Chinese Medical Journal®

A systematic review of the role of TREM2 in Alzheimer's disease

Yunsi Yin, Hanchen Yang, Ruiyang Li, Guangshan Wu, Qi Qin, Yi Tang

Department of Neurology & Innovation Center for Neurological Disorders, Xuanwu Hospital, Capital Medical University, National Center for Neurological Disorders, Beijing 100053, China.

Abstract

Background: Given the established genetic linkage between triggering receptors expressed on myeloid cells 2 (TREM2) and Alzheimer's disease (AD), an expanding research body has delved into the intricate role of TREM2 within the AD context. However, a conflicting landscape of outcomes has emerged from both *in vivo* and *in vitro* investigations. This study aimed to elucidate the multifaceted nuances and gain a clearer comprehension of the role of TREM2.

Methods: PubMed database was searched spanning from its inception to January 2022. The search criteria took the form of ("Alzheimer's disease" OR "AD") AND ("transgenic mice model" OR "transgenic mouse model") AND ("Triggering receptor expressed on myeloid cells" OR "TREM2"). Inclusion criteria consisted of the following: (1) publication of original studies in English; (2) utilization of transgenic mouse models for AD research; and (3) reports addressing the subject of TREM2.

Results: A total of 43 eligible articles were identified. Our analysis addresses four pivotal queries concerning the interrelation of TREM2 with microglial function, Aβ accumulation, tau pathology, and inflammatory processes. However, the diverse inquiries posed yielded inconsistent responses. Nevertheless, the inconsistent roles of TREM2 within these AD mouse models potentially hinge upon factors such as age, sex, brain region, model type, and detection methodologies.

Conclusions: This review substantiates the evolving understanding of TREM2's disease progression-dependent impacts. Furthermore, it reviews the interplay between TREM2 and its effects across diverse tissues and temporal stages.

Keywords: TREM2; Alzheimer's disease; Mouse model; Microglia; Amyloid-β accumulation; Tau pathology; Inflammation

Introduction

Alzheimer's disease (AD) stands as a chronic neurodegenerative ailment, reigning as the foremost cause of dementia on a global scale.[1] Characterized by the presence of intracellular neurofibrillary tangles (NFTs) composed of hyperphosphorylated tau (p-tau) protein within neurons, alongside an abundance of extracellular plaques housing the amyloid-β peptide (Aβ) in the brain,[2] AD's identity is further woven with the fabric of progressively emerging "neuroinflammation". This chronic phenomenon materializes as microgliosis, astrogliosis, and escalated expression of inflammatory mediators.[3] However, the intricate role of neuroinflammation within AD's tapestry appears multifaceted, capable of bestowing both benefit and detriment to the disease process.

In the span of the last two decades, the landscape of genetic-associated risk factors for AD has broadened considerably. Notably, amyloid precursor protein (APP), presenilin 1 (PSEN1), and presenilin 2 (PSEN2) have emerged as genetic risk factors for early-onset familial AD.[4] Conversely, late-onset AD (LOAD) is a more intricate genetic puzzle, with apolipoprotein E (APOE) reigning as the most potent risk contributor. Encoded by the alleles: ε_2, ε_3, and ε_4, one instance of the ε_4 allele elevates AD risk four-fold.[5] Moreover, genes entwined with microglial reactivity and innate immunity, including APOE, clusterin (CLU), the cluster of differentiation 33 (CD33), and triggering receptor expressed on myeloid cells 2 (TREM2), have etched their presence as human genetic risk factors for AD.[6,7] Notably, the rare variant TREM2 R47H has surfaced as a pivotal player, bearing the highest risk association with LOAD development,[8,9] boasting effect magnitudes akin to the *APOE* ε_4 allele. This revelation has sparked a cascade of research endeavors to delineate the impact of TREM2 on AD.

TREM2 emerges as a type I transmembrane cell surface receptor spanning 230 amino acids.[10] Limited to expression within microglia within the central nervous system (CNS),[11] TREM2 wields a critical role in microglial

Access this article online

Quick Response Code:

Website: www.cmj.org

DOI: 10.1097/CM9.0000000000003000

Correspondence to: Qi Qin, Department of Neurology & Innovation Center for Neurological Disorders, Xuanwu Hospital, Capital Medical University, 45 Changchun Street, Beijing 100053, China
E-Mail: qinqibao@126.com;
Yi Tang, Department of Neurology & Innovation Center for Neurological Disorders, Xuanwu Hospital, Beijing 100053, China
E-Mail: tangyi@xwhosp.org

Chinese Medical Journal 2024;137(14)

Received: 30-12-2023; **Online:** 24-06-2024 **Edited by:** Ting Gao and Xiuyuan Hao

function. Its duties encompass fortifying proliferation, orchestrating inflammatory responses, and arranging responses to neurodegeneration.[12,13] The robust genetic connection between TREM2 and AD underscores microglia's pivotal role in the disease's genesis and progression. Thus, it becomes imperative to untangle the mechanisms through which TREM2 regulates microglial activation in the context of AD pathogenesis, offering insights into the disease's underlying pathology.

