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Review Article

The Role of Apolipoprotein E in Guillain-Barré Syndrome and Experimental Autoimmune Neuritis

Hong-liang Zhang,[1,2] Jiang Wu,[1] and Jie Zhu[1,2]

[1] *Department of Neurology, The First Hospital of Jilin University, 130021, Changchun, China*
[2] *Department of Neurobiology, Care Sciences and Society, Karolinska Institute, Karolinska University Hospital Huddinge, SE-141 86, Stockholm, Sweden*

Correspondence should be addressed to Jiang Wu, sjnkwujiang@vip.sina.com and Jie Zhu, jie.zhu@ki.se

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Apolipoprotein E (apoE) is a 34.2 kDa glycosylated protein characterized by its wide tissue distribution and multiple functions. ApoE has been widely studied in lipid metabolism, cardiocerebrovascular diseases, and neurodegenerative diseases like Alzheimer's disease and mild cognitive impairment, and so forth. Recently, a growing body of evidence has pointed to nonlipid related properties of apoE, including suppression of T cell proliferation, regulation of macrophage function, facilitation of lipid antigen presentation by CD1 molecules to natural killer T (NKT) cells, and modulation of inflammation and oxidation. By these properties, apoE impacts physiology and pathophysiology at multiple levels. The present paper summarizes updated studies on the immunoregulatory function of apoE, with special focus on isoform-specific effects of apoE on Guillain-Barré syndrome (GBS) and its animal model experimental autoimmune neuritis (EAN).

1. Introduction

Apolipoprotein E (ApoE) is a 34.2 kDa glycosylated protein with 299 amino acid residues. The *APOE* gene is located on chromosome 19q13.2, consisting of four exons and three introns and spanning 3597 nucleotides [1]. There are three isoforms in human (apoE2, apoE3, and apoE4) due to different amino acid residues at positions 112 and 158, among which apoE3, with a cysteine residue at position 112 and an arginine residue at position 158, is the most common. The other two "variants," apoE2 and apoE4, respectively, contain two arginines and two cysteines at positions 112 and 158 [2]. However, there is only one isoform of apoE in rodents, which resembles human apoE3 in terms of lipoprotein binding and metabolism, preferably associating with high density lipoprotein (HDL), the clearance of which is mediated principally by hepatic low density lipoprotein receptors (LDLRs) [3, 4].

ApoE is synthesized predominantly in the liver, but also by cells in the spleen, brain, lung, kidney, ovary, adrenal, and muscle tissues. Hepatic parenchyma cells are the main apoE producing cells in mammalian body, probably accounting for two thirds to three fourths of the plasma apoE [5]. In the nervous system, apoE mRNA is present in neurons, astrocytes, ependymal cells, nonmyelinating Schwann cells, but not in microglia, oligodendroglia, choroidal cells, or myelinating Schwann cells [6–8]. As reported by a variety of studies, apoE produced by mammalian cells exists in different forms, monomers, dimers, modified, unmodified, lipid-rich, and lipid-poor, and so forth [9–13]. It is noteworthy that there is limited permeability of the blood brain barrier (BBB) to apoE, and local synthesis and production by brain tissue contribute to the homeostasis of apoE in brain tissue and cerebrospinal fluid (CSF) [14].

ApoE has been widely studied in lipid metabolism, cardiocerebrovascular diseases [15], multiple sclerosis (MS) [16, 17], neurodegenerative diseases such as Alzheimer's disease [18, 19], and mild cognitive impairment [20, 21]. In addition, growing evidence points to nonlipid-related properties of apoE. An immunoregulatory role of apoE has been proposed for decades. This role was originally described as suppression of lymphocyte activation [22–25]. Only in

the recent years, with the development of *APOE* knockout mice and APOE transgenic (Tg) mice, have the studies on the specific mechanism of immunomodulation been greatly deepened. In this paper, we outlined the immunoregulatory functions of apoE, with exclusive focus on the isoform-specific effects of apoE on Guillain-Barré syndrome (GBS) and its animal model experimental autoimmune neuritis (EAN).

