [36]. Phytochemicals inhibit the NF-κB pathway by

preventing phosphorylation and ubiquitination, which inhibits the degradation of IκB, thereby preventing the translocation of NF-κB into the nucleus [37]. Given the detrimental effects that an overactive NF-κB pathway has on neurodegeneration, attenuating the NF-κB pathway may improve neurodegenerative conditions, such as AD.

3. APOE and Inflammation

APOE and its receptors play important roles in inflammatory responses that modulate the clearance of Aβ. APOE genotypes affect Aβ plaque deposition and can cause cerebral amyloid angiopathy (CAA) [38]. APOE is deposited in the plaques of patients with AD, and is more abundant in APOE4 carriers compared with non-APOE4 carriers [39–42]. PET scanning using Pittsburgh compound B (PiB) showed that fibrillar aggregates of Aβ were more common in people who are APOE4 carriers [43,44]. APOE4 carriers have high rates of fibrillar Aβ in frontal, posterior cingulate-precuneus, temporal, parietal, and basal ganglia regions of the brain [45]. Cognitively normal APOE4 carriers received PiB PET imaging that indicated fibrillar aggregates of Aβ at approximately 56 years of age, compared to approximately 76 years of age in non-APOE4 carriers [46]. These results have led to speculation that increases in fibrillar Aβ in APOE4 carriers in cognitively normal people may result in an increased risk of developing mild cognitive impairment (MCI) and/or AD in the future [47].

Since the 1990s, transgenic mice have been used to model AD in the presence of mouse APOE. As previously mentioned, APOE has three different isoforms; however, mice express a single isoform, and it differs from the human APOE isoforms by approximately 100–300 amino acids [48]. The difference between human APOE and mouse APOE has led researchers to investigate the role of transcription factors in the expression of APOE, such as the LXRE consensus sequences in human and mouse APOE [49–51]. APOE knock-out mice were crossed with a transgenic mouse model of AD overexpressing a human mutant APP gene, resulting in PDAPP+/+; APOE −/− mice, which exhibited reduced Aβ deposits compared to PDAPP+/+; APOE +/+ mice [52]. PDAPP+/+; APOE −/− mice that expressed either human APOE2, APOE3, or APOE4 showed a reduction in Aβ40 in plasma as they aged for each isoform [53]. However, levels of Aβ40 and Aβ42 increased in the brain as the mice aged, regardless of the APOE isoform. Hippocampal insoluble Aβ40 and Aβ42 levels increased in an APOE isoform-dependent manner, with the highest levels in the APOE4 mice and the lowest levels in APOE2 mice.

APOE4 mice had increased levels of microglia, astrocytes, and invading T-cells after a brain infusion of LPS. In addition, the APOE4 mice had increased cytokine responses compared with APOE2 and APOE3 mice [54,55]. Cortical levels of IL-1β and the microglial reactivity in cortical plaques of APOE4 mice were increased compared to APOE3 mice [56]. Experimental autoimmune encephalomyelitis impaired learning and memory in APOE4 knock-in mice, suggesting that neuroinflammation affects learning and memory in APOE4 carriers [57]. Intravenous LPS administration increased pro-inflammatory cytokines, TNFα, and IL-6 in APOE4 mice compared to APOE3 mice [58]. Additionally, the administration of APOE mimetic peptide from the receptor-binding region decreased systemic and brain pro-inflammatory responses after administration with LPS. The APOE peptide was associated with the decreased activation of c-Jun N-terminal kinase (JNK) signaling [59]. The microglial lipoprotein receptors regulate JNK activity, and are necessary for APOE's regulation of inflammation. The APOE mimetic peptide crosses the blood–brain barrier (BBB), and using peptides that can cross the BBB may be a novel therapeutic strategy for the treatment of AD [60].

While there is mounting evidence that APOE4 is associated with pro-inflammatory responses, an in vitro study using cultured rat glia found that APOE4 decreased the oligomeric Aβ production of nitric oxide synthase and cyclo-oxygenase-2, suggesting that APOE4 has anti-inflammatory properties [61]. APOE has anti-inflammatory effects in isolated macrophages via the APOE receptor-2, which result in macrophage conversion from pro-inflammatory M1 to the anti-inflammatory M2 [62]. Endogenous APOE from glial

cell cultures inhibits microglial nitric oxide production [63]. The inhibition of inflammatory signaling increased APOE expression, which indicates that inflammation and APOE levels are involved in a negative feedback loop [64]. APOE deletion upregulates TLR4 and TLR2, and increases TLR activation [65,66]. The APOE protein is involved with an anti-inflammatory state, with APOE4 being the least anti-inflammatory, APOE2 being the most anti-inflammatory, and APOE3 being in the middle of the anti-inflammatory scale [67].