A burgeoning body of studies has delved into TREM2's involvement in AD. Exploiting an array of transgenic AD models and *in vitro* assays, these inquiries have yielded crucial insights connecting TREM2 with amyloid plaques. *In vitro* explorations have unveiled TREM2's role in facilitating microglial absorption of Aβ40 and Aβ42.[11] Correspondingly, *in vivo* investigations have disclosed that *Trem2* deficiency escalates amyloid load in 5XFAD mice.[14] However, an alternate study employing the APPPS1-21 mouse model has indicated that *Trem2* deficiency retards amyloid load in the initial stages.[15] Furthermore, this model demonstrated that *Trem2* deficiency marginally diminishes plaque deposition at the age of 2 months, but exacerbates deposition by the age of 8 months,[16] painting a portrait of TREM2's progression-dependent influence. Hence, deciphering the intricacies of how TREM2 shapes microglial reactions to Aβ accumulation stands as an imperative objective.

Emerging studies have cast a spotlight on TREM2's profound association with tau pathology. Clinical observations have illuminated that patients bearing the TREM2 R47H variant exhibit heightened cerebral spinal fluid levels of p-tau protein compared to AD patients.[8] In parallel, human tau (hTau) mice demonstrated that *Trem2* deletion worsened tau phosphorylation and aggregation.[17] In contrast, Leyns *et al*[18] presented data indicating that *Trem2* deficiency intensified tau pathology in the early stages but fostered synapse preservation and abated neurodegenerative atrophy without tampering with p-tau or insoluble tau levels in 9-month-old PS19 mice. This tapestry of evidence emerges TREM2's intriguing role in tau pathology, a role that warrants further exploration.

To decipher the ways through which TREM2 amplifies AD risk and fuels its advancement, a constellation of vital queries beckons for answers. (1) How does TREM2 activate microglia or steer them into a "disease-associated microglia" (DAM) phenotype amid AD pathogenesis? (2) How does TREM2 mold the microglial response to Aβ accumulation? (3) In what manner does TREM2 intertwine with tau pathology? (4) How does TREM2 choreograph the inflammatory retort? Resolving these queries stands to unveil the mazelike signaling pathways of TREM2 in microglia and neurodegeneration. In tandem with TREM2's intricate stance in AD pathogenesis, the models employed in preceding research assume significance. *In vitro* tests, sequestered to isolated cells or controlled environments, fall short of the dynamic interplay occurring within the human body, where pathways and cells incessantly converse and metamorphose. *In vivo* experiments involving diverse transgenic AD models simulate the organism holistically, better mirroring potential interactions during disease processes. Herein, our methodical review assembles original studies in a mouse model, summarizing the emergence of *Trem2* transgenic mouse models deployed to address these crucial inquiries. This systematic review strives to unravel TREM2's role within AD pathologies, allowing avenues for ensuing mouse model investigations and the development of novel therapeutic strategies for the disease.

Methods

Information sources and search terms

Our systematic search rigorously adhered to the Cochrane Handbook of Systematic Reviews (https://training.cochrane.org/handbook) and incorporated the Preferred Reporting Items for Systematic Reviews and Meta-Analyses extension for Scoping Reviews (PRISMA-ScR) checklist. Our exploration encompassed the PubMed databases, encompassing papers available up to January 31, 2022. Employing a combination of stand-alone and interlinked terms, we employed keywords such as "TREM2", "Alzheimer's disease", and "transgenic mice model". The search criteria took the form of ("Alzheimer's disease" OR "AD") AND ("transgenic mice model" OR "transgenic mouse model") AND ("Triggering receptor expressed on myeloid cells" OR "TREM2"). Augmenting this algorithm, we conducted an auxiliary manual search by meticulously scrutinizing references within pertinent articles and reviews.

Study selection and eligibility criteria

In a concerted effort, two independent reviewers meticulously reviewed the title and abstract of all retrieved articles. In case of discordance, a comprehensive full-text evaluation will be conducted to reach a consensus. To qualify for inclusion, studies needed to satisfy the following criteria: (1) original studies presented in English; (2) transgenic mouse models tailored for AD research; and (3) investigations spotlighting TREM2. Any material classified as a review, systematic review, meta-analysis, or pertaining to human subjects was categorically excluded from consideration.

Data extraction

Crucial attributes encapsulated within the included studies, encompassing references, mouse models, ages, strains, genders, methodologies, and key findings, have been succinctly tabulated for reference in tables.

Results

Our thorough investigation yielded a collection of 43 studies conducted across diverse mouse models [Figure 1], offering insights into the influence of TREM2 on the emergence of quintessential AD pathologies. The focal points of these studies encompassed Aβ plaques, phosphorylated tau protein aggregates, microglial operations, and neuroinflammatory mechanisms. Nevertheless, the precise regulatory roles of TREM2 within these AD mouse models potentially hinge upon factors such as age, sex, brain region, model type, and detection methodologies.

