Chapter

Microglia, TREM2, and Therapeutic Methods of Alzheimer's Disease

Siwei Xu, Yaya Ji, Tianle Sha and Haoming Li

Abstract

Alzheimer's disease (AD) is one of the most common causes of dementia all around the world. It is characterized by the deposition of amyloid-β protein (Aβ) and the formation of neurofibrillary tangles (NFTs), which contribute to neuronal loss and cognitive decline. Microglia, as innate immune cells in brain, plays dual roles in the pathological process of AD. Expression in different subtypes of microglia is diverse in AD genes. Triggering receptor expressed on myeloid cells 2 (TREM2) is a transmembrane glycoprotein mainly expressed on microglia in the central nervous system (CNS). Soluble TREM2 (sTREM2), a proteolytic product of TREM2, which is abundant in the cerebrospinal fluid, shows a dynamic change in different stages and ameliorates the pathological process of AD. The interplay between the different subtypes of apolipoprotein and TREM2 is closely related to the mechanism of AD and serves as important regulatory sites. Moreover, several therapeutic strategies targeting TREM2 have shown positive outcomes during clinical trials and some novel therapies at different points are in progress. In this review, we mainly talk about the interrelationships among microglia, TREM2, and AD, and hope to give an overview of the strategies of AD.

Keywords: Alzheimer's disease (AD), microglia, TREM2, sTREM2, APOE

1. Introduction

Nowadays, Alzheimer's disease (AD) is one of the most common causes of dementia in the United States [1]. Alois Alzheimer discovered AD in 1907 and characterized AD as amyloid plaques, brain atrophy, neurofibrillary tangles, loss of neurons and synapses, and dystrophic neurites in histopathology [2].

Microglia are the resident immune cells in the CNS. They derive from erythromyeloid progenitor cells and then migrate to the brain [3]. Developing and adult microglia demonstrate distinct morphological features as ramified or ameboid [4], which was proved by recent comprehensive transcriptomic analyses [5]. Relative analyses also demonstrate the heterogeneity, abundance, steady state in embryonic, postnatal, juvenile, and adult mouse models [6, 7]. They are also featured as self-renewing, which requires several factors such as colony-stimulating factor-1 receptor (CSF1R) and transforming growth factor β (TGF-β) [8–10]. Moreover, the murine signature of microglia in AD was present in human microglial subtypes, especially clusters 4, 5, 7, and 8. Among which, cluster 7 stands out in the

consequence of its high expression of AD gene decrease in the tissue sections in both AD dementia and pathological AD [11]. This can be a diagnostic standard for AD when the frequency of cluster 7 was diminished.

Hippocampus is an elongated structure that is part of the cerebral cortex [12]. It is one of the most severely affected structures in neurodegenerative diseases like AD [13]. Hippocampus, along with its accessory structure, was suggested to be related to space [14, 15], time [16, 17], and the creation of declarative memories (memories that can evoke conscious awareness and be verbalized) [18].

Hippocampus is vulnerable to the harmfulness of diseases such as epilepsy, hypoxia, ischemia, or encephalitis [18]. The entorhinal cortex is usually the first region that demonstrates tau pathology in AD patients [18]. Somatostatin-positive interneurons are also found lost in the hippocampus of AD patients [19]. In AD patients, degenerative cholinergic neurons in the basal forebrain were proved to lead to dysfunctional cholinergic neurotransmission in regions like hippocampus [20].

2. Harmful and beneficial effects of microglia

Microglia play the role of phagocytes in the CNS, thus, maintaining the homeostasis of the brain [21]. In aging brains, microglia will cause synaptic clearance leading to forgetting *via* complement pathway [22]. In AD pathology, microglia also prove to be phagocytose synapses [23, 24]. Nevertheless, with CSF1R blockade to remove microglia in Aβ models, increased Aβ is detected [25]. Despite negative outcomes of microglia, synapse loss and behavior deficits can be avoided [26, 27]. The production of neurotoxic inflammatory cytokines and reactive oxygen species are found to be related to chronic activation of microglia [28]. However, it still remains unclear whether microglia play positive or negative roles in the process of neurodegenerative diseases.