2. The Role of ApoE in Immune Responses

To date, there has been strong evidence supporting a role for apoE as an immunomodulatory agent in immune responses. Effects of apoE on immune system are extensive and some of them are dependent on different ligands of the protein, different concentrations, and lipid-binding state. The properties include suppression of T cell proliferation [26], stimulation of cultured neutrophils [27], regulation of macrophage functions [28–32], facilitation of lipid antigen presentation by CD1 molecules to natural killer T (NKT) cells [33, 34], and modulation of inflammation and oxidation [35, 36], and so forth. By these properties, apoE impacts physiology and pathophysiology at multiple levels.

This role of apoE was originally discovered as an immunoinhibitory activity of plasma lipoproteins in vitro by a variety of experiments [23, 37–44]. Succedent studies ascribed this activity to immunoregulatory functions of apoE. A series of studies demonstrated both apoE containing lipoproteins and multimers of synthetic apoE peptides inhibited proliferation of cultured lymphocytes by inhibiting DNA synthesis and reducing phospholipid turnover in T cells [26, 45–48]. *APOE* knockout mice greatly facilitate apoE research. ApoE-deficient mice showed abnormal humoral and cellular immune responses. Significantly higher levels of antigen-specific IgM and significantly decreased antigen-specific delayed-type hypersensitivity responses were shown in apoE-deficient mice after immunization with tetanus toxoid as compared with control C57BL/6 mice [49]. Moreover, spleen weights of apoE-deficient animals were greater than age- and sex-matched C57BL/6 controls, indicating an idiopathic immune dysfunction in apoE-deficient mice [49]. In vivo, apoE downregulates T helper (Th) 1 immune responses, which is postulated to be mediated by either modification of macrophage or T cell functions [50, 51]. ApoE can also affect innate and acquired immune responses in vitro by its ability to suppress stimulation of cultured neutrophils [27]. Hypercholesterolaemia resulting from *APOE* knockout, can facilitate Th2 immune responses in mice [52], indicating that apoE plays a double-role in immune responses.

ApoE can bind lipopolysaccharide (LPS), attenuate the inflammatory response, and thus reduce LPS induced lethality [53]. Injection of LPS stimulated higher expression of inflammatory cytokines like tumor necrosis factor-α (TNF-α), interleukin (IL)-1ß, IL-12, and interferon-γ (IFN-γ), as well as IL-6, and so forth, in the brains of apoE-deficient mice compared with wild type controls [49, 50, 54]. And apoE-deficient mice have impaired immune responses to bacterial challenge with *Listeria monocytogenes*, and increased susceptibility to endotoxemia after intravenous LPS injection [55, 56]. Moreover, these mice are highly susceptible to tuberculosis, which has been suggested to depend upon the severity of hypercholesterolemia [57], and *Klebsiella pneumoniae* infection [58]. The deficiency of neutralization of Gram negative LPS seems to be one of the reasons that may explain this susceptibility. As regards isoform-specific effects that may exist, *APOE* ε2 Tg mice appear to be more susceptible to endotoxin or bacterial infection [59]. Ophir et al. have shown that either intraperitoneal or intraventricular injection of LPS results in significantly higher production of proinflammatory cytokines, defense response genes or chemotaxis genes in *APOE* ε3 Tg mice than in *APOE* ε4 Tg ones [60].

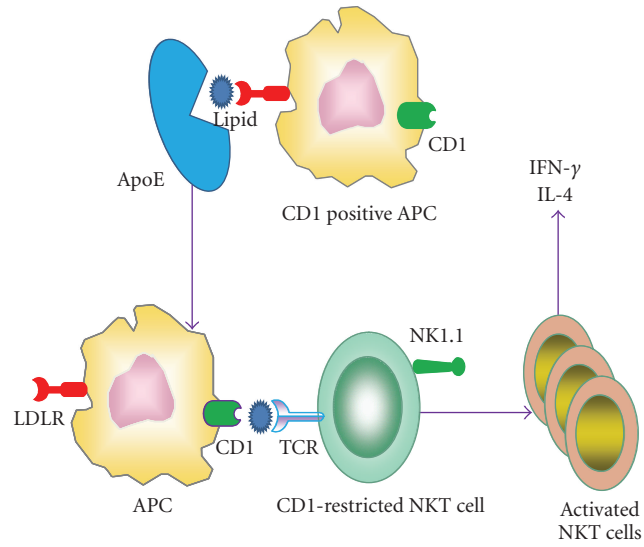
In the immune system, apoE is primarily produced by macrophages, which act as principal effector cells in both innate and adaptive immunity [61–63]. It is observed that pretreatment with apoE reduces inflammatory signaling in astrocytes and microglia in the brain [35, 64–67], and classical activation of macrophages by proinflammatory stimuli such as IFN-γ, TNF-α, IL-1β and LPS, down-regulates apoE production [68–73]. However, transforming growth factor-β and estrogen promote apoE synthesis and release [73–76]. ApoE suppresses proinflammatory signaling in macrophages, and vice versa, indicating an intricate apoE-mediated feedback regulation of inflammation and immune responses.

