

The Pathogenesis in Alzheimer's Disease: TREM2 as a Potential Target

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Abstract

Review

Alzheimer's disease (AD) is ranked as the third-most expensive illness and sixth leading cause of mortality. It is associated with the deposition of extracellular amyloid- β (A β) in neural plaques (NPs), as well as intracellular hyperphosphorylated tau proteins that form neurofibrillary tangles (NFTs). As a new target in regulating neuroinflammation in AD, triggering receptor expressed on myeloid cells 2 (TREM2) is highly and exclusively expressed on the microglial surface. TREM2 interacts with adaptor protein DAP12 to initiate signal pathways that mainly dominant microglia phenotype and phagocytosis mobility. Furthermore, *TREM2* gene mutations confer increased AD risk, and TREM2 deficiency exhibits more dendritic spine loss around neural plaques. Mechanisms for regulating TREM2 to alleviate AD has evolved as an area of AD research in recent years. Current medications targeting A β or tau proteins are unable to reverse AD progression. Emerging evidence implicating neuroinflammation may provide novel insights, as early microglia-related inflammation can be induced decades prior to the commencement of AD-related cognitive damage. Physical exercise can exert a neuroprotective effect over the course of AD progression. This review aims to (1) summarize the pathogenesis of AD and recent updates in the field, (2) assess the concept that AD cognitive impairment is closely correlated with microglia-related inflammation, and (3) review TREM2 functions and its role between exercise and AD, which is likely to be an ideal candidate target.

Keywords: AD; pathogenesis; neuroinflammation; TREM2

1. Introduction

Alzheimer's disease (AD) is an irreversible and progressive neurological disorder [1,2]. Various pathological factors are found in the postmortem brains of AD patients, such as abnormal amyloid- β (A β) plaques, hyperphosphorylated tau protein, and damaged neurons and synapses [3,4]. Such lesions affect brain areas important for learning and memory, including the cerebral cortex, striatum, and hippocampus [5]. According to Global Alzheimer's Information, AD affected 46.8 million individuals globally and is projected to affect 82 million by 2030 [6]. Without effective intervention, this figure will likely triple by 2050 with the aging of the population. Accumulating evidence from clinical investigations demonstrates the absence of effective treatments for curing AD or restricting its progress. In vitro and in vivo studies have shown that $A\beta$ plaques are key drivers in AD pathogenesis [7]. However, findings from unsuccessful partial clinical studies directly targeting the A β protein indicate that reducing the A β load does not ameliorate cognitive impairment [8,9]. The challenges in disease diagnosis have undermined the improvements made in the prevention and treatment of AD. The prevention and treatment of AD are impeded by the similarities between AD and other forms of dementia [10]. Many AD experiments have shown that microglia play a key role in regulating inflammation in the central nervous system [11]. Neuroinflammation aggravated by microglia contributes to AD

pathogenesis and promotes protein aggregation, implying that microglia may function as a novel target in AD [12].

Triggering receptor expressed on myeloid cells 2 (TREM2) is expressed in myeloid progenitors. It is an innate immune receptor that is located on the microglial membrane. Findings from genome-wide association experiments have revealed rare TREM2 (R47H) mutations that are linked to an increased possibility of developing AD, as TREM2 is one of the most important receptors because of it's effects on neuronal/microglia health [13]. The type I transmembrane glycoprotein TREM2 communicates with an immune adaptor DNAX activation protein of 12 kDa (DAP12) transmembrane area to facilitate signaling via the immune-receptor tyrosine-based activation motif (ITAM) domain of DAP12 in migration, phagocytosis, cell survival, and inflammatory cytokine release [14,15]. TREM2 is also implicated in the etiology of AD as it regulates microglial function and innate immunity [16]. The function of TREM2 in neuroinflammation and its relationship with AD have not been fully elucidated. This review focuses on current understanding of the pathogenesis of AD and the shift from the initial focus on abnormal A β plaques and hyperphosphorylated tau proteins to the current concept that AD cognitive impairment is closely correlated with microgliainduced neuroinflammation, suggesting it may be an ideal candidate target. Here, we summarize our current understanding of TREM2 function and its role in AD.