In recent research, microglia in patients with AD show specific characteristics such as aging and upregulation of apolipoprotein E (APOE) [29]. The fat droplets appearing in microglia of aged mice suggest that the main manifestations of aging are the accumulation of fat droplets and excessive secretion of pro-inflammatory factors [30], which may be a new biological hallmark of AD. Additionally, it is not difficult to find that the branching of microglia has been reduced in aged brains, thus cutting the size of microglia's area for surveillance and leading to the harm of homeostatic functions [31–34]. One important function of microglia in AD is the phagocytosis of Aβ amyloid. For instance, microglia can mediate clearance of Aβ *via* receptors including β1 integrin in neurodegenerative diseases [35]. The acute inflammatory response can also promote phagocytosis of impaired neurons and neuronal toxic accumulation [36]. Despite the protection of microglia, prolonged inflammatory reaction will exacerbate neuronal degeneration [37]. The TAM receptor tyrosine kinases (RTKs) are a distinct family of three protein tyrosine kinases, namely Tyro3, Axl, and Mer3, which play an important role in phagocytosis and phagocytic clearance of apoptotic cells and cell membranes in the adult tissues [38, 39]. Axl and Mer play pivotal roles in macrophages like phagocytosis of apoptotic cells and negative feedback inhibition of toll-like receptor and cytokine receptor signaling. In AD mice with double knockout of Axl or Mer, the ability of microglia to phagocytize the plaque is weakened, suggesting the inhibition of TAM signal promotes plaque formation [40]. A cluster of differentiation-22 (CD22), a canonical B-cell receptor and a negative regulator of phagocytosis, is found highly expressed in microglia of aged brains, and rarely in young brains [41]. The finding suggests that the inhibition of CD22 can delay aging-related dysfunction and

neurodegenerative diseases. The pellino-1 (peli1) is a ubiquitin E3 ligase, expressed in many kinds of nerve cells in the mouse brain, and with the highest expression level of microglia [42]. Similarly, Peli1 negatively regulates the ability of phagocytosis of microglia to Aβ, resulting in the inability of clearance of deposition, leading to the deterioration of AD [43].

Perineuronal nets (PNNs), with their structure remaining unknown in detail, surround the cell bodies and dendrites, and spare free space for synaptic contact [44]. In the AD mice model and human cortical tissue, PNNs are largely lost in proportion to plaque burden and depletion of microglia. Loss is prevented regardless of plaque persistence and suggests that microglia can enhance the loss of PNNs in the AD brain [45]. Besides, CD163-positive amyloid-responsive microglia are depleted in TREM2 and APOE variants in AD like TREM2 R47H and APOE4 [46].

Microglia may be detrimental to neurons in the pathological process. Recently, interleukin 3 (IL-3) from astrocytes was found to re-encode microglia, thus improving the situation of Aβ pathology [47]. Injection of IL-3 enables microglia to focus on clearing amyloid deposition and neurofibrillary tangles instead of causing extensive neuroinflammation [47]. This signaling pathway is expected to provide ideas for new drug research and development in the future and bring new drugs for the treatment of AD. A study suggested that some damaging characteristics of microglia behavior may be reversible by short-term treatment with CSF1R inhibitors [48–50]. In the mice model, removal of microglia did not improve the cognitive ability in a traumatic brain injury (TBI) [51]. Interestingly, repopulating microglia can reverse the decrease of nerve regeneration caused by brain injury and improve cognitive dysfunction in mice in an IL-6-dependant manner [51]. This study opens up a new understanding of the role of microglia in the brain injury. Remarkably, the ubiquitin ligase COP1 (also called RFWD2) is shown to dampen the neuroinflammation through inhibiting the expression of the transcription factor CCAAT/enhancer-binding protein beta (c/EBPβ), which regulates the pro-inflammatory gene of microglia [52], marking a new target for suppressing neuroinflammation in AD patients.

