The triggering receptor expressed on myeloid cells 2–apolipoprotein E signaling pathway in diseases

Shukai Lyu[1], Zhuoqing Lan[1], Caixia Li[1,2]

[1]Department of General Practice, The Fourth Affiliated Hospital, School of Medicine, Zhejiang University, Yiwu, Zhejiang 322000, China;
[2]The First Affiliated Hospital, School of Medicine, Zhejiang University, Hangzhou, Zhejiang 310003, China.

Abstract

Triggering receptor expressed on myeloid cells 2 (TREM2) is a membrane receptor on myeloid cells and plays an important role in the body's immune defense. Recently, TREM2 has received extensive attention from researchers, and its activity has been found in Alzheimer's disease, neuroinflammation, and traumatic brain injury. The appearance of TREM2 is usually accompanied by changes in apolipoprotein E (ApoE), and there has been a lot of research into their structure, as well as the interaction mode and signal pathways involved in them. As two molecules with broad and important roles in the human body, understanding their correlation may provide therapeutic targets for certain diseases. In this article, we reviewed several diseases in which TREM2 and ApoE are synergistically involved in the development. We further discussed the positive or negative effects of the TREM2–ApoE pathway on nervous system immunity and inflammation.

Keywords: Triggering receptor expressed on myeloid cells 2; Apolipoprotein E; Alzheimer's disease; Neuroinflammation; Atherosclerosis; Traumatic brain injury

Introduction

Triggering receptor expressed on myeloid cells 2 (TREM2) plays an important role in the regulation of life activities of many cells, including survival,[1,2] proliferation,[3,4] differentiation, phagocytosis,[1,5-7] and inflammatory response.[8-10] TREM2 can recognize different ligands of apoptotic cells, phospholipids, glycolipids, and lipoproteins: low-density lipoprotein (LDL) and high-density lipoprotein (HDL), clusterin (CLU), plexin A1, Hsp60, and apolipoprotein E (ApoE)[11-13]; particularly, ApoE has attracted more and more attention in recent years. To date, more than 60 coding TREM2 variants have been identified, showing various degrees of population frequency.[14] TREM2 variants have altered binding to their ligands, including R47H, R62H+, and T96K.[15-17]

ApoE is a glycoprotein containing 299 amino acids. As a lipid carrier that regulates lipid homeostasis,[18-20] its role in lipid transport is crucial. ApoE is involved in pathogenesis of atherosclerosis,[21] and plays an important role in transporting cholesterol and other lipids in the brain.[19,22,23] There are three ApoE alleles: E2, E3, and E4.[24,25] Lipids play a vital role in immune regulation and act as ligands for many immune receptors.[26] This is achieved through cell signaling and membrane fluidity. Therefore, ApoE has an irreplaceable position in the body. ApoE binds to receptors in the LDL receptor family, such as low-density lipoprotein receptor (LDLR), LDLR-related protein 1, very-low-density lipoprotein receptor, and ApoE receptor 2.[27]

Data show that TREM2 and ApoE are positively correlated in the physiological condition and many diseases.[28,29] There is a growing interest in studying the role of TREM2 and ApoE pathway in health and disease.

Triggering Receptor Expressed on Myeloid Cells 2

The gene of human *TREM2* is on chromosome 6p21.1, in the TREM gene cluster.[30,31] The structural components of TREMs include an extracellular immunoglobulin-like domain, a transmembrane domain, and a small cytoplasmic tail. The function of TREM proteins is related to the removal of extracellular waste materials.[32] Soluble TREM2 (sTREM2) is produced by proteolytic cleavage of the extracellular domain of TREM2.[33] sTREM2 can pass

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Correspondence to: Dr. Caixia Li, The Fourth Affiliated Hospital, School of Medicine, Zhejiang University, Yiwu, Zhejiang 322000, China
E-Mail: li_caixia@zju.edu.cn