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2. AD Pathology

AD is the most widespread age-related neurodegenerative disorder, with no effective cure that can help alleviate the financial and emotional burden of the disease [17,18]. Studies on the pathogenesis and development of therapies are vital for preventing or alleviating AD symptoms. A number of hypotheses explain AD pathophysiology, including the hypotheses of the A β cascade, A β -tau cooperative action, and cholinergic and γ -aminobutyric acid (GABA) functions.

2.1 $A\beta$ Cascade Hypothesis

 $A\beta$ is found in various assembly forms, such as fibrils, protofibrils, and oligomers [19]. $A\beta$ is non-neurotoxic in its monomeric form. In contrast, protofibrillars and oligomers are regarded as effective blockers of long-term potentiation and strength. Fiber formation is strongly linked to protein misfolding [20].

 $A\beta$ induces fatality in neuronal cells, which is the primary cause of AD [21]. Significant evidence has shown that the production of $A\beta$ oligomers (AbOs) in cortical neurons initiates AD [22-24]. AbOs acting on entorhinal neurons assist in tau oligomer development with progression to associated neurons. This occurs in the hippocampus and subsequently in the subiculum and associated neocortex [25]. The toxicity of tau oligomers can be damaging to neurons, where they are formed and subsequently released into neurons and synapses. Tau proteins are propagated and disseminated from neurons. AbOs may interact with tau oligomers during this phase to enhance neuronal and synaptic dysfunction [26]. Data further demonstrates that $A\beta$ is not a bystander in AD [27]. Recent advances have revealed that extracellular A β deposits can be released from the brain via the blood-brain barrier (BBB) and other systems [28]. The structure and function of the BBB are damaged in AD [29]. The destruction of the BBB allows neurotoxic blood-derived debris and microbes to enter the brain, which is closely linked to neuroinflammation and immune responses that can trigger numerous neurodegenerative pathways [30,31].

2.2 A_β-tau Cooperated Hypothesis

Tau pathology is a hallmark of AD progression [32]. Tau present in the medial temporal lobe binds and stabilizes the microtubule architecture, where it is normally concentrated. However, hyperphosphorylated tau protein produced in AD dissociates from microtubules and accumulates inside neurons [33]. Once it spreads from the medial temporal lobe to the surrounding neocortex, hyperphosphorylated tau protein can cause cognitive impairment.

Findings from animal models have shown that $A\beta$ spreads via neuronal connections from cell to cell [34,35]. An increasing body of evidence demonstrates that the synergistic effects of $A\beta$ on tau plays a vital role in AD pathogenesis [36,37]. Busche *et al.* [38] recently showed that

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 $A\beta$ and tau interaction promotes neural circuit damage: *in vivo* multiphoton imaging showed that the combined existence of tau and $A\beta$ pathology in the neocortex is linked to repressed neuronal activity and increase in spine loss and microglia injury. The repression of tau or $A\beta$ pathology alone is not conducive to salvaging functional damage. In addition, the impact of tau and $A\beta$ co-expression on neuronal activity was analyzed in Busche and Angulo's studies. Their findings [39] showed that extracellular expression of $A\beta$ caused hyper-excitability, whereas tau expression led to activity suppression. The co-expression of $A\beta$ and tau also repressed activity, where the tau phenotype appeared to play a dominant role.

2.3 Cholinergic Hypothesis

Cholinergic neurons have been demonstrated to modulate neuronal circuits in the hippocampus and cortical regions and play an important role in hippocampus-dependent memory [40,41]. Normally, endogenous nerve growth factor (NGF) is produced by hippocampal and post-synaptic cortical neurons and is expressed through related receptors present on presynaptic cholinergic terminals [42,43]. Stimulated NGF is then transported from the target regions (hippocampus and cortex) to cholinergic nuclei, consequently initiating cholinergic signaling in these brain areas [44].

Findings from various animal models and human studies have shown that cholinergic neuron degeneration in the basal forebrain is linked to cognitive impairments in AD [45,46]. The cholinergic hypothesis primarily focuses on the gradual damage of limbic and neocortical cholinergic innervations, which is linked to neurofibrillary degeneration and inefficient axonal transport and signaling [47]. The crosstalk between postsynaptic cortical/hippocampal neurons and presynaptic cholinergic terminals is altered during AD. These variations are related to the accessibility of mature NGF (mNGF) to basal forebrain cholinergic neurons, which subsequently results in cholinergic degeneration in hippocampal and cortical areas [48,49].