Disease-associated microglia (DAM), which was identified in AD patients by single-cell RNA sequencing (RNA-seq) [53], has recently become a hot topic, characterized by molecules including Iba1, Cst3, and Hexb, typically expressed in microglia. DAM also experiences downregulation of physiologically expressed genes such as P2ry12, P2ry13, Cx3cr1, CD33, and Tmem119 [9]. It is remarkable to find that DAM is identified in areas that are affected by diseases such as cortical tissue [53] and postmortem human AD brain [54]. The evidence suggests that DAM is specifically expressed in CNS pathological process, serving as an important pathological diagnostic standard. However, in the late set of neurodegenerative diseases, its role still remains unclear, which needs further investigation.

3. Physiological function on microglia of TREM2

Recent years have witnessed the central role of TREM2 as a hub in diverse pathology. TREM2 is a receptor that interacts with a variety of ligands, many of which are markers of tissue damage. TREM2 is a single-pass transmembrane protein known to regulate immune responses in peripheral macrophages through lipopolysaccharide binding and bacterial phagocytosis [55–57]. RNA-seq data were analyzed across human tissues to investigate TREM2 expression, and it has been confirmed that TREM2 is expressed physiologically in a small group of macrophages that are tissue specific [58]. In CNS, TREM2 is mostly expressed on microglia. In addition to the expression on microglia, the analysis also showed its expression in macrophages

from the adrenal gland, placenta, and adipose tissue [59]. TREM2 was thought to bind a wide range of molecules [60], and the interaction with different ligands can regulate the signal intensity and direction of TREM2 in turn [61]. Downstream signals mainly consist of those arrangements; for example, DAP10 is the key to activate extracellular signal regulated-kinase (ERK) and serine/threonine protein kinase (AKT1), while in murine macrophages, DAP12 is necessary for calcium mobilization [61–63]. Functional loss of TREM2 is related to polycystic lipomembranous osteodysplasia with sclerosing leukoencephalopathy (PLOSL) [64].

Mice lacking TREM2 had defects in survival and differentiation of myeloid cells [65], as well as osteopenia and loss of microglia in CNS [62, 66]. TREM2-lacking cells may undergo a similar differential process as normal cells do despite a reduced life cycle [67]. Microglia deprived of TREM2 or expressing T66M variant demonstrated the impaired process of brain glucose metabolism and cerebral perfusion [68]. Mice TREM2 was involved in synaptic pruning through a microglia-dependent way to shape neuronal circuitry [69]. In rodents, TREM2-positive macrophages are found to be important regulators related to hair follicle stem cells [70]. Additionally, in TREM2-deficient microglia, increased autophagic vesicles can be found with defective activation of mTOR pathways [63], which partially regulate autophagy [71].

Deletion or impairment of TREM2 was proved to be detrimental to phagocytosis of lipoproteins, cellular debris, bacteria, and Aβ [68, 72, 73]. Moreover, overexpression of TREM2 in cells that are not functionally phagocytic like Chinese hamster ovary (CHO) cells showed induced phagocytosis of apoptotic cells and bacteria [57, 72].

TREM2 was also found to ameliorate neuroinflammation and neuronal apoptosis *via* PI3K/AKT signaling pathway in 5xFAD mice [74, 75]. TREM2 overexpression can also rescue cognitive barriers by reducing neuroinflammation *via* JAK/STAT/SOCS pathway [76] and the suppression of TREM2 demonstrated a defective ability to regulate the PI3K/Akt and NF-κB signaling pathways [77].

Recently, genome-wide association studies (GWAS) demonstrated a link between single-nucleotide polymorphisms (SNPs) and inflammation-related genes to increased AD risk, such as the R47H variant in TREM2 [78], which is one of the strongest genetic risk factors for AD [79]. TREM2 variant R47H, whose foundation was dysregulated peroxisome proliferator-activated receptor-γ (PPARγ)/p38MAPK signaling [80], was shown to decrease the expression of TREM2, thus deteriorating myeloid cell responses to Aβ pathology [81]. Furthermore, the R47H variants and R62H variants of TREM2 demonstrate a defective microglial transcriptional activation, implicating fully functional TREM2 seems to be the key for development of the human DAM [82].