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through the brain-cerebrospinal fluid (CSF) barrier and can be identified in CSF.[34]

TREM2 activates downstream molecules DNAX-activating protein of 12 kDa (DAP12) and DAP10 through charge interactions in the transmembrane domain.[35,36] DAP12, also known as TYRO protein tyrosine kinase binding protein, mediates the activation of spleen tyrosine kinases Syk and p85,[37] regulating cell fate. TREM2 induces the recruitment of multiple ligands to the DAP12 complex, which requires DAP10. DAP10 is a transmembrane receptor closely related to DAP12, and may form a DAP12-DAP10 heterodimer.[36] The TREM2/DAP12 pathway ultimately causes Ca^{2+} mobilization in mouse macrophages. The TREM2/DAP10 pathway can lead to the activation of serine/threonine protein kinase and extracellular signal-regulated kinase (ERK).

Apolipoprotein E

The C-terminal lipid binding domain of ApoE is located at positions 244–272.[23,38] In humans, the amino acid composition of ApoE differs at position 112 or 158.[20] ApoE2 has cysteine (Cys) residues at both positions, whereas ApoE3 has Cys residue at 112 and arginine (Arg) residue at position 158,[39] and ApoE4 has Arg residues at both positions. Other mammals have a single ApoE isoform with Arg residue at the position equivalent to human ApoE 112.[40]

In the brain, ApoE is mainly synthesized *de novo*, and rarely comes from the exchange between ApoE circulating in the blood and the brain.[41] It is mainly secreted by astrocytes and lipidated by adenosine triphosphate binding cassette transporters A1 (ABCA1) and G1 (ABCG1).[42] ABCA1 can interact with enough cholesterol and phospholipids to undergo conformational changes and form dimers. The lipidated dimer of ABCA1 is attached to the actin filaments on the plasma membrane until the lipid-free apolipoprotein directly binds to the ABCA1 dimer. ApoE binds to cholesterol and phospholipids transported by ABCA1 to form disc-shaped HDL particles.[43] The disc-shaped HDL particles are composed of >100 lipid molecules, surrounded by two apolipoprotein molecules.[44] Afterwards, the ABCA1 dimer dissociates, returns to the monomer state, and starts the process again.[44]

Experiments in ApoE knockout mice have proved that ApoE plays an important role in synaptic integrity, plasticity, and dendritic complexity.[45,46] Impaired synaptic function is a pathological feature of many neurodegenerative diseases, including Alzheimer's disease (AD).[47,48] At the same time, more and more evidence shows that changes in ApoE subtypes can affect its function and change the integrity and plasticity of synapses.[49]

Interaction of TREM2 and ApoE

TREM2 and ApoE are jointly responsible for the movement of phagocytes and myeloid cells, indicating that the activities of this group of closely related genes affect the same cellular functions.[50] In $TREM2^{-/-}$APP-PS1 mice (overexpressing mutated genes for human amyloid precursor protein [APP] and presenilin 1 [PS1]), ApoE signal transduction is inhibited, and the homeostatic phenotype of microglia is restored.[29] When TREM2 was highly expressed, plaques in the hippocampus and cortex increased co-staining with ApoE. In contrast, inhibition of TREM2 results in a decrease of ApoE-positive microglia and ApoE-related plaques.[28] In APP/PS1 mouse and human tissue sections, loss-of-function variants of TREM2 can reduce the accumulation of microglia around amyloid plaques and the expression of ApoE.[51] It also results in a reduction of co-localization of amyloid plaques and ApoE.[51] These data indicate that the expression and function of TREM2 are positively correlated with the expression of ApoE in amyloid plaques. Thus, the level of ApoE expression may depend on the regulation of TREM2. One study has proven that the ApoE hinge region, in particular residues 192–238, and a separate hydrophobic surface of TREM2, most strongly contribute to TREM2–ApoE binding [Figure 1]. The lipidation of ApoE alters its binding to TREM2, as the hinge region undergoes major conformational changes upon lipid loading. Moreover, it is possible that the C-terminal domain of ApoE contributes to direct interactions with TREM2.[15] However, the specific molecular mechanism of their interplay is still unclear.