The cholinergic hypothesis has transformed different areas of AD research, from the field of neuropathology to the modern concept of synaptic neurotransmission [50]. It was developed based on three parameters: (1) diminished presynaptic cholinergic indicators in the cerebral cortex [51,52], (2) the nucleus basalis of Meynert (NBM) in the basal forebrain is a source of cortical cholinergic innervation that undergoes intense neurodegeneration in AD [53,54] (3) cholinergic antagonists impair memory whereas agonists have a contrasting effect on memory [55].

2.4 GABAergic Hypothesis

GABAergic activity is important for brain development and plasticity. Under normal conditions, GABA is produced in the presynaptic membrane and helps synthesize glutamic acid decarboxylase (GAD) from glutamate. GABA can bind to GABA receptors present on the postsynaptic membrane through the synaptic cleft, which inhibits the post-synaptic neuron [56,57]. However, in AD, imbalances in GABAergic neurons is associated with several disorders. In the AD brain, $A\beta$ is toxic to GABAergic synapses and promotes the degeneration of axons and synaptic loss. At first, $A\beta$ enhances neural activity, which supports $A\beta$ release. The cycle between neural activity and $A\beta$ can involve $A\beta$ -induced GABAergic terminal loss, which results in impaired cognition and repressed longterm potentiation (LTP). In addition, β -site APP cleaving enzyme 1 (BACE1), Apolipoprotein E4 (APOE ϵ 4), and TREM2 can induce GABAergic dysfunction [58].

These outcomes have shown that GABAergic dysfunction is related to the E (excitation)/I (inhibition) imbalance in AD [59]. As mentioned Govindpani *et al.* [60], because of the narrow scope of existing treatments for disease modification, better insights into GABAergic remodeling in AD may help introduce innovative and unique therapeutic options.

3. The Relationship between Microglial Activation and Inflammation in AD

AD pathology involves the clustering of $A\beta$ proteins and hyperphosphorylation of tau protein. However, therapies targeting tau and $A\beta$ have failed in clinic trial. Several researchers have emphasized the significant contribution of neuroinflammation in initial and late AD stages, which is strongly associated with microglia activation [61,62]. Inflammation during AD is predominantly associated with continuous microglia activation in response to cell death and $A\beta$ plaque deposition [63]. Classical microglial activation appears to contribute to neuronal impairment in neurodegenerative disorders; however, the advantageous characteristics of microglial alternative activation were also observed [64,65]. In this section, we report findings from an advanced report to highlight the link between microglial activation and inflammation in AD and the critical function of TREM2 in AD progression.

3.1 Neuroinflammation in AD

In recent decades, AD investigations have prioritized the mechanisms related to extracellular neural plaques (NPs) and intracellular neurofibrillary tangles (NFTs). Data from genetic, preclinical, and clinical findings have focused on the neuroinflammatory mediation of the innate immune system [66]. Many neurodegenerative diseases, particularly AD, have been linked to inflammation [67,68]. Increasing evidence suggests that systemic inflammation plays a key role in AD [69]. Tau-protein tangles and A β plaques in the brain trigger cells, such as microglia and astrocytes, to release anti-inflammatory and pro-inflammatory mediators, including reactive oxygen species (ROS), neurotransmitters, chemokines, and cytokines [70,71]. The release of mediators causes lymphocytes and monocytes to pass through the BBB, which boosts the release of inflammatory components. These findings indicate that inflammation promotes AD progression and accelerates disease progression [72,73]. Trovato *et al.* [74] eported that an increase in oxidative stress and altered antioxidant systems cause NOD-like receptor thermal protein domain associated protein 3 (NLRP3) inflammasome activation, resulting in cell damage and cognitive impairment.