4. TREM2 and AD

TREM2 gives protection against neurodegenerative disease. Depletion of TREM2 can induce impaired phagocytosis of the critical substrates such as APOE [83] and exacerbates tau pathology in AD [84].

4.1 TREM2 gets involved in AD pathogenesis via microglia

TREM2 is found to reduce tau seeding in neuritic plaques [85], which is essential for synapse clearance in the early stage of brain development, and TREM2-KO mice demonstrate altered sociability [69]. Moreover, TREM2 can induce microglia to gather around Aβ and restrict plaque expansion found in murine models of AD [86].

Similar conditions can also lead to exacerbation of axonal dystrophy and dendritic spine loss [87]. Another research shows that a dosage of TREM2 can reprogram the microglial response in downregulating the expression of DAM genes and ameliorating the pathological phenotype in AD mice [88]. In the absence of functional TREM2, amyloid plaque seeding increased, and microglial aggregation decreased [88]. A similar study shows that in human pluripotent stem cell (PSC), monocytes and transdifferentiated microglia-like cells, TREM2 R47H variant and loss of TREM2 on heterozygous or homozygous, display a significant decreased in phagocytosis [89]. On a recent finding, IL-4 and IL-10 enhance the phagocytosis of microglia *via* upregulation of TREM2 [90]. These findings support the hypothesis that reactive microglia and TREM2 are functionally necessary to alleviate neuronal damage. However, other studies give opposite outcomes that loss of TREM2 may be protective in AD mice [91].

Genetically, the immune cell-specific phospholipase C isoform γ2 (PLCG2), a rare coding variant, is identified [92]. Recent research has demonstrated that TREM2 can mediate phagocytosis, cell survival, lipid metabolism, and process neuronal debris through PLCG2 of microglia derived from human-induced pluripotent stem cell (iPSC) [93]. PLCG2 P552R variant has protective functions including weak-enhancing enzyme functions [94] and promoting survival functions of microglia in Plcγ2-P522R knock in mice [95]. These studies highlighted the critical role of the TREM2 pathway in AD and provided genetic evidence for the increase of TREM2 in the pathologic process of AD.

In recent years, different TREM2 ligands have been found and proposed, such as β-amyloid peptide [96] and APOE [97]. APOE-dependent molecular signature in microglia is identified in AD patients, mediating a switch from homeostatic to neurodegenerative status [98]. This can be a target in treating AD patients through restoring the homeostatic microglia.

4.2 TREM2 regulates APOE mediating AD risk

Although there is no difference in the quantity of activated microglia and reactive astrocytes between APOE4 carriers and noncarriers in the postmortem neocortex [99], relative transcriptomic studies have shown the connection between APOE and glia. Human APOE is expressed in three allelic variants, APOE2, APOE3, and APOE4, which exhibit different receptor binding properties [100]. APOE upregulation has been proved to be TREM2-dependent [101]. To some extent, TREM2 and APOE may have some special links [102], and the lack of TREM2 leads to a decrease of APOE4, while APOE3 remains unchanged [103]. Microglial plaque coverage and TREM2 are the highest in APOE3 male mice while significantly low in both APOE4 genotype and female sex [104], implicating a possible mechanism of AD between sex and APOE genotype. A reduction in plaque-associated APOE is also found in the brains of AD patients [105]. In another research, APOE3 is shown to promote the proliferation of microglia to injected Aβ, contribute to the uptake of Aβ, and improve cognition related to Aβ in preclinical models of AD [106]. Moreover, APOE was proven to stimulate different signal transduction cascades, ApoE4 > ApoE3 > ApoE2, in proportion to their AD risk [107]. This suggests that neuronal pathways may be related to the pathogenesis of AD. Human TREM2 (hTREM2) was bind to APOJ and APOE that are ligands of TREM2 under normal circumstances [73]. However, this binding is reduced in diseases or TREM2 KO mice microglia, leading to the impaired uptake of Aβ [73]. TREM2 is also an attractive target for drug regulation, but needs to be cautious because it is an important upstream mediator of microglia activation and phenotypic changes [53, 98]. In addition, single-cell transcriptomic studies pointing at microglia have shown a fascinating TREM2

ligand gal-3 that is related to neurodegenerative diseases [108]. Increased gal-3 is found in AD patients and 5xFAD mice, while decreased gal-3 shows improved cognitive ability and attenuates immune responses related to the TREM2-DAP pathway [109]. Therefore, suppressing gal-3 in the AD process may be a potential target in treatment.