TREM2/ApoE Signaling Pathway

Microglia are important for homeostasis of the central nervous system (CNS).[54] In physiological condition, TREM2 is only expressed in microglia in CNS. The activity of TREM2 is related to a few physiological processes. However, the TREM2 pathway is becoming the center of detecting tissue damage and restricting its spread.[20] Along with important ligand ApoE, TREM2/ApoE signaling pathway plays an important role in many diseases, such as AD, traumatic brain injury (TBI), and neuroinflammation.

Neurodegeneration occurred in APP transgenic mice (the earliest established mouse AD pathological model) with potential changes in the AD brain microglia at the transcriptome level from steady state to disease-related state.[29,55] This disease-associated microglia (DAM) has lower gene expression of key homeostatic markers, such as Tmem119, P2ry12, and Cx3cr1. The differentiation of steady-state microglia to DAM involves two sequential stages.[56] The stage 1 DAM conversion is required to further activate the stage 2 DAM program.[57] The transition from steady-state microglia to stage 1 DAM is independent of TREM2, but the transition from stage 1 to stage 2 DAM depends on TREM2 signaling. Interestingly, in the APP mice deficient in TREM2 or ApoE, microglia cannot transition from a steady state to a disease-related state.[29,55] The existence of DAM accelerates the progression of the disease and the decline of cognitive function.[57]

In several neurodegenerative models, phagocytosis of apoptotic neurons induces the microglial neurodegenerative (C) phenotype.[29] This neurodegenerative microglia (MGnD) phenotype is found in the neuritic β-amyloid (Aβ) plaque associated microglia in mouse AD model and human AD patients, consistent with the existence of

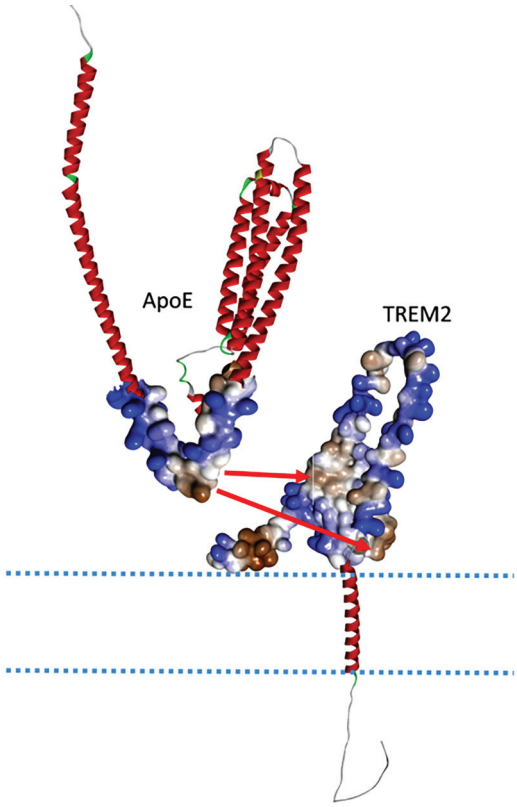

Figure 1: The potential binding mechanism of TREM2 and ApoE. The main hinge region of ApoE (shown in hydrophobic surface) potentially binds to the hydrophobic surface (brown color) of TREM2 extracellular domain (shown in hydrophobicity surface). The predicted structural models of ApoE and TREM2 were downloaded from the AlphaFold Protein Structure Database (https://alphafold.ebi.ac.uk/)[52,53] and visualized with the Discovery Studio Visualizer (BIOVIA, San Diego, CA, USA). Two dotted lines delineate the plasma membrane. Arrows indicate potential hydrophobic interactions between two proteins. ApoE: Apolipoprotein E; TREM2: Triggering receptor expressed on myeloid cells 2.