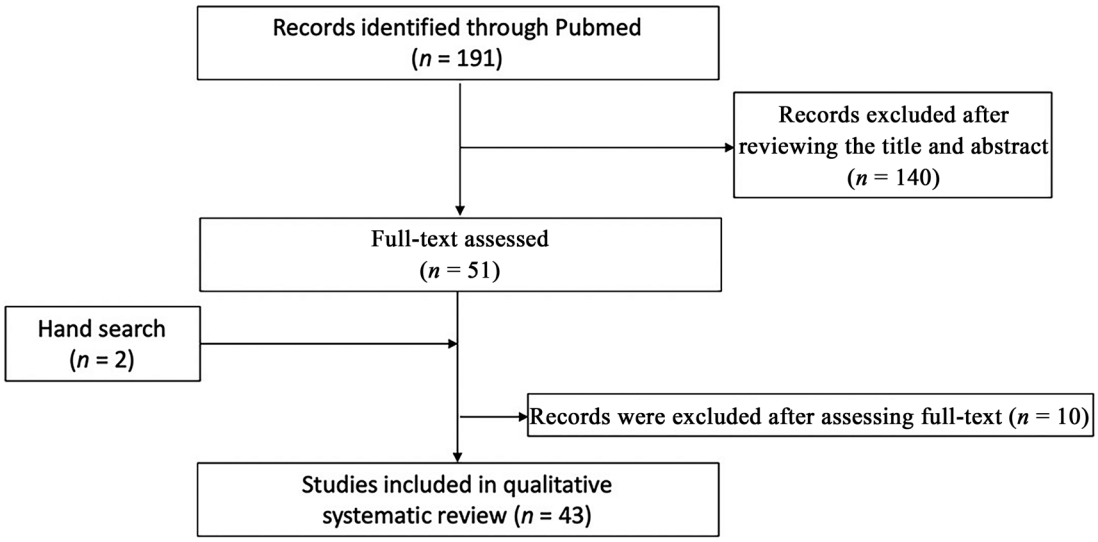

Figure 1: Flow diagram of literature search and study selection.

Generation of the Trem2 mouse model

An array of mouse models was harnessed to dissect the role of TREM2 in shaping AD pathologies [Supplementary Table 1, http://links.lww.com/CM9/B880]. A prevalent approach entailed crossing AD models with *Trem2* transgenic mice, a maneuver often accomplished via analogous methodologies. These *Trem2* transgenic models diverged in their strategies to enhance *TREM2* gene expression, encompassing techniques such as lentiviral injection[11,19] or integration of additional human *Trem2* copies using bacterial artificial chromosome (BAC) technology.[20] It is worth noting, however, that studies adopting lentiviral injection failed to definitively establish the efficacy of microglial gene transfer. Furthermore, they did not assess the transduction efficiency in these models, potentially introducing confounding variables.[11,19]

Furthermore, the *Trem2* knockout (*Trem2*$^{-/-}$ or *Trem2* KO) mouse model was pursued via three distinct targeting strategies. For clarity, we designate these as Velocigene *Trem2*$^{-/-}$ mice, Colonna lab *Trem2*$^{-/-}$ mice, and clustered regularly interspaced short palindromic repeats (CRISPR/Cas9) *Trem2*$^{-/-}$ mice throughout the remainder of this paper. Velocigene *Trem2*$^{-/-}$ mice employed a LacZ reporter introduced in place of exons 2, 3, and most of exon 4 within the *Trem2* locus.[1,16,21–31] In contrast, Colonna laboratory *Trem2*$^{-/-}$ mice underwent a redesign, entailing the deletion of transmembrane and cytoplasmic domains encoded by exons 3 and 4. This maneuver was executed by substituting exons 3 and 4 with a neomycin cassette, subsequently excised with cytomegalovirus cyclization recombinase (CMV Cre).[14,15,32–42] The CRISPR/Cas9 *Trem2*$^{-/-}$ mice, procured from the Jackson Laboratory (Bar Harbor, Maine, USA), bore an allele with a non-homologous end joining (NHEJ)-generated 175 bp deletion that instigated a stop codon at amino acid 17.[43–47] Notably, a distinctive trait of the Velocigene *Trem2*$^{-/-}$ mice entailed a marked overexpression of triggering receptor expressed on myeloid cells-like protein 1 (TERML1) during basal conditions, a phenomenon not mirrored in the other two models. As such, findings derived from the Velocigene *Trem2*$^{-/-}$ mice might be attributed to either *Trem2* knockdown, elevated *Treml1*, or their synergistic interplay.

Furthermore, to replicate mutations observed in patients, a loss-of-function TREM2 model was fashioned through CRISPR/Cas9 technology, leading to the emergence of *Trem2*^{R47H} mice,[48] *Trem2*^{Y38C} mice,[43] and *Trem2*^{T66M} mice.[36] BAC technology was also employed to introduce human *TREM2* or human *TREM2* mutation variants[39,42,48,49] into mouse models. This endeavor yielded h*Trem2*^{R47H} m*Trem2*$^{-/-}$ mice and h*Trem2*^{CV} m*Trem2*$^{-/-}$ mice, in which mouse *Trem2* was replaced with the normal human *TREM2* or human *TREM2* R47H variant. The utilization of these mouse models founded upon human *TREM2* underpins the potency and credibility of their outcomes.