3.2 Overactivation of Microglia is a Key Contributor to Neuroinflammation in AD Models

Microglia are the primary macrophages and provide basic immunological protection in disorders and injuries of the central nervous system [75,76]. Plastic cells have dual functions in neuronal damage and healing and can adopt multiple phenotypes [77,78]. Microglia have a ramified phenotype under normal physiological conditions, characterized by a small cell body and several processes, such as in "resting microglia". Even in the resting state, microglial processes are dynamic and constantly scan to preserve central nervous system (CNS) cell types with neurons [79]. Evidently, they scan the brain environment continuously and contact synapses by using their fine branches to detect infections and damage in their environment [80].

Microglia, which represent the immune cells of the brain, engage in diverse functional programming, known as polarization, for responding to external stimulating In the activated state, microglial phefactors [81]. notypes are categorized by two major states: classical activation (pro-inflammatory microglia) and alternative activation (anti-inflammatory microglia) [82,83]. Proinflammatory microglia primarily release proinflammatory substances, whereas anti-inflammatory microglia release anti-inflammatory cytokines. When triggered by lipopolysaccharide (LPS), the pro-inflammatory phenotype is acquired by microglia, which leads to neurotoxicity via secreted pro-inflammatory factors such as tumor necrosis factor- α (TNF- α) and Interleukin 1 (IL-1) [83]. In contrast, microglia acquire an anti-inflammatory state via the release of anti-inflammatory cytokines (e.g., Interleukin 4.), which aids neuroprotection and promotes tissue repair, both of which play crucial roles in maintaining the physiological environment [84,85].

3.3 Microglial Activation Modulation is a Potential Target in AD-Induced Neuroinflammation

In neurodegenerative conditions, especially in AD models, persistently activated microglia may restrict CD3⁺/CD8⁺ T-cell entry into the brain. Local macrophages constitute a link between innate and adaptive immunity [86]. In response to A β aggregation, including disease progression, the production of proinflammatory cytokines downregulates the expression of A β clearance components and promotes A β -mediated neurodegeneration and A β aggregation [87]. The early activation of microglia during AD progression provides neuroprotection by supporting $A\beta$ clearance. However, pro-inflammatory cytokines promote $A\beta$ aggregation during disease progression. Evidence from multiple animal studies provides strong support for the production of $A\beta$, which increases AD deficits by upregulating microglial activation. $A\beta$ -excess neurons, as primary proinflammatory factors, implicate the intraneuronal aggregation of $A\beta$ as an important immunological element in AD pathogenesis [88].

Microglia show different phenotypic states in AD modesl, especially under chronic inflammatory conditions [89]. Some receptors (receptor for advanced glycation endproducts [RAGE] and NLRP3) of the proinflammatory microglial phenotype secrete proinflammatory cytokines, such as TNF- α and IL-1 β , by triggering a signaling cascade to induce neuronal cell death. Meanwhile, other receptors (the class a macrophage scavenger receptor type I [SR-AI], TREM2) of the M2-like microglia participate in clearing $A\beta$ by stimulating $A\beta$ fibril internalization and synthesizing anti-inflammatory cytokines such as TGF- β , IL-10, and IL-4 [90,91]. Activated microglia play a key role in enhancing the spreading of tau protein in the presence of A β . A β in its soluble form, along with additional elements, can activate microglia via microglial surface receptors. Tau is taken up by activated microglia and released into further bioactive types. The released tau can be taken up by neurons and subsequently released into the neuropil, in an activation-dependent manner [92]. Therefore, finding a method to transform pro-inflammatory microglia into anti-inflammatory microglia has a prospective advantage in treating AD.

4. The Function and Role of TREM2 in AD

Receptors located on microglial membranes are composed of soluble and membrane proteins that can receive various stimuli and trigger a series of responses to maintain microglial homeostasis [93]. The receptor TREM2 is primarily expressed on the microglial surface. Substantial evidence has shown that TREM2 has bioactive potential and the ability to connect with ligands, stimulate microglia, and regulate the immune system in AD progression, including proliferation, survival, and phagocytosis. Furthermore, a lack of TREM2 expression has been shown to increase the accumulation of A β and induce neuronal death in various AD animal models [94].