senescent microglia,[58] which lose sensome function including transforming growth factor-β signaling.[59] ApoE binds to TREM2 and promotes the phagocytosis of apoptotic neurons through the TREM2 pathway under physiological and pathological conditions.[29] ApoE signaling also induces expression of miR-155 microRNA in MGnD.[29]

MiR-155 is a major pro-inflammatory miRNA in a variety of neuroinflammation mouse models, such as amyotrophic lateral sclerosis and superoxide dismutase 1 (SOD1) models,[60] and it destabilizes microglia and accelerates disease progression[61] by directly targeting myocyte specific enhancer factor 2A (Mef2a)[62] and PU.1.[63] At the same time, TREM2 knockout in phagocytic microglia and SOD1 mice can down-regulate miR-155 expression.[29] Together, these data indicate that TREM2/ApoE signaling via miR-155 can modulate the microglia enhancer, thereby controlling the core microglia-specific molecular markers.

ApoE promotes the phagocytosis of apoptotic neurons by microglia through the TREM2 pathway.[64,65] Engulfed apoptotic neurons form phagosomes in the microglia. This will activate TREM2 and up-regulate lipid metabolism genes through downstream molecules DAP12 and DAP10, activate lysosomes, and break down phagocytic neuronal debris.[50,64,65] Part of the breakdown product cholesterol enters the endoplasmic reticulum of microglia and is converted into cholesterolis (CEs) by acetyl coenzyme A acetyltransferase 1 for metabolism and physiological activities. Another part of CEs is transported out of microglia through the action of ABCA1 and ABCG1 transporters, and then transported to other places after binding to ApoE to maintain the physiological activity of microglia.[50,65]

Furthermore, studies have shown that TREM2 and ApoE binding can promote the metabolism and transport of CEs in microglia. Deletion of TREM2 or ApoE can lead to disorders of cholesterol transport and metabolism in microglia, and further cause dysfunction of microglia.[50,64,65] In the microglia of the demyelinating mouse, TREM2 participates in the transport and metabolism of intracellular CEs by sensing lipids. *TREM2* gene knockout decreases both the expression of intracellular ApoE and CEs level. Moreover, ApoE gene knockout causes down-regulation of TREM2, DAP12, and lipid metabolism-related gene expression, which affects neuronal function.[66] Most of the cholesterol in the brain is contained in myelin, so the excessive release of myelin fragments in disease conditions may result in cholesterol accumulation and cytotoxicity because cholesterol cannot be effectively metabolized and is harmful to cells in high concentrations.[66] After chronic demyelination, the metabolic flux of cholesterol in microglia is impaired. Key lysosomal genes, such as *Ctse* and *Ctsl*, are up-regulated in microglia, and microglia are converted into the reactive state, namely DAM.[66] The accumulation of cholesterol in phagocytes may hinder the clearing of metabolites and is not conducive to the successful regeneration of tissues. Cholesterol accumulation may drive unfavorable immune responses, thereby impairing the regression and repair of inflammation.[64,67] At the same time, the regulation of intracellular lipids by the two proteins also plays a role in peripheral atherosclerosis.[68]

Phosphatidylinositol 3-kinase (PI3K) can phosphorylate protein kinase B (Akt), thereby regulating cell survival, growth, and angiogenesis in response to extracellular signals.[36] PI3K/Akt signaling has anti-neuroinflammation, anti-oxidative stress, and anti-apoptotic properties in neurons.[36] PI3K/Akt signaling is also the downstream target of ApoE/TREM2 pathway and participates in the TREM2-mediated inflammatory response.[69] Activation of TREM2 with apoE-mimetic peptide COG1410 inhibited microglia/macrophage activation, neutrophil infiltration, and neuronal apoptosis, and downregulated the expression of inflammation related cytokines, tumour necrosis factor alpha, the cytokine interleukin-1β, B cell lymphoma 2 (Bcl-2), and Bcl-2-associated X protein, which was, at least in part, mediated by activation of PI3K/Akt signaling pathway.[69]