Additionally, the evolution of induced pluripotent stem cell (iPSc) technologies has paved the way for studies involving human microglia. These studies have recently surged, investigating the role of TREM2. This exploration involved transplanting iPSC-derived microglia from human iPSC cell lines into the brains of AD mice.[50–52]

Collectively, an array of mouse models has been harnessed to illuminate the function of TREM2 across various disease stages. However, it is imperative to acknowledge that these models, while insightful, may introduce complexities as they inherently simulate only segments of the intricate pathological cascade witnessed within the human brain.

Influence of TREM2 on cognitive performance in basal and pathological conditions

Numerous investigations have delved into the role of TREM2 concerning cognitive performance under basal conditions [Table 1]. Employing assessments such as the open field assay, elevated plus maze, 3-chamber social test, and conditioned fear assays, a consensus emerged: no discernible behavioral deviations were detected between

six-month-old Velocigene and Colonna *Trem2*$^{-/-}$ mice and their wild-type (WT) counterparts.[24,39] Similarly, no significant cognitive distinctions manifested between WT mice and overexpression TREM2 mice.[19] Intriguingly, one study illuminated that Colonna *Trem2*$^{-/-}$ mice exhibited no influence on learning and memory function in young mice (6 months old), yet unexpectedly showcased a protective influence that forestalled cognitive decline in aged counterparts (18 months old).[39]

These cognitive nuances potentially find explication in the realm of neuronal plasticity [Supplementary Table 2, http://links.lww.com/CM9/B880]. In 6-month-old Colonna *Trem2*$^{-/-}$ mice, a surge in cortical neuronal spine density materialized, while aged mice exhibited augmented hippocampal long-term potentiation (LTP).[39] Conversely, a stark disruption in hippocampal neuronal plasticity marked 6-month-old CRISPR/Cas9 *Trem2*$^{-/-}$ mice, characterized by diminished pre- and post-synaptic elements and attenuated LTP magnitude.[43] Contrarily, 1-month-old Velocigene *Trem2*$^{-/-}$ mice showcased synapse reduction during development, a trend reversed in adulthood (4 months).[30] These TREM2-mediated alterations reverberate across the spectrum, potentially mediated by astrocyte-driven synaptic engulfment, microglial phagocytosis, age-related synaptic loss, and inflammatory responses.[30,39]

However, when confronted with environmental stress or pathological triggers, TREM2's influence becomes more intricate. Recent revelations indicate that TREM2 might ameliorate memory impairments within AD pathological contexts. Elevation of TREM2 levels substantially ameliorated cognitive function in AD mice, including 5XFAD,[20] APPPS1,[11] and P301S[19] mice. In stark contrast, the absence of *Trem2* fostered learning and memory decline in APPPS1,[44–46] 5XFAD,[32] and P301S[53] mice.

It is surmised that TREM2 might attenuate neurodegeneration within pathological settings, consequently enhancing cognitive faculties. TREM2 overexpression in 7-month-old APPPS1 and P301S mice forestalled

Table 1: TREM2 influences cognitive performance in basal or pathological disease states.

References	Experiment	Mouse model	Age* (months)	Cognitive function
Kang *et al*, 2018[24]	Open-field test	*Trem2*$^{-/-}$ mice	6	–
	Elevated plus-maze	WT		
	Conditioned fear behavioral testing			
Qu *et al*, 2020[39]	Open-field test	*Trem2*$^{-/-}$ mice	6	–
	Morris water maze	WT		
	Elevated plus-maze			
Jiang *et al*, 2015[53]	Morris water maze test	WT silencing of TREM2	7	–
		WT		
		P301S silencing of TREM2		↓
		P301S		
Jiang *et al*, 2016[19]	Open-field test	Overexpression TREM2 P301S	7	↑
	Y-maze test	P301S		
	Morris water maze			
Jiang *et al*, 2014[11]	Morris water maze	Overexpression TREM2 APPPS1	9	↑
		APPPS1		
Lee *et al*, 2018[20]	Contextual fear-conditioning	5XFAD; BAC-TREM2	10	↑
		5XFAD		
		BAC-TREM2 mice	10	–
		WT		
		APPPS1; BAC-TREM2	11	↑
		APPPS1		
Cui *et al*, 2020[45]	Morris water maze	APPPS1; *Trem2*$^{-/-}$ mice	4	↓
		APPPS1		
Fitz *et al*, 2020[44]	Novel object recognition	APP; APOE3; *Trem2*$^{-/-}$	6.5	↓
	Contextual fear conditioning paradigms	APP; APOE4; *Trem2*$^{-/-}$		
		APOE3; *Trem2*$^{-/-}$		
		APOE4; *Trem2*$^{-/-}$		
Griciuc *et al*, 2019[32]	Open-field test	5XFAD; *CD33*$^{-/-}$ mice	7	↓
	Morris water maze	5XFAD; *CD33*$^{-/-}$;*Trem2*$^{-/-}$ mice		
Sheng *et al*, 2019[46]	Morris water maze test	APPPS1; *Trem2*$^{-/-}$ mice	12	↓
		APPPS1		
Vautheny *et al*, 2021[37]	Elevated plus maze	Tau22 mice	10	–
	Novel object recognition	Tau22; *Trem2*$^{-/-}$ mice		
	Morris water maze test			