The production of nitric oxide (NO) represents one of the principle features of activated macrophages, and NO is considered to be a principal effector of macrophage-mediated immune responses. In mononuclear-phagocyte system, NO is formed enzymatically from L-arginine by inducible NO synthase (iNOS), which yields L-citrulline as a coproduct [77]. Treatment of microglia and peripheral macrophages with apoE could increase NO production stimulated by IFN-γ, and LPS, and so forth [78]. This effect supports its potential role in innate immune responses [29, 79]. ApoE alone is unable to induce the production of either iNOS mRNA or protein. Its action results from alteration of arginine availability by apoE [80]. Interestingly, the effect of apoE on NO production is not found only in macrophages. NO production in platelets can be stimulated likewise by apoE [81]. Further studies demonstrated that microglia and peripheral macrophages from male *APOE* ε4 Tg mice could produce significantly higher levels of NO than from *APOE* ε3 Tg mice. This increase in nitrite production reflects an increase in the innate immune response of the *APOE* ε4 Tg macrophages [30, 32]. Similar results were found also in human studies [82]. The increased NO production was shown to be coupled with an increased arginine uptake in male *APOE* ε4 Tg mice and to depend on p38 mitogen activited protein kinase (MAPK) [83, 84]; whereas it is not the case in female mice. Macrophages from female *APOE* Tg mice produced higher level of NO than male ones, and there is no isoform-dependent difference as in male ones [30, 85, 86].

Activation of macrophages and microglia is important in both the innate immunity and adaptive immunity [87, 88]. ApoE can down-regulate microglial activation [89].

Duan et al. in our group found that apoE deficiency enhances activation of microglia in CNS and aggravates kainic acid (KA) induced hippocampal neurodegeneration. Increased CC chemokine receptor 3 expression on microglia in apoE-deficient mice after KA administration appeared to facilitate the microglial recruitment and accumulation in the injured areas [90]. Macrophages of apoE-deficient mice stimulated by exogenous antigen are more effective in the upregulating of main histocompatibility complex (MHC) class II molecules and costimulatory molecules like CD40 and CD80, with increased IFN-γ secretion in responding T cells [91]. Furthermore, apoE suppressed the secretion of TNF-α and IL-1β in an isoform-specific fashion (E2 > E3 > E4) [84]. A significantly higher level of TNF-α was observed in the supernatant of cultured macrophages derived from adult male *APOE* ε4 Tg mice compared with macrophages from *APOE* ε3 ones [28]. ApoE genotype significantly affects the cellular immune response in stably transfected murine macrophages. In apoE4 versus apoE3 macrophages, higher levels of proinflammatory cytokines including TNF-α appeared evident followed by LPS stimulation [92]. ApoE displayed an isoform-specific effect on inflammation in primary adult microglia, with apoE4 potent to stimulate production of prostaglandin E2 and IL-1β [93]. *APOE* ε4 targeted replacement (TR) mice demonstrate a proinflammatory phenotype including increased iNOS mRNA synthesis and NO production, and higher proinflammatory cytokine production (TNF-α, IL-6, IL-12p40) in glial cell culture, compared with *APOE* ε3 TR mice [28]. Activation of primary astrocytes from *APOE* TR mice with LPS led to genotype-dependent differences in cytokine secretion that were the greatest in *APOE* ε2 TR mice [94]. Taken together, these findings suggest immunomodulatory dysfunction in apoE 4 isoform. Similar to apoE-deficient mice, *APOE* ε4 Tg mice seem to bear an insufficiency to deal with an inflammatory insult.