Recently, lipid-droplet-accumulating microglia (LDAM) has entered our field of vision.[70] They appear under the condition of continuous stimulation of chronic inflammation and aging, and the accumulation of large numbers of lipid droplets (LDs) is a characteristic of this microglia

group. Studies have found that LDAM has the characteristics of defective phagocytosis, high levels of reactive oxygen species, and secretion of pro-inflammatory cytokines.[70] The LDs in LDAM mainly include triglycerides (TG), a small amount of diglycerides and CEs, which are organelles for the production and storage of eicosanoids and inflammatory cytokines, and are involved in antigen presentation and removal of necrotic substances.[70] The relationship between TREM2–ApoE pathway and LDAM is further explained in detail below.

Some transmembrane proteins on the membrane of microglia can regulate TREM2/ApoE pathway. CD33 (or siglec-3) is a transmembrane protein abundantly expressed in microglia. It inhibits autoimmune activation by binding to sialylated self-associated molecular patterns.[71,72] The binding of ApoE and CD33 activates SH2-containing protein tyrosine phosphatase (SHP) 1 and SHP2 phosphatases, thereby inhibiting the TREM2/DAP12 pathway.[73] The increase in CD33 expression in the frontal cortex of human AD patients after death is related to the decrease in Aβ phagocytosis after the TREM2/DAP12 pathway is inhibited. Similarly, CD33 knockout results in a decrease in Aβ load.[71] In addition, TREM2 promotes the accumulation of CD68-positive microglia around amyloid plaques. These microglia increase the expression of ApoE.[70] The increased ApoE in the plaque promotes plaque fibrosis and compaction, maintaining the stability of the plaque.

Roles of TREM2/ApoE signaling pathway in AD

AD is the major neurodegenerative disease. More than 40 million people worldwide suffer from the disease, which is the main cause of dementia in the elderly.[74] There are two types of AD: early-onset AD, and late-onset AD (LOAD). LOAD is estimated to affect about 50% of people who are aged ≥85 years.[75] There are more than 30 AD genetic risk loci identified.[76] Many of these genetic risk factors are the genetic variations of the genes related to innate immunity and microglial function, including ApoE and TREM2 variants,[5] which are related to the formation of DAM in the progression of AD.

AD is characterized by senile plaques composed of Aβ peptide and neurofibrillary tangles of hyper-phosphorylated tau protein.[20] The brain accumulation of Aβ peptide is the initial event in the AD process. Due to the defect of the brain's immune clearance function, Aβ begins to appear in the brain 15 to 20 years before the presence of clinical symptoms. Studies have proposed that ApoE captures Aβ, and TREM2 promotes the endocytosis and clearance of ApoE-Aβ complex.[20] When Aβ forms a complex with LDL, CLU, and ApoE, ApoE transfers Aβ to microglia by binding to TREM2, so that the microglia can phagocytose Aβ more effectively.[77]

The most common TREM2 variant is the Arg to histidine mutation at position 47 (R47H), which impairs ligand binding of TREM2. This can result in a four-fold increase in the risk of AD.[78] There is a significant association between TREM2–R62H variants and LOAD. Even if this variant was deleted from the analysis, the association between TREM2 variants and LOAD was still significant, indicating there are other TREM2 risk variants.[79] The AD risk of ApoE E4 variants is that one copy increases by 3 to 4 folds, and the risk of two copies increases by 10 to 12 folds.[20] The increased risk of AD may be due to the above variants affecting the combination between TREM2 and ApoE.