*Age referred to observation age. –: No significant differences were found in the origin article; ↑: Increased cognitive function were found in the origin article after Trem2 transgenosis; ↓: Declined cognitive function were found in the origin article after *Trem2* transgenosis. APOE: Apolipoprotein E; APP: Amyloid precursor protein; BAC: Bacterial artificial chromosome; CD: Cluster of differentiation; TREM2: Triggering receptor expressed on myeloid cells 2; WT: Wild-type.

neuronal and synaptic attrition.[11,19] The augmentation of TREM2 in microglia alleviated neurite dystrophy linked with plaques in 5XFAD mice.[20] Inversely, *Trem2* deficiency culminated insignificantly fewer neurons within 5XFAD;*Trem2*$^{-/-}$ mice compared to 5XFAD mice.[32,51] Moreover, *Trem2* deletion accentuated axonal dystrophy in PS2APP[26] and TauPS2APP[27] mice. Notably, *Trem2* deficiency exacerbated both axonal dystrophy and hippocampal atrophy in TauPS2APP[27] mice at 9 months and more markedly at 17 months. Additionally, *Trem2*^{R47H} intensified plaque-linked neuritic dystrophy in 4-month-old APPPS1–21 mice.[25] However, divergent outcomes emerged for P301L mice[29] and PS19 mice.[18] In these models, *Trem2* deletion translated to reduced synaptic loss and safeguarded against atrophy.[18,29] Intriguingly, the presence of human *TREM2*^{R47H} markedly mitigated brain atrophy by curbing microglial synaptic phagocytosis in PS19 mice, contrasting with mice expressing TREM2 CV due to lower C1q accumulation in synapses.[48] These human *TREM2*-based models not only highlighted the dampening effects of the R47H variant on neurodegeneration but also suggested its neuroprotective role within tauopathy settings.

However, the intricacies multiply when delving into the coalescence of TREM2 with environmental stressors or pathology. In the context of THY-Tau22 mice, *Trem2* deficiency attenuated atrophy arising from tau pathology; however, it neither exacerbated nor ameliorated memory deficits in 10-month-old THY-Tau22 mice.[37] Ergo, beyond the protective influence on neurodegeneration, cognitive performance within this framework might result from the intersection of aggravated tau pathology and other mechanisms. As such, the impact of TREM2 on cognitive performance in pathological contexts assumes a much more intricate form.

In summation, a consistent thread eludes regarding how TREM2 shapes cognitive performance and neurodegeneration within basal and pathological conditions. This might stem from the condition-dependent sway of TREM2. Given the divergence in age, mouse models, and pathological contexts across various studies, different factors might predominate across distinct disease stages.

Modulation of microglial function by TREM2

The confined expression of TREM2 in microglia within the CNS underscores its pivotal role in microglial function regulation, warranting a closer exploration of its impact [Supplementary Table 3, http://links.lww.com/CM9/B880].

Primarily, TREM2 was established as a prerequisite for microglial activation. Depletion of *Trem2* led to notable morphological alterations in microglia. In 5XFAD mice, microglia exhibited hypertrophic amoeboid shapes with shortened and thickened processes, indicative of canonical reactive microglia.[14] Yet, these changes were absent in *Trem2*$^{-/-}$; 5XFAD mice, wherein microglial processes failed to align with plaque boundaries.[15] Conversely, 5XFAD; BAC mice exhibited elongated and ramified plaque-associated microglial processes compared to their 5XFAD counterparts.[20] Additionally, a reduction in size, fewer branches, and shortened processes featured in 8–9-month-old P301S mice[29,44] and hTau mice,[17] both *Trem2* deficient.

The intricate mechanisms underlying TREM2-mediated microglial activation remain elusive. Several investigations have scrutinized the transcriptome. In the context of Colonna lab *Trem2*$^{-/-}$ mice, gene expression demonstrated minimal deviations compared to WT mice,[14] implying limited *Trem2* deficiency impact in basal settings. Contrarily, gene expression discrepancies emerged between Velocigene *Trem2*$^{-/-}$ mice and WT mice, demonstrating a time- and tissue-specific effect.[22] Disparities in gene expression proved more pronounced at 4 months old *vs*. 8 months old, with cortical alterations more prominent in young mice and hippocampal changes more prevalent in aged mice.[22] This divergence might be attributed to the considerable upregulation of triggering receptor expressed on myeloid cells like 1 (TREML1) expression in Velocigene *Trem2*$^{-/-}$ mice. In addition, *Trem2*^{R47H} mice exhibited dysregulated genes implicated in myeloid cell function, encompassing DNA replication, cell cycle control, proliferation, cell death, chemokine/cytokine modulation, and the complement pathway, albeit not directly linked to phagocytosis.[54] This hints at TREM2 loss-of-function contributing to fundamental deficits in proliferation and survival, subsequently cascading into reduced phagocytic capacity.[54] Notably, the sole presence of the TREM2 variant, devoid of other genetic risk factors, underpinned a loss of myeloid function, potentially exacerbated within an AD context.[33]