4.1 TREM2's Structure and Signal

TREM2 is an innate immunological receptor found only on the surface of myeloid cells in the brain, such as microglia, macrophages, and monocytes [95,96]. Mature TREM2 protein weights approximately 40 kDa. *In situ* hybridization and immunohistochemical labeling have been used to detect the protein [97]. TREM2 has a long ectodomain that interacts with the extracellular setting to control microglial function [98]. Current research indicates that minor changes in soluble TREM2 (sTREM2) levels (approximately 7%–10%), are sufficient for modulating AD risk [99]. According to Piccio *et al.* [100,101], AD and other inflammatory central nervous system diseases have considerably higher CSF sTREM2 levels than normal controls. Deming *et al.* [102] discovered for the first time that, as a vital contributor in TREM2's biological processes, the membrane-spanning 4domains subfamily A (*MS4A*) gene cluster plays a significant role in regulating soluble TREM2 expression as well as AD pathology.

4.2 TREM2's Function

TREM2 is crucial for cell maturation, proliferation, and survival during development under homeostatic conditions [103,104]. Multiple TREM2 functions have been identified in the last decade, including the regulation of phagocytosis and modulation of inflammatory signaling [105,106].

4.2.1 Regulation of Phagocytosis

The CNS, with its greater phagocytic potential, has myeloid cell subsets expressing TREM2 [107,108]. Knockout animal studies have shown reduced phagocytosis in apoptotic neurons [109]. The overexpression or activation of TREM2 has been shown to increase substrate uptake [110,111]. According to Yao *et al.* [112], phagocytosis depending on TREM2 requires the activation of the SYK/PI3K/AKT/PLC pathways. A novel TREM2 agonistic antibody treatment accelerated the clearing of myelin debris from the CNS demyelination model [113].

4.2.2 Modulation of Microglial Activation and Inflammatory Responses

TREM2 is traditionally classified as an antiinflammatory receptor [114–116]. Its silencing stimulates an early pro-inflammatory response through the PI3K/NF- κ B pathway, which downregulates CD163 expression, leading to virus repression [117]. TREM2 is vital for regulating the *in vivo* activation of microglia in response to damaged tissue [118]. TREM2 increases the survival of microglia by stimulating the Wnt/-catenin pathway, and Wnt/-catenin signaling can be restored when TREM2 activity is interrupted [119]. More recently, studies have shown that the TREM2-APOE pathway is the primary regulator of microglial phenotypic changes in neurodegenerative disorders and may serve as a target to restore homeostatic microglia [120].

4.3 TREM2 in AD

Genetic variations in TREM2 have been linked to several neurodegenerative diseases [121,122]. Recent research has shown that microglial TREM2 expression is associated with AD pathology. The most common AD-associated TREM2 variant is rs75932628, a single-nucleotide polymorphism encoding an arginine-to-histidine missense substitution at amino acid 47 (R47H), which significantly increased sporadic AD incidence and impaired phospholipid ligand binding [123,124]. Recent studies have proposed that R62H and R47H are partial loss-of-function variants and predominantly lead to minimized affinity for TREM2 ligands [125]. In contrast, upregulated TREM2 signaling can lead to several possibilities for immune-linked AD treatments [126,127]. The regulation of TREM2 in AD represent a novel therapeutic approach that is currently under investigation in clinical trials [128,129]. Therefore, microglial TREM2 is a potential therapeutic target for ameliorating neurodegeneration disease. However, caution should be exercised when targeting TREM2 as a therapeutic entry point for AD until its involvement in tau aggregation and propagation is better understood [130].

4.3.1 Interaction with A β and Tau Proteins

The accumulation of neurotoxic forms of tau and $A\beta$ is a pathological characteristic of AD. TREM2 is an A β receptor that transduces AD-linked pathological and physiological effects. TREM2 is specifically upregulated in plaque-associated microglia [131]. Karanfilian et al. [132] and Singh et al. [133] reported that TREM2 is involved in modulating amyloid plaque deposition and removing amyloid plaques in AD. Findings from numerous studies have shown that plaque-associated microglia may regulate the pathogenesis of $A\beta$ via plaque phagocytosis [134,135]. TREM2-dependent microglia activity has been demonstrated to reduce amyloid plaque development by increasing A β phagocytosis [136]. Kim *et al.* [137] demonstrated that TREM2 enhances the phagocytosis of $A\beta$ via the upregulation of C/EBP α depending on expression of CD36 in the microglia, which is necessary for protecting against memory loss and improving learning in cases of AD.