4. APOE and NF-κB

APOE is shown to modulate neuroinflammation via the NF-κB pathway. APOE4 mice showed increased NF-κB-regulated genes compared to APOE3 mice [68]. However, another study found that both APOE3 and APOE4 downregulated the NF-κB pathway [69]. These discrepant results may be due to the differences in methodology used between the two studies, with the in vivo experiment showing an increase in NF-κB activity and the in vitro experiment showing a decrease in NF- κB activity. APOE knock-out mice had increased inflammation and oxidative stress via activation of the NF-κB pathway [70]. PDAPP+/+; APOE −/− mice have reduced Aβ deposits in the cortex and hippocampus, and future studies should examine the NF-κB pathway in PDAPP+/+; APOE −/− mice [52]. Administration of the anti-inflammatory compounds Tanshinone IIA and Astragaloside IV in APOE knock-out mice suppressed the TLR4/NF-κB signaling pathway in vivo and in vitro [71]. Brain infusions of LPS in APOE4 mice were associated with the increased activation of the NF-κB pathway compared to APOE3 mice [72]. APOE4 mice showed increased nuclear translocation of NF-κB and increased IL-1β. The activation of the NF-κB pathway was increased after traumatic brain injury (TBI) in APOE4 mice compared to APOE3 mice [73]. APOE3 may inhibit the NF-κB pathway after TBI to alleviate BBB impairment. Schwann cells from APOE4 and APOE2 mice showed impaired cytokine production, which may have resulted from activation of the NF-κB pathway [74]. APOE activates the NF-κB pathway, inducing the expression of immunosuppressive chemokines Cxcl1 and Cxcl5 in tumor cells [75].

A high-fat diet and sedentary lifestyle can affect many medical conditions, including AD. APOE knock-out mice fed a high-fat diet had hypothalamic inflammation, glial cells activation, and cognition decline, which were reversed with diet control and exercise [76]. The diet control and exercise resulted in increased expressions of SIRT1 and the inhibition of the NF-κB pathway. Chronic stress is another important lifestyle factor that can influence various health conditions. Chronic unpredictable mild stress in APOE knock-out mice upregulated TLR4/NF-κB expression [77], and the administration of an NF-κB inhibitor downregulated the NF-κB pathway [78]. APOE knock-out mice that received AGEs via injection displayed increased Aβ formation and NF-κB p65 expression [79]. The statin medication atorvastatin decreased Aβ formation and suppressed AGEs-induced NF-κB p65 expression. PDAPP+/+; APOE −/− mice have decreased Aβ deposits, which contrasts with the previously mentioned experiment with increased Aβ formation. PDAPP+/+ mice are generated using a platelet-derived growth factor promoter with a human APP gene mutation associated with AD. Modafinil is prescribed for narcolepsy patients to increase wakefulness, and has anti-inflammatory effects. In APOE knock-out mice, modafinil inhibited the NF-κB pathway [80].

Vascular defects occurred in APOE4 mice before the neurodegenerative impairments occurred [81]. Astrocytes that secreted APOE3 and APOE2 but not APOE4 inhibited the cyclophilin A (CypA)-NF-κB–matrix-metalloproteinase-9 (MMP-9) pathway in pericytes, suggesting that APOE4 is a key target for the treatment of neurovascular conditions [82]. CypA has a variety of roles, including protein folding, trafficking and T cell activation, and is secreted from cells in response to inflammation [83]. MMP-9 is a type of enzyme in the zinc-metalloproteinases family involved with the breakdown of the extracellular matrix in both normal and pathological processes, including neurodegeneration [84]. The pro-inflammatory CypA–NF-κB–MMP-9 pathway causes BBB impairment via the MMP-9 degradation of tight junction proteins, which is associated with the onset of neurode-

generative disorders [81]. Additionally, astrocytes that secrete APOE3 and APOE2 have high binding affinities with lipoprotein receptor-related protein 1 (LRP1) [81]. However, astrocytes that secrete APOE4 have a low binding affinity with LRP1. In pericytes, the weak binding affinity of APOE4 to LRP1 leads to a reduction in Aβ clearance and a subsequent Aβ accumulation, resulting in neurodegeneration (see Figure 1). The inhibition of the CypA–NF-κB–MMP-9 pathway in APOE4 mice increased the coverage of tight junction proteins, prevented the loss of neurons and axon density, and improved cognitive function [85]. However, the inhibition of the CypA–NF-κB–MMP-9 pathway does not protect against Aβ accumulation.