Emerging insights from single-cell RNA sequencing (scRNAseq) unveiled a novel microglial subtype in AD models, christened DAM or microglial neurodegenerative phenotype (MGnD).[38] This subpopulation, linked to neurodegenerative pathology, potentiated inflammatory processes, and likely held a beneficial role by inducing the phagocytosis of deceased or damaged neurons and toxic substances. In 5XFAD mice, DAM spatially correlated with AD plaques.[38] DAM displayed significant gene expression shifts relative to microglia, signified by dwindling levels of several microglia homeostatic genes including *P2ry12*/*P2ry13*, *Cx3cr1*, and *Tmem119*. Concurrently, a surfeit of genes within DAM were upregulated, including established AD risk factors like *Apoe*, *Ctsd*, *Tyrobp*, and *Trem2*.[38,48] ScRNA-seq on *Trem2*$^{-/-}$ 5XFAD mice uncovered a two-step mechanism facilitating microglia transformation from the homeostatic state to DAM.[38] This trajectory encompassed: a shift to an intermediate state, marked by partial DAM program expression (*Tyrobp*, *Apoe*, *B2m*, and *Ctsd*), distinctly more abundant in the *Trem2*$^{-/-}$ AD model.[14,38] Subsequently, a TREM2-dependent mechanism propelled microglial progression, involving lipid metabolism and phagocytic pathways.[38,42] This scenario found reinforcement through RNA sequencing (RNA-seq) studies. *Trem2* deficiency downregulated genes linked to the adaptive immune response, innate immune response, inflammation, integrin-mediated signaling, phagocytosis, and chemotaxis, and many microglial-specific (e.g., *DAM* genes) or homeostatic genes (e.g., *P2ry12*, *P2ry13*, *Cx3cr1*, and *Tgfb1*).[19,32,40,49] Similar trends emerged in PS2APP mice,

where *DAM* genes exhibited *Trem2*-dependency while "homeostatic" genes did not.[26] Furthermore, *Trem2* deletion yielded fewer transcripts in 5XFAD microglia, encompassing those associated with microglial activation, inflammation, and neurotrophic factors,[14,27] solidifying TREM2's importance in reactive microgliosis within AD pathological states.[14,55] Reprograming of *DAM* gene expression was evident in 5XFAD; BAC-TREM2 mice as well.[20] Additionally, *Trem2* deletion engendered subdued *DAM* gene effects in TauPS2APP mice, fostering smaller populations of interferon-responsive or classically activated microglia.[27] Reduced microglial activation and decreased inflammatory gene expression materialized in PS; $Trem2^{-/-}$ mice.[27] Furthermore, the R47H polymorphism subdued microglial activation,[56] with related transcripts (*Spp1*, *Gpnmb*, *Cst7*) elevated in PS19; $Trem2^{CV}$ mice compared to PS19; $Trem2^{R47H}$ mice.[49] This observation resonated in PS19; $Trem2^{R47H}$ mice,[48] which exhibited suppressed expression of all *DAM* genes (e.g., *Axl*, *Cst7*, *Cd9*) relative to PS19; $Trem2^{CV}$ mice, alongside an elevation in the homeostatic gene *P2ry12*, suggesting a more homeostatic microglial status.[48] Ergo, *Trem2* deletion likely attenuates the DAM response, exacerbating neurodegeneration.

Fascinatingly, the gene-dose-independent TREM2 effects encompass disparate pathways. P301S;$Trem2^{+/-}$ mice revealed 232 differentially expressed transcripts compared to P301S;$Trem2^{+/+}$ mice, enriched in microglial development pathways (transforming growth factor-β [TGF-β], interleukin-2 [IL2], signal transducers and activators of transcription 5 [STAT5], tumor necrosis factor-α [TNF-α] via nuclear factor kappa-B [NF-κB]). On the other hand, P301S;$Trem2^{-/-}$ mice showcased differential gene enrichment, predominantly linked to metabolism (oxidative phosphorylation, glycolysis, mechanistic target of rapamycin complex 1 [MTORC1] signaling) and complement-mediated and inflammatory responses.[29]

Influence of TREM2 on Aβ accumulation

TREM2 activation during Aβ accumulation

In the Aβ milieu, the augmented expression of TREM2 emerges as a protective factor against AD advancement, orchestrating microglial function modulation.[57] Analysis of 7-month-old APPPS1 mice unveiled higher TREM2 expression in each microglial cell compared to WT counterparts.[11] Corroboratively, heightened TREM2 expression was observed in microglia upon Aβ aggregation in 5XFAD mice[14] and APPPS1-21 mice.[21] Elucidating the mechanistic underpinnings, Jiang *et al*[11] induced varying Aβ1-42 doses into the cerebral cortex and hippocampus of WT mice, directly correlating elevated Aβ1-42 levels with enhanced TREM2 expression. Consequently, the most potent Aβ variant, Aβ1-42, potentially wields a pivotal influence on the interplay between TREM2 and Aβ accumulation. Notably, the activation dynamics of TREM2 in the presence of Aβ warrant exploration. Aβ has been recently identified as a ligand for TREM2, instigating direct TREM2 binding and activation of signaling pathways.[58] Furthermore, TREM2 serves as a sensor for an array of acidic and zwitterionic lipids.[14] Aβ exhibits robust interactions with membranes harboring such lipids, inducing Aβ peptide conversion to fibrillar Aβ. Of significance, some TREM2 lipidic ligands on neuronal and glial cell surfaces might encounter damage due to Aβ accumulation, potentially triggering an indirect activation of TREM2 signaling. Additionally, Claes *et al*[50] transplanted human microglia derived from iPSCs into an AD mouse model, observing reduced lipid droplet accumulation in $Trem2^{R47H}$ DAM xenografted human microglia, albeit potentially as a secondary response to TREM2-mediated shifts in plaque proximity and reactivity.