5. sTREM2

sTREM2, a soluble form of TREM2, is derived from the non-proteolytic-mediated secretion of some TREM2 isoforms or due to extracellular domain of TREM2 being cleaved by different sheddases [110]. Years before the onset of dementia symptoms, sTREM2 increased in cerebrospinal fluid (CSF) of people with AD biomarker characteristics [111–114]. Recently, it is found that in preclinical AD, CSF sTREM2 changes are dynamic. In the absence of tau deposition and neurodegeneration, sTREM2 is decreased with Aβ pathology [115]. Different mutants of sTREM2 showed differences in concentration in CSF [114]. sTREM2 has a protective effect on Aβ and AD, such as reducing amyloid plaque load and restoring spatial memory [116]. Similarly, in the absence of TREM2 [105], sTREM2 enhances microglial proliferation, migration, clustering around Aβ, and contributing to the uptake and degradation of Aβ [116]. sTREM2 administration can also stimulate the expression of inflammatory cytokines and induce morphological changes of microglia such as decreased cell process and increased cell body size, thus enhancing microglial survival [117]. In TREM2 KO mice, administration of sTREM2 also showed positive feedback, like rescuing apoptosis upon colony-stimulating factor (GM-CSF) withdrawal, inducing the proliferation and cell viability of the primary microglia [118, 119], compared with WT mice [117]. These results indicate the tremendous therapeutic potential of sTREM2, but warn that pro-inflammatory activation in the brain may lead to negative functional outcomes. Under stress, sTREM2 can promote myeloid cell survival too in a manner dependent on PI3K/AKT [117, 120]. Consequently, sTREM2 can be a target for AD therapy. But it is shown less potent for sTREM2-R47H and sTREM2-R62H variants to suppress apoptosis in AD context [117]. Among the three polymorphic forms (APOE2, APOE3, and APOE4), APOE4 proved to be more related to AD [121] and high levels of sTREM2 are associated with the decrease of APOE4 [122] and slower rates of Aβ accumulation [123]. In conclusion, the changes of sTREM2 can also be a biological hallmark for AD.

6. The prospect of treatment of AD

For a long time, it is considered that Aβ accumulation is the central and initial event in the pathological process of AD. The famous amyloid cascade hypothesis thinks that the increase of Aβ levels leads to the pathological events of AD [124, 125]. Extensive clinical medicine trials of Aβ finally come to an end, and results showed that reduced Aβ load does not affect the cognitive ability of patients with AD [126, 127]. So, finding a new target rather than Aβ may be our priority. Microglia play pivotal roles in the pathological process, and interfering with their detrimental process in AD can become our next focus.

Microglia are shown to maintain the function of neurons by clearing toxic damage in the early stage of AD [128]. Consequently, interfering with the activation of microglia to lengthen the period of anti-inflammatory seems to be a therapy for AD [129]. Other anti-inflammatory cytokines such as IL-2, IL-4, and IL-33 have

the potential to ameliorate AD pathology by regulating microglial activation [128], despite its results are not decisive [130].

Moreover, TREM2 is shown to be a positive target for treating AD. Recently, AL002c, an anti-human TREM2 agonistic monoclonal antibody (mAb), gives a positive outcome in 5xFAD mice expressing both the R47H variant and the common variant (CV). Prolonged administration of AL002c ameliorates filamentous plaques, causes neurodystrophy, and regulates microglial inflammation. AL002 is a derivative product of AL002c, which is modified for clinical use. AL002 is proven safe and well-tolerated in a first-in-human phase I clinical trial [131]. Overexpression of TREM2 can attenuate the pro-inflammatory effect caused by LPS, which can contribute to the increase of NO, LDH, TNF-α, IL-1b, and the activation of AKT [132]. Thus, relative experiments can be conducted in CNS.