Although the antigen presenting function of antigen presenting cells (APCs) in adaptive immunity appears to increase in apoE-deficient mice, there still lacks direct evidence that apoE functions directly on antigen presentation process. The difference might either be due to the increased susceptibility to proinflammatory stimulation, resulting in the high expression of MHC class II molecules and costimulatory molecules on innate immune cells like macrophages, or be due to tendency to Th1 cytokine production in apoE-deficient mice. However, a role of apoE in facilitating lipid antigen presentation by CD1 molecules to NKT cells has been presented and confirmed, which appears of great importance in autoimmune diseases [95, 96]. Naïve NKT cells express high level surface marker NK1.1 and an invariant T cell receptor (TCR) [34, 97–100]. Upon TCR ligation, they respond rapidly to secrete high levels of IFN-γ and IL-4, which has been postulated to be of great importance in the shaping of adaptive immune responses and the shifting between Th1 and Th2 immune responses [101–103] (Figure 1). CD 1 molecules (CD1a-d in humans and CD1d in mice), similar in structure to MHC molecules, resemble MHC II molecules in function in that they present lipid antigens to NKT cells, in which process, apoE is implicated.



Schematic illustration of apoE-facilitated CD1-restricted NKT cell activation process

Figure 1: ApoE facilitates activation of CD1 restricted NKT cells. Inactivated NKT cells express surface marker of NK1.1 and an invariant TCR. ApoE facilitates lipid antigen presentation by CD1 positive APCs mainly through binding to LDLR. And then CD1 molecules present lipid antigen to NKT cells. Upon TCR ligation, naive NKT cells respond rapidly to secrete high levels of IFN-γ and IL-4.

ApoE, the major serum factor that binds lipids, could efficiently bind lipid antigens and dramatically facilitate their presentation by CD1b, CD1c and CD1d molecules via the binding to LDLR [33, 104]. More recently, human B cells have been demonstrated to utilize apoE-mediated pathways of lipid antigen presentation more efficiently than dendritic cells [105]. In terms of CD1-mediated self-lipid presentation, apoE might be involved in autoimmune diseases due to facilitation of self-lipid antigen presentation by CD1 molecules to NKT cells. ApoE might provide a pathway for the delivery of self-antigens and subsequently contribute to inflammatory diseases like MS [31, 106–109]. Kattan et al. suggested that apoE treatment also promoted a Th1 cytokine response in a rat model of sepsis. Whether this is partly due to facilitation of CD1 restricted lipid antigen presented by apoE remains to be clarified [110], and whether this effect of apoE is isotype-dependent is not yet known.

In vitro, apoE can inhibit proliferation of antigen and mitogen stimulated CD4+ and CD8+ T cells, which although not precisely known, has been suggested to be mediated by modification of IL-2 receptor or modification of intracellular signaling pathways perhaps involving calcium and phosphatidylinositol [111–113], while there seems no isoform-dependent suppression on T cell proliferation stimulated by phytohemagglutinin, or anti-CD3, as revealed by an in vitro human study [49]. Of note is that apoE is naturally presented by murine MHC II molecules. In a pathophysiological state this might be of immunological significance [114, 115]. And a naturally processed self-peptide from

apolipoprotein E, Ep1.B, is capable of inducing dendritic cell differentiation. Nuclear factor κB (NFκB), a transcription factor essential for DC differentiation, is fundamental in mediating the effects. [116]. A peptide containing the receptor binding region (residues 133–149), other than apoE holoprotein, is enough to suppress inflammation [117]. This peptide is almost the same as the one proposed by Pham et al. to be responsible for antioxidant properties [118]. In addition, apoE deficiency results in elevated autoimmune activity in mice, which can be detected as early as 7 weeks of age, and might explain the susceptibility of deficient mice to either EAN or EAE [119]. Moreover, apoE deficiency in mice leads to impaired clearance of apoptotic cells and a systemic proinflammatory condition, independent of its role in lipoprotein metabolism [120], providing another possible mechanism by which apoE may influence immune responses and autoimmune diseases.