Roles of TREM2/ApoE signaling pathway in neuroinflammation

Neuroinflammation plays an important role in in several neurodegenerative diseases.[80,81] Similar to DAM, TREM2, and ApoE have multiple effects on the regulation of microglia in neuroinflammation: (1) downregulating the steady-state transcription factors of microglia, including Mef2a, Mafb, and Smad3; (2) inducing inflammation program, and up-regulating transcription factors Bhlhe40, Tfec, and Atf3 and transcription and translation regulator miR-155;[61] (3) accelerating intracellular cholesterol transport and maintaining cell function. Certain defects prevent microglia from transitioning from a steady state to a disease-related state, thereby impairing basic physiological defense functions such as chemotaxis, proliferation, phagocytosis, and survival.[2]

In neuroinflammation, the result of activating the TREM2–ApoE pathway is the loss of the ability of DAM to prevent neuronal loss and provide tolerogenic signals to T cells; this would amplify the pro-inflammatory properties of T cells and cause neuronal damage.[29]

The self-limitation of inflammation is very important for the reconstruction process after tissue injury. Uncontrolled inflammatory storm will leave permanent marks and continue to change the homeostasis of the tissue.

Therefore, regulating the phenotype of MGnD by targeting TREM2 and ApoE can be used as a method to restore microglia in the body and treat neurodegenerative disorders. It is worthy of pointing out that TREM2 reverses A1 astrocyte activation, inhibits neuroinflammation, and suppresses dementia caused by hypertension.[82] Is ApoE also involved in this process? How does it participate in "cross-talk" between M1 microglia and A1 astrocytes? This conjecture remains to be verified.

Roles of TREM2/ApoE signaling pathway in TBI

TBI is one of the main causes of death and disability. The surviving patients of TBI in the long term may develop cognitive impairment, anxiety, and depression.[83] There is a strong genetic influence on brain susceptibility and recovery of the TBI patients.[84] TBI is closely related to the increased risk of dementia, including chronic traumatic encephalopathy and AD.[85] ApoE4 is associated with chronic traumatic encephalopathy in TBI patients.[86] TBI can cause cognitive impairments and increase expression of TREM2 and DAP12 surrounding the injury site in both ApoE3 and ApoE4 mice.[87] The presence of high levels of microglia proliferation at the injury site indicates that microglia are recruited to the injury site. Studies show that in the acute phase of TBI with different ApoE subtypes, the

gene network including TREM2 and DAP12 has changed dramatically.[87] After TBI, ApoE would bind to TREM2 on the microglia membrane to activate DAP12, helping the microglia recognize damaged tissues through related downstream pathways. This will activate the phagocytic function of microglia, and strengthen the phagocytosis of microglia on damaged tissues, causing acute neuroinflammation.

Roles of TREM2/ApoE signaling pathway in intracerebral hemorrhage

Intracerebral hemorrhage (ICH) accounts for approximately 15% to 20% of all strokes and has a high mortality and morbidity rate.[88] Cell debris from necrosis and disintegration of red blood cell and other blood components can cause secondary brain damage after ICH. This can result in neuroinflammation, oxidative stress, mitochondrial dysfunction, blood-brain barrier disruption,[89,90] and neuronal apoptosis. The apoptosis of neurons leads to the infiltration of peripheral immune cells in the brain tissue, which further aggravates the inflammatory damage.[91,92]

The combination of TREM2 and ApoE gives the brain a powerful neuroprotective effect by reducing the neuroinflammatory storm in ICH. As a peptide derived from ApoE, COG1410 treatment can inhibit acute neuroinflammation 24 h after ICH. Furthermore, TREM2 knockdown by small-interfering RNA and PI3K inhibition by the specific inhibitor LY294002 significantly reversed the anti-inflammatory and anti-apoptotic effects of COG1410.[69]

We can speculate that the ApoE-mimic peptide inhibited neuroinflammation and neuronal apoptosis, and even reduced mortality by activating the PI3K/Akt pathway through TREM2 after ICH.