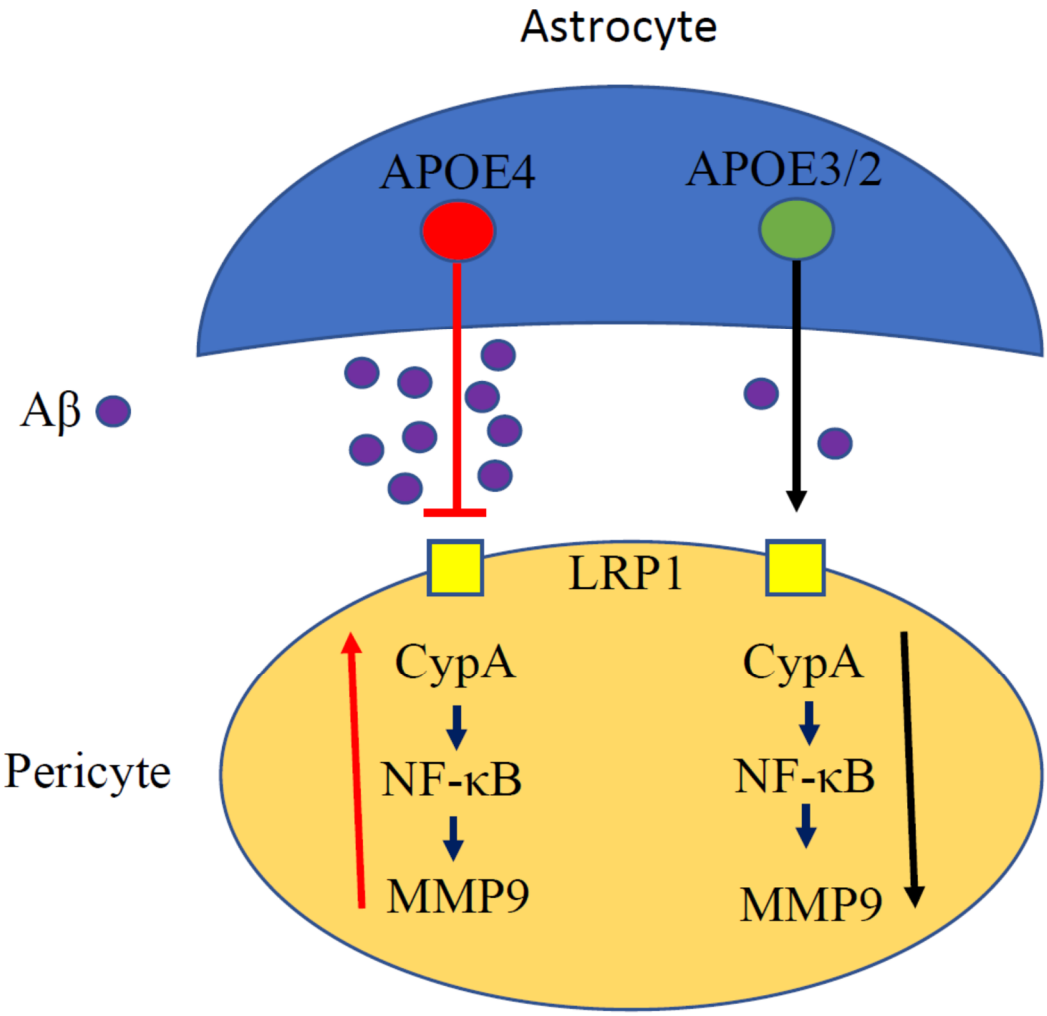

Figure 1. The proposed pathways involved with the interaction of apolipoprotein E (APOE) and nuclear factor kappa B (NF-κB). APOE4 protein secreted from astrocytes has a low binding affinity with the low-density lipoprotein receptor-related protein 1 (LRP1) and results in an increase in the cyclophilin A (CypA)–NF-κB–matrix metalloproteinase 9 (MMP-9) pathway (as represented by the red line). This also results in blood–brain barrier (BBB) damage via degradation of tight junctions. In contrast, the APOE3 and APOE2 (APOE3/2) protein has a high binding affinity to LRP1, which suppresses the CypA–NF-κB–MMP-9 pathway as represented with the black line. Damage to the BBB is also associated with the accumulation of β-amyloid (Aβ). The weak binding affinity of APOE4 to LRP1 results in reduced Aβ clearance. The high binding affinity of APOE3/2 to LRP1 results in greater Aβ clearance.

5. Conclusions

APOE4 and the NF-κB pathway have emerged as targets for the prevention/treatment of AD. Targeting the APOE4 isoform may suppress the NF-κB pathway, given that the weak binding of APOE4 to LRP1 leads to increased NF-κB activity. Novel therapeu-

tic approaches focus on removing APOE4 with antibodies and modifying the structure of the APOE4 protein to shift to the APOE3 and APOE2 isoforms [86]. Using CRISPR in cell culture showed that APOE4 can be converted into APOE3, and does not affect the expression of APOE3 [87,88]. However, in vivo experiments converting APOE4 to APOE3 have not been reported. The overexpression of the NF-κB pathway in AD has gained increased recognition, making it a therapeutic target. The NF-κB pathway triggers a cascade of pro-inflammatory cytokines and chemokines, and compounds including resveratrol, indomethacin, quercetin, adiponectin, caffeic acid, aspirin, and sodium salicylate may suppress the NF-κB pathway, leading to the development of a novel therapeutic for AD [89]. Future research should examine the interactions among the APOE–LRP1–CypA–NF-κB–MMP-9 pathway for the development of novel therapeutics to prevent/treat AD.

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