The exact molecular mechanisms by which apoE isoforms alter the immune responses still remain undefined. However they have been postulated to influence different signaling pathways. ApoE isoforms might be in part responsible for the differential modulation of the redox sensitive transcription pathways such as NFκB and MAPK [36, 86, 94]. Alternatively, apoE can act by binding to cell surface receptors. LDLR-related protein (LRP) is postulated to be implicated to mediate the immunomodulatory effects of apoE, albeit there is no difference in the binding affinity of apoE isotypes with LRP [121, 122].

3. The Role of ApoE in GBS and EAN

GBS is presently defined as an organ specific immune mediated disorder resulting from a synergistic interaction between cellular and humoral immune responses to incompletely characterized antigens in the peripheral nervous system (PNS) [123, 124]. As yet, there has been no evidence that *APOE* genotype may influence susceptibility to GBS or its clinical course [125]. It might be either due to the small sample size of the experiment or due to the difference of *APOE* allele distribution and GBS clinical features among populations.

In several studies attempting to find specific biomarker of GBS in the serum and CSF, apoE was shown to decrease in CSF in GBS patients. Our group used comparative proteomic methods to show a decreased level of apoE in CSF, which was later confirmed by other researchers [126, 127]. This was further confirmed by enzyme-linked immunosorbent assay in our group (unpublished data). As there is limited permeability of the BBB to lipoproteins [14, 128, 129], this change might be due to a decrease of local apoE synthesis and secretion by brain tissue, as part of systemic decrease of apoE synthesis in acute phage reaction [4].

The blood nerve barrier (BNB) breakdown and autoreactive T cell penetrating BNB are crucial in the initiation of GBS [130, 131]. Data from animal experiments suggested that BNB dysfunction resulting from apoE deficiency might lead to more susceptibility to GBS, and exacerbate clinical GBS [132, 133]. Although there still lacks evidence that apoE isoforms contribute differently in maintaining BNB or BBB integrity, considering the preference of apoE isoforms binding to different lipoprotein and apoE receptors, it might be presumed that apoE isoforms might influence the recovery of GBS due to cholesterol transport difference in regeneration and remyelination [134, 135].

EAN, first described in rabbits in 1955 by Waksman and Adams [136], is a CD4+ T cell mediated autoimmune disease of PNS, characterized by perivascular infiltration of T cells and macrophages, and demyelination in the peripheral nerves in pathological feature, which can be induced in susceptible animal strains including mouse, rat, sheep, chicken, and monkey by active immunization with peripheral nerve myelin [136] or its component P0 or P2 proteins or their neuritogenic peptides [137, 138] together with complete Freud's adjuvant. EAN shares many of clinical, immunological, electrophysiological, and morphological characteristics with GBS, thus serves as a useful model for exploring the pathogenesis and immunotherapy of GBS. ApoE can modulate immune responses in EAN through modification of functions of macrophages, T cells, and BNB, shifting Th1/Th2 balance, as well as other effects (Figure 2). Autoreactive T cells penetrating the broken-down BNB to accumulate in peripheral nervous tissue gives rise to the effector phase of the immune response in EAN [139]. A number of observations support the role of apoE in maintaining the integrity of the BNB or BBB. And apoE-deficient mice were shown to suffer impaired BNB and BBB, which might be one of the reasons why apoE-deficient mice underwent more severe EAN [132, 133]. ApoE may inhibit the migration of blood derived inflammatory cells across the BNB or the transduction of chemotactic signals for migration. This is a critical step in the migratory process of inflammatory cells across tight endothelial junctions [140, 141].

Previously, we explored the role of apoE in P0 peptide 180–199 induced EAN. Our data, in accordance with data from other studies, showed that apoE deficiency increased antigen presentation capacity of macrophages, which can explain the elevated susceptibility to EAN in apoE-deficient mice [91, 133]. We further revealed an increased susceptibility to EAN after upregulation of the autoreactive T cell response to peripheral nerve components in *APOE* knockout mice. The results provided strong evidence that apoE might act as an inhibitor for EAN by inhibiting the Th1 response and P0-specific antibody production. Shifting the Th1/Th2 to the Th1 direction is one mechanism underlying increased susceptibility to EAN in apoE-deficient mice. Th cells can differentiate to Th1 and Th2 subpopulations with cross-regulating cytokine profiles that may play a decisive role in the initiation and termination of an autoimmune process [142]. Dysregulation of the Th1/Th2 balance can result in autoimmune diseases [143]. In EAN, Th1 cytokines predominate and mediate inflammatory damage, whereas Th2 cytokines are associated with recovery from the disease [144–147]. ApoE-deficient mice were shown to produce higher levels of IFN-γ, IL-12, and TNF-α and lower levels of IL-10 than C57BL/6 mice in EAN.