TREM2/ApoE signaling pathway in atherosclerosis

Macrophages play an important role in the development of atherosclerosis.[93,94] Most of the foam cells that play a leading role in atherosclerosis are derived from macrophages in the blood, and a small portion is derived from smooth muscle cells in the blood vessel wall. The lipids deposited in atherosclerotic plaque mainly come from the necrosis and disintegration of foam cells. Existing data indicate that after absorbing large numbers of lipids, mainly through scavenger receptors, macrophages transform into foam cells.

ApoE is the most important factor for the metabolism of peripheral lipids and lipoproteins. It can promote the removal of lipoproteins rich in TG (containing apoB) from the circulation to the liver. ApoE$^{-/-}$ mice are a common animal model of atherosclerosis,[93] suggesting that this protein is essential in atherosclerosis.

Aortic TREM2^{hi} macrophages are a new subset of diseased macrophages, which are characterized by high expression of TREM2. Gene Ontology term enrichment analysis shows that TREM2^{hi} macrophages have highly specialized functional characteristics, such as lipid processing and catabolic processes that are abnormally active in this subset of macrophages.[68] Interestingly, the gene expression characteristics of atherosclerosis-related TREM2^{hi} macrophages showed striking similarities to DAM in AD.[68] As mentioned before, DAM is localized in the vicinity of Aβ plaques in neurodegenerative diseases. Similarly, in atherosclerotic lesions, apolipoprotein A-I-derived amyloid deposits increase the likelihood that the diseased TREM2^{hi} macrophages will appear nearby. In addition, TREM2^{hi} macrophages may participate in the formation of such amyloid deposits in atherosclerosis.[68]

TREM2^{hi} macrophages are observed in ApoE$^{-/-}$ mice.[68] Based on the interaction of the above two molecules in ICH, it can be speculated that ApoE deficiency is a catalyst for the increase of TREM2. Combined with the above regulation of TREM2–ApoE on lipids in microglia, we can speculate that ApoE deficiency leads to an imbalance of lipid transport in macrophages, abnormal accumulation of lipids in macrophages, and increased expression of TREM2, which promotes lipid transport, finally affecting the process of atherosclerosis.

Summary

TREM2 and ApoE can interact with each other, which is likely done through the binding of the ApoE hinge region to a hydrophobic surface of the TREM2 extracellular domain. Their effects on microglia and peripheral macrophages are not unique. In particular, they promote the activation of microglia in neurodegenerative diseases to transform into different disease-related phenotypes, enhance the phagocytic function of microglia through DAP12, and enhance acute neuroinflammation. However, microglia can also inhibit the up-regulation of inflammatory factors through the downstream molecule PI3K/Akt, and protect neurons from excessive immune response damage [Figure 2].

In summary, the TREM2–ApoE pathway induces multiple inflammatory reactions of microglia in the CNS or macrophages in the periphery. The TREM2–ApoE pathway is a promising therapeutic target for restoring homeostasis of microglia or macrophages in neurodegenerative disorders, neuroinflammation, or atherosclerosis. Currently, there are still many unanswered questions. More in-depth research will allow us to further understand the relationship between these two molecules and their detailed roles in diseases. Future structural studies of the TREM2–ApoE complex are needed to elucidate the structural details of the molecular interaction between TREM2 and ApoE. Such research should focus on how to moderately regulate this pathway to maximize benefits. In addition, the biological significance of this pathway and its immune function has yet to be elucidated, especially in terms of its regulation of lipid metabolism in macrophages.

Although these promising findings explain the role, mechanism, and therapeutic significance of the TREM2–ApoE pathway in the pathogenesis and progression of diseases, the use thereof is still far from clinical