Disease progression-dependent effects of TREM2 during Aβ accumulation

TREM2's influence on amyloid burden might exhibit disease progression-dependent effects, manifesting as an early amelioration followed by late-stage exacerbation of amyloid pathology [Supplementary Table 4, http://links.lww.com/CM9/B880]. In response to heightened TREM2 expression, diminished Aβ deposition was evident in 9-month-old APPPS1 mice.[11] Analogously, conspicuous reduction in amyloid plaque load was discerned in 7-month-old 5XFAD;BAC-TREM2 mice relative to 5XFAD counterparts.[20] Remarkably, the composition of Aβ plaques shifted significantly toward less filamentous and more inert forms, with notable reductions in both soluble and insoluble Aβ1-42 observed in BAC-TREM2 mice.[20] Implantation of bone marrow-derived MSCs overexpressing TREM2 into APPPS1 mouse brains also curtailed Aβ production and deposition.[51] Conversely, *Trem2* deficiency amplified Aβ deposition in 4-month-old APPPS1-21 mice[45] and 8.5-month-old 5XFAD mice.[14] Intriguingly, hippocampal amyloid burden was attenuated in 4-month-old APPPS1-21 mice with Velocigene-targeted *Trem2* deficiency.[21] Haplodeficiency of *Trem2* by the Colonna lab augmented amyloid plaque compaction and expanded total fibril surface area in 4-month-old APPPS1-21 mice.[15] Notably, full *Trem2* deficiency preserved total amyloid coverage while abating plaque compaction in 6.5-month-old APPPS1-21 mice.[44] Furthermore, Velocigene-based *Trem2* deficiency revealed divergent effects on APPPS1-21 mice at early and late disease stages.[16] At 2 months, *Trem2* absence decreased cortical total plaque area and plaque count, contrasting with an elevation in total plaque area by 8 months of age.[16] Conversely, aged PS2APP mice registered reduced plaque load upon *Trem2* deficiency (Velocigene-targeted).[26] This observation, however, may stem from the utilization of specialized silver staining for "amber core", a distinctive mark of compact plaques. The study noted that the "amber core", a highly condensed plaque form, was less prevalent in PS2APP; $Trem2^{+/-}$ mice and nearly absent in PS2APP;$Trem2^{-/-}$ mice relative to PS2APP mice.[26] Notably, *Trem2* absence correlated with decreased plaque consolidation and escalated neurotoxic Aβ species, as evidenced by differential "amber core" presence. This effect was substantiated through the injection of amyloid seeds into APPPS1 mice, demonstrating that, in the presence of *Trem2*, seeded amyloid plaques exhibited a punctate appearance at 4 months. Conversely,

Trem2 absence led to increased area occupied by seeded amyloid plaques, with greater diffusion in 4G8 staining and segregation of individual ThioS-positive fibrillar Aβ puncta.[36] Thus, TREM2 exerted an impact on plaque consolidation at later disease stages as well.

TREM2-mediated microglial involvement in Aβ accumulation

TREM2 orchestrates shifts in microgliosis and summons microglia to amyloid plaques during Aβ accumulation.[44] In *Trem2* KO mice, microglial recruitment to plaques was hampered in 6.5-month-old APPPS1 mice.[44] Absence of *Trem2* translated into diminished plaque-associated microglia in 4-month-old APPPS1 mice,[21] 6.5-month-old APPPS1 mice,[44] and 8.5-month-old 5XFAD mice.[14] This reduction in microglial presence around amyloid plaques suggested impaired microglial chemotaxis in *Trem2* KO mice, restraining microglial migration toward Aβ and nearby damage zones.

TREM2's influence on microgliosis might be attributed to its mediation of myeloid cell processes encompassing death, proliferation, and migration. Initial evidence hinted at heightened microglial apoptosis due to *Trem2* deficiency, evident by augmented TUNEL$^+$ microglia in *Trem2*$^{-/-}$; 5XFAD mice relative to 5XFAD counterparts.[14] Moreover, in 5XFAD mice, *Trem2* deletion spurred autophagy in microglia by dampening mechanistic target of rapamycin (mTOR) signaling.[33] Furthermore, the absence of *Trem2* diminished plaque-associated myeloid cell accumulation by curtailing cell proliferation, particularly at later disease stages.[16] Notably, transcripts linked to microglial proliferation were markedly diminished in PS2APP; *Trem2*$^{-/-}$ microglia compared to PS2APP microglia, and many of these genes were regulators of canonical Wnt signaling.[26] Pertinently, a study introducing LiCl to activate Wnt/β-catenin signaling in *Trem2*$^{-/-}$ mice demonstrated that such treatment rescued microglial cell death and microgliosis, indicating that TREM2 propagated microglial survival via Wnt/β-catenin pathway activation.[23] These findings hint at Wnt/β-catenin signaling as a prospective therapeutic avenue for AD. Moreover, *Trem2*$^{+/-}$ microglia were the slowest to respond and extended the fewest processes toward the site of injury compared with *Trem2*$^{-/-}$ and WT. This was further proven by RNA-seq as cellular movement was the most significantly altered biological pathway in *Trem2*$^{+/-}$ microglia. The FAK/Rac1/Cdc42 signaling pathway critical for microglial migration was also demonstrated to be modulated by TREM2. Its absence or the presence of the R47H loss-of-function mutation impeded the FAK/Rac1/Cdc42-GTPase pathway and microglial migration. This effect was partially rescued by pathway activation through CN04, particularly in response to oligomeric Aβ1-42 in *Trem2*$^{-/-}$ and *Trem2*^{R47H} mice.[1]