Recent evidence demonstrates that TREM2 insufficiency has varying effects on AD progression and initially suppresses amyloid pathology. However, the pathology is exacerbated in later disease stages [138]. Furthermore, deficiency of microglial TREM2 leads to heightened tau pathology coupled with widespread increases in activated neuronal stress kinases [139]. Tau is a neuronal intracellular protein. TREM2 insufficiency enhances the hyperphosphorylation of tau, even in the preliminary stages of AD and other neurodegenerative diseases [140]. Jiang T et al. [141] described that suppressing brain TREM2 expression increased tau pathology, a phenomenon that can be linked to neuroinflammation-induced tau kinase hyperactivation. The authors also pointed out that TREM2 suppresses kinase activity through tau by limiting neuroinflammation and therefore protects against tau pathology.

4.3.2 Modulation of Inflammatory Responses and Microglia Activation

An increase in inflammation and the classical activation of microglia are associated with AD [142,143]. Human and *in vivo* studies have revealed that the NLRP3 inflammasome is triggered in AD and ASC specks are indicated in the amyloid plaque core [144]. Some studies have shown that TREM2 has anti-inflammatory functions. In cell lines, TREM2 insufficiency enhanced levels of pro-inflammatory mediators, such as TNF- α , IL-6, and IL-1 [145]. TREM2 anti-inflammatory activities can also be facilitated by the C-terminal fragment of TREM2 [146].

Furthermore, a critical function of TREM2 is to modulate microglial function in the CNS [147,148]. A decrease in microglia surrounding plaque coverage was shown in TREM2-deficient mice, especially in plaques with higher volume [149]. In an AD model, TREM2-mediated early microglial responses reduced amyloid plaque transport and toxicity [150]. A genomic transgene-guided enhancement in TREM2 expression was shown to reprogram the responsivity of microglia and improve behavioral and neuropathological symptoms in AD rodent experients [151]. Recent reports suggest that TREM2 is an A β receptor that mediates function in microglia [152]. Zhao et al. [153] further demonstrated that TREM2/A β interaction mediates the downstream TREM2/DAP12 signaling pathway, thereby inducing the degradation of $A\beta$ protein around microglia and microglial activation. Recent data have corroborated these findings by revealing that TREM2 promotes microglial survival and maintains microglial responses to $A\beta$ [154]. In addition, TREM2 controls microglial function by modulating cellular energy and biosynthetic metabolism in an AD model [155].

4.3.3 Participation in the Formation of Dendritic Spines

Dendritic spines are important for forming neuronal connection and signal transmission in the nervous system and can alter the motility, density, and morphology of neurons in relatively shorter periods [156]. The characteristics of dendritic spines have attracted attention in investigations on neurobiological behavioral platforms. For instance, the structural aspects of dendritic spines are linked to variations in learning and memory, synaptic efficiency, and other cognitive functions [157]. Reportedly, microglia reshape synapses through presynaptic nourishment and spinal head filamentous foot induction [158].

TREM2 is crucial for microglia-assisted synaptic refinement during the preliminary stages of brain development. A lack of TREM2 expression causes ineffective synapse pruning, increases excitatory neurotransmission, and minimizes long-range functional connectivity [159]. Maturation studies have shown that variations in the structure and activity of synapses and dendrites are preliminary and critical occurrences in the pathogenesis of AD neurodegenerative procedures [160]. A β -induced changes in dendritic spine pathology has also been observed in the preliminary stages of AD [161]. *In vivo* dendritic spine analysis revealed that neuroinflammation alters the structural plasticity of dendritic spines, which can be ameliorated by antiinflammatory drugs [162]. TREM2 deletion aggravated the loss of dendritic spines and axons in a transgenic AD mouse model. This indicates that serious neuron damage is more commonly a result of TREM2 insufficiency than of amyloid plaque load.