Another way to increase TREM2 expression in microglia is by preventing ADAM10/17 family proteases from shedding extracellular domain [133, 134]. To stabilize TREM2 on the cell surface and enhance its activity, a specific mAb against TREM2 called 4D9 was screened to selectively compete for α-secretase-mediated shedding [133]. Shedding is considered to end cell-autonomous TREM2 signaling, and data show an increased phagocytic capacity of cells that express TREM2 by inhibiting ADAM proteases [135]. Combined with another research, Aβ clearance is TREM2-dependant [136], and future treatments can combine anti-Aβ antibodies with microglia-stimulating antibodies (4D9). This view opens a new door to the treatment of AD. Another study evaluated aducanumab as another antibody that may treat AD, but clinical trial results are still unsatisfactory [137]. In addition to cross-linking and activating the TREM2-DAP12 signal, 4D9 also inhibits the shedding of TREM2, resulting in the decrease of soluble TREM2 *in vitro* and the increase of total TREM2 in the brain [133]. This research may consider the role of sTREM2 in AD [91]. Since TREM2 is expressed in peripheral myeloid cells, any effects of treatment for TREM2 should be evaluated for peripheral adipose tissue in liver, lung, bone, and spleen. However, this has not been thoroughly investigated [91].

A novel property, cyclocreatine, the creatine analog, which can generate a supply chain for ATP demand regardless of the TREM2-mTOR pathway [138], is found to ameliorate autophagy, induce microglia around Aβ, and decrease neuronal dystrophy during dietary administration in 5xFAD mice [63]. Based on metabolism, this is a new era for treating AD.

Another research provides a creative angle in treating AD. It is known that meningeal lymphatic vessels drain macromolecular substances from the brain into the deep cervical lymph nodes [139], in which meningeal lymphatic serves as a channel to transport substances such as an antibody. But ablation of meningeal lymphatic vessels in 5xFAD mice can lead to a switch of microglia from homeostasis to DAM [140] and inhibit the transportation of antibodies to specific locations, thus exacerbating the cognitive ability of AD patients. It may bring unexpected clinical effects to patients with AD, if the treatment is placed in the early stage, thus enhancing the meningeal lymphatic function and combined with immunotherapy, to better play the role of meningeal lymphatic vessels.

Recently, tau pathology is the study focus. Tau hyperphosphorylation causes abnormal aggregation and neurodegeneration in AD brains [141], and protein phosphatase 2A (PP2A) has the most robust dephosphorylation activity to tau protein *in vitro* and *in vivo* [142]. A novel DEPho-sphorylation Targeting Chimaera (DEPTAC) was designed to enhance the combination of tau and PP2A-Bα, which shows high efficiency in preventing tau accumulation *in vitro* and *in vivo* [143]. Further studies showed that DEPAC significantly improved the microtubule assembly, neurite plasticity, and hippocampus-dependent learning and memory in transgenic mice [143].

7. Conclusion

Microglia play important roles in the pathological process of AD. The dual role it plays (positive or negative outcomes), its distinctive phenotype, DAM, which is specifically expressed in certain regions in AD, still needs further investigation. In most findings, TREM2 exhibits positive feedback in inhibiting detrimental factors. sTREM2, a soluble form of TREM2 in CSF, and its soluble form in CSF and sTREM2 can be biological hallmarks for diagnosis. Moreover, a close relationship between the TREM2-APOE pathway and AD demonstrates an important pathological feature. A new therapeutic method based on TREM2 to manipulate the function of microglia is currently being tested. Although there are still numerous obstacles ahead to treating AD, it is expected that this field will move closer to understanding the influence of microglia regulation in AD, which is a breakthrough result for patients. Most therapeutic treatments targeting Aβ do not get expected feedback. Thus, genetic evidence and metabolic mechanism related to AD should be more explored in future studies.

Author details

Siwei Xu, Yaya Ji, Tianle Sha and Haoming Li*
Department of Human Anatomy, Medical School of Nantong University, Nantong, China

*Address all correspondence to: lihaoming@ntu.edu.cn

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