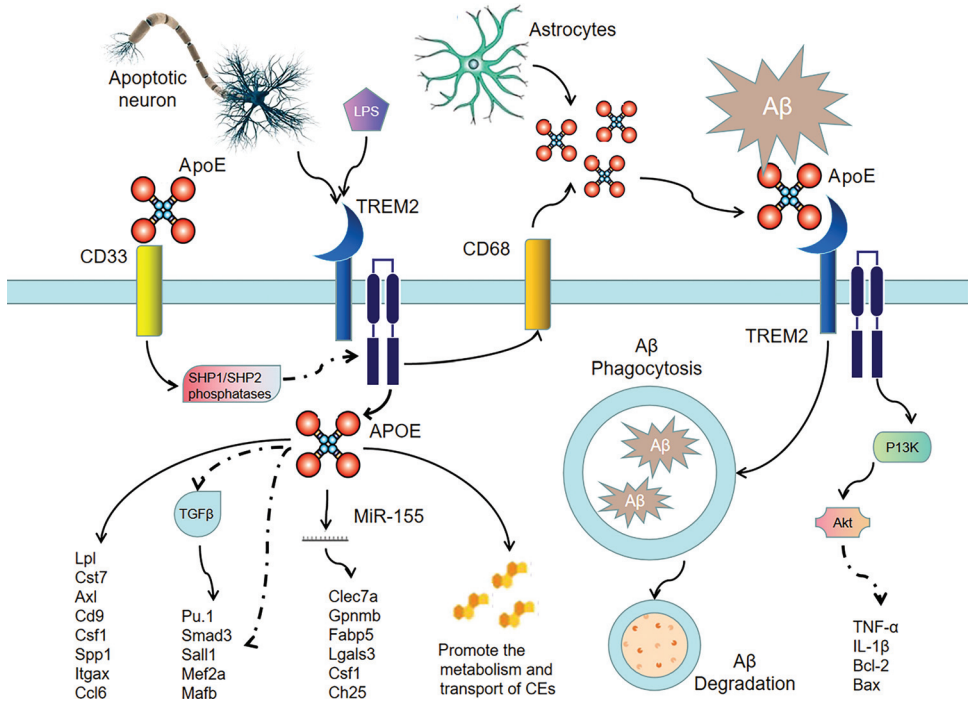

Figure 2: Signal pathway involved in TREM2 and ApoE in microglia. (1) After apoptotic neurons or inflammatory substances, such as LPS, stimulate TREM2, the intracellular ApoE expression is up-regulated, causing microglia to transform into a disease-related phenotype. At the same time, it promotes intracellular lipid metabolism. (2) After being secreted by astrocytes, ApoE binds to cellular wastes, such as Aβ or apoptotic neurons in CNS, and then activates TREM2. On one hand, it causes the enhancement of microglia phagocytosis. In addition, it inhibits the inflammation of microglia through the PI3K/Akt pathway. (3) CD33 and CD68 play a regulatory role in this pathway. ApoE: Apolipoprotein E; Aβ: β-amyloid; Bax: Bcl-2 associated X protein; Bcl-2: B cell lymphoma 2; Ccl6: Chemokine ligand;CEs: Cholesterolis; Ch25 h: Cholesterol-25-hydroxylase; Clec7a: C-type lectin domain family 7 member A; CNS: Central nervous system; Csf1: Colony stimulating factor 1; Cst7: Cystatin F; Fabp5: Fatty acid-binding proteins; Gpnmb: Glycoprotein nonmetastatic melanoma protein B; IL-1β: Interleukin-1β; Lgals3: Lectin galactoside-binding soluble 3; Itgax: Integrin, alpha X; Lpl: Lipoprteinlipase; LPS: Lipopolysaccharide; mafb: MAF bZIP transcription factor B; Mef2a: Myocyte specific enhancer factor 2A; PI3K: Phosphatidylinositol 3-kinase; Sall1: Sal-like 1; Spp1: Secreted phosphoprotein 1; TNF-α: Tumor necrosis Factor alpha; TREM2: Triggering receptor expressed on myeloid cells 2.

application. Elucidating the detailed mechanism of the TREM2–ApoE interaction would facilitate structure-based drug design to precisely target different steps along the pathway. This would enable the development of therapeutics with high selectivity and low side effect for a variety of neurological diseases.

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Conflicts of interest

None.

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