4.4 The Role of TREM2 in the Connection between Exercise and AD

There is plenty of literature demonstrating that regular physical exercise may slow disease progression or ameliorate symptoms in AD by increasing cerebrospinal biomarkers [163] and cardiovascular fitness [164], as well as decreasing AD-related biomarkers [165]. In addition, various animal models have demonstrated that exercise exerts neuroprotective effects on cognition in AD, such as object recognition memory [166], spatial learning and memory [167], and anxiety behavior [168]. Dao AT et al. [169] demonstrated that AD-impaired basal synaptic transmission and suppression of early-phase long-term potentiation in the dentate gyrus was prevented by prior moderate treadmill exercise. Using a transgenic model, Mu L et al. [170] demonstrated that strengthening structural synaptic plasticity may represent a potential mechanism by which treadmill exercise prevents decline in spatial learning and memory and synapse loss in $3 \times \text{Tg-AD}$ mice. Liu Y *et al.* [171] reported that short-term resistance exercise inhibits neuroinflammation and attenuates neuropathological changes in AD mice. Lu Y et al. [172] demonstrated that treadmill exercise is neuroprotective and regulates microglial polarization and oxidative stress in AD model. Furthermore, pharmacological mimetics of exercise, such as by enhancing adult hippocampal neurogenesis (AHN) and elevating brain derived neurotrophic factor (BDNF) levels, may improve cognition in AD. Furthermore, when applied at early stages of AD, these mimetics may protect against subsequent neuronal cell death [173].

The interaction between microglia and neurons, mediated by TREM2, has been shown to contribute to AD pathogenesis. Therefore, the regulation of TREM2 to alleviate AD has garnered major interest in AD research. Recently, findings from an animal study showed that upregulation of TREM2 ameliorated inflammatory responses, neuronal injury, and cognitive deficits [174,175]. More importantly, exercise can be viewed as a safe and economic option for improving cognitive performance in both normal and diseased states, including AD. However, few studies have revealed the critical role of TREM2 in exercise and AD.

Currently, the mechanism underlying the exerciseinduced neuroprotective effect on cognitive function associated with TREM2 in an AD model can be illustrated from three major findings. First, exercise has been shown to regulate microglial function through TREM2 regulation in the brain. Improvement in recognition memory in an AD rat model is linked to the upregulation of the hippocampal TREM2/DAP12 pathway, which can inhibit excessive microglial activation as well as neuroinflammation [176]. Recent research using the APP/PS1 mouse model demonstrated that long-term running inhibits TREM2 shedding to maintain the levels of TREM2 protein as well as microglial metabolic activity [177]. Second, exercise can increase dendritic spine density by modulating TREM2 expression. TREM2 deficiency was shown to exacerbate dendritic spine loss in an AD mouse model [162]. In contrast, Mu et al. [170] showed that exercise protects memory function by enhancing dendritic spine density in the brain in a $3 \times Tg-AD$ mouse model. Thus, it was widely speculated that exercise modulates TREM2 expression to protect dendritic spines in AD models. However, the in vivo/in vitro evidence should be validated further to confirm this hypothesis. Third, the enhancing effect of physical exercise onsTREM2 was measured in the cerebrospinal fluid of patients with AD. The experiments performed by Jensen et al. [178] indicated that the levels of sTREM2 in the cerebrospinal fluid of patients with AD increased with physical exercise intervention.

5. Conclusions

The pathology of AD is well-studied. The demand for AD prevention or treatment methods has increased owing to more than 15 years of failure in clinical studies. Fortunately, research on AD is currently underway. Emerging evidence implicating TREM2 can provide new insights into AD diagnostics and treatments because early TREM2-participated microglial inflammation may be present decades before the onset of AD-related cognitive impairments. TREM2 deficiency is closely associated with AD and other neurodegenerative disorders. In contrast, TREM2 upregulation in response to exercise can ameliorate AD-related neuropathological changes. Further studies are required to elucidate the protective mechanism of TREM2 in AD.

Author Contributions

GTL, LLZ and WLJ designed the research study. YZF conducted a literature review and revised the manuscript. YZF and WLJ supervised the study. All authors contributed to editorial changes in the manuscript. All authors read and approved the final manuscript. All authors have participated sufficiently in the work and agreed to be accountable for all aspects of the work.

Ethics Approval and Consent to Participate

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Conflict of Interest

The authors declare no conflict of interest.

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