The mechanisms governing Aβ clearance differ across various phases of amyloid pathology, pivoting on microglial phagocytosis *vs*. efflux through the blood–brain barrier (BBB). In the initial stages of amyloid deposition, low molecular weight oligomers and monomers dominate brain interstitial fluid, easily cleared via BBB efflux with a 1.5-h half-life. Notably, microglia sense amyloid buildup before plaque emergence in AD, altering morphology and intensifying interactions with neuronal cell bodies and neurites even before plaque formation. TREM2 played a role in these morphological shifts in response to early amyloid accumulation.[28] However, TREM2 was not essential for microglial processes gravitating toward amyloid-laden neurons or for neurite uptake.[28] This TREM2-dependent early morphological alteration might hold implications for the disease process warranting further exploration.

With advancing pathology, an escalation in high molecular weight Aβ oligomers extended Aβ half-life in interstitial fluid, impairing the BBB's swift clearance mechanism and augmenting microglia-mediated clearance inefficiencies. As amyloid accumulation progressed, TREM2 emerged as a coordinator of microglial phenotypic changes, plaque-surrounding microglial accumulation, and amyloid species clearance. As amyloid amassed in mice, microglia began to envelop individual fibrils within early filamentous plaques, promoting compaction. In the absence of *Trem2*, these barriers eroded, leading to diminished amyloid plaque compaction.[15] Moreover, elevated TREM2 gene dosage amplified phagocytic microglia markers such as CD68 and galectin 3 (Lgal3), aligning with findings in other amyloidosis models upon *Trem2* deletion.

An intriguing facet of this phenomenon is the ambiguity surrounding the origin of plaque-associated cells. Are they peripherally derived TREM2 myeloid cells or resident TREM2 microglia? Notably, TREM2$^+$ plaque-associated myeloid cells in APPPS1 mice exhibited elevated CD45 expression, usually attributed to peripheral macrophages.[21] However, these cells expressing high levels of CD45 (CD45^{hi}) indicate that Aβ-reactive myeloid cells originated from brain-resident microglia in 5XFAD mice.[34] Thus, the origin of TREM2-associated microglia remains enigmatic.

In summation, TREM2 contributes to microgliosis, moderates microglial function, and bolsters microglial barrier integrity to clear amyloid species and foster compaction. Nevertheless, the disease progression-dependent pattern of plaque accumulation does not consistently correlate with uniform changes in microgliosis. This disease progression-dependent model suggests that TREM2 may restrict initial plaque seeding and concurrently bolster Aβ sequestration and compaction within existing plaques. These findings suggest a more intricate role for TREM2 in microglial function. Moreover, TREM2's effect on brain immune cell populations may contribute in a disease progression-dependent manner, evident in the decreased number of CD45hi myeloid cells at both early and late disease stages, with a reduction in cells expressing low levels of CD45 (CD45^{lo}) only during late stages.[16] The underlying mechanisms behind the reduction in CD45^{hi} myeloid cells and its impact on amyloid pathology remain to be explored.

Interaction between TREM2 and tau pathology

The intricate role of TREM2 in tau phosphorylation and aggregation has sparked debate among various studies.

Most investigations point to *Trem2* deficiency exacerbating tau pathology [Supplementary Table 5, http://links.lww.com/CM9/B880]. Notably, Jiang *et al*[19] introduced lentiviral TREM2 overexpression in P301S mice, showing reduced tau hyperphosphorylation at AT8 and AT180 epitopes. Nonetheless, this overexpression had no discernible impact on tau aggregation, as total tau levels remained unchanged. Crucial kinases, cyclin-dependent kinase 5 (CDK5), and glycogen synthase kinase-3β (GSK3β), responsible for tau hyperphosphorylation, displayed marked reduction in activity.[19] Echoing these findings, another study suppressed TREM2 through lentiviral injection in P301S mice, reinforcing the observation that TREM2 silencing worsened tau pathology, particularly elevating p-tau protein levels.[53] Remarkably, silencing *Trem2* also facilitated hyperphosphorylation of endogenous tau and increased CDK5 and GSK3β activities in WT mice brains.[53] Considering the close tie between neuroinflammation and tau kinase hyperactivity, this increase in tau kinases could be attributed to heightened proinflammatory