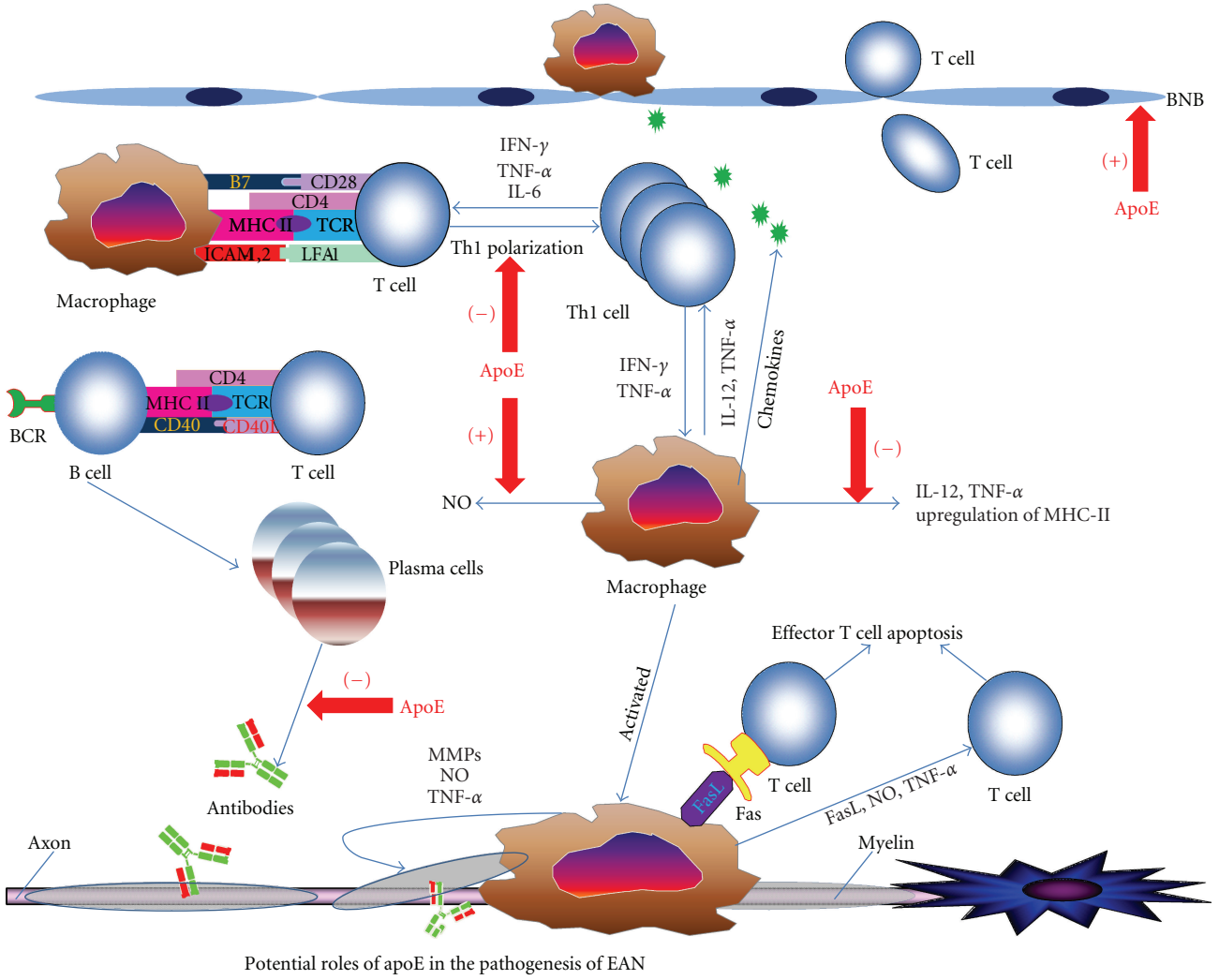


Figure 2: Schematic illustration of the potential role of apoE in the pathogenesis of EAN. ApoE can modulate immune responses in EAN through modification of functions of macrophages, T cells, and BNB, and through shifting Th1/Th2 balance. (−) suppressive function; (+) supportive function.

Macrophages are the principal antigen presenting cells and effector cells in the pathogenesis of EAN. In demyelinated peripheral nerves, the MHC class II positive cells are mainly macrophages [148]. The pivotal role of macrophages in immune-mediated nerve damage is direct phagocytic attack on myelin, and the release of proinflammatory cytokines including TNF-α, IL-1; and IL-6 and other noxious molecules [149, 150]. A variety of studies demonstrated an isoform-specific effect of apoE on macrophage functions, including NO production and cytokine secretion [28, 30, 79]. Considering the critical importance of NO and cytokines in the pathogenesis of EAN, this effect might contribute to isoform-dependent susceptibility or clinical severity of EAN [151, 152]. Schwann cells can function as facultative antigen presenting cells in certain conditions (see review by Meyer zu Hörste et al.) [153]. Duan et al. in our group, further revealed that the antigen presenting capacity of Schwann cells in apoE-deficient mice was enhanced, which might occur via down-regulation of intracellular IL-6 production. SCs may actively participate in local immune resonses as a source of IL-6 in the PNS [154]. ApoE-deficient mice were observed to reduce the expression of intracellular IL-6 accompanied with higher levels of MHC II and CD 40 expression on SCs. Moreover, an enhanced antigen-presenting function of SCs was found in apoE-deficient mice to P0 peptide 180-199 specific T cells [155].

Ongoing studies in our group have shown a preliminary result of an isotype-specific effect of apoE in EAN, with the most severe clinical course occurring on *APOE* ε4 Tg mice, while with the least severe EAN on *APOE* ε3 Tg mice (unpublished data). Apart from all above, strong evidence supports a crucial role of apoE in peripheral nerve regeneration and remyelination [156]. ApoE has been proposed to scavenge lipid debris from the degenerating myelin and provide it to sprouting axons via LDLR-mediated endocytosis [157, 158]. Despite this, regenerating nerves in

both apoE-deficient and control mice were morphologically indistinguishable one month after sciatic nerve crush [159], indicating a surrogate effect of other apolipoproteins in PNS regeneration.

4. Conclusions and Prospective

The immunomodulatory functions of apoE have been extensively studied in the past decades. Increasing studies have focused on the ambiguous or even controversial isotype-dependent effects. It appears difficult partly due to the difficulty of interpretation of results from animal experiments to a general conclusion. For example, the difference of serum and tissue apoE concentration in *APOE* $\varepsilon 2$, $\varepsilon 3$, and $\varepsilon 4$ Tg mice might be a confounding factor when comparing the isotype-dependent effects of apoE on immune system and immune responses [28, 160–163]. Domain interaction, which distinguishes apoE4 from apoE2 and apoE3 in biological function, has been suggested to contribute to the detrimental effects of apoE4 [163, 164]. Because of domain interaction, apoE4 bind preferentially to very low density lipoproteins, which are more rapidly removed from plasma than other lipoproteins such as HDL, to which apoE3 and apoE2 binds preferentially [164–166]. Also of note is that apoE levels in the CNS vary during the estrous cycle and estrogen could increase ApoE levels [76, 167–169]. Moreover, the lipid-free apoE was shown only to bind LRP [93, 170, 171]. Therefore in interpreting the effects of apoE on immune responses, its lipidation state, its concentration, and its location of action must be taken into consideration. It still remains to be defined whether a crucial, isoform-dependent activity of apoE role exists in GBS, or MS, considering the different distribution of *APOE* allele in the whole population. Anyhow, preliminary findings about the role of apoE in immune system and immune responses have shed light on the research of autoimmune diseases such as GBS and MS. The elucidation of the exact mechanisms by which apoE functions on immunity is appealing in that it may provide new insight to preventive or therapeutic strategies of autoimmune diseases and even other diseases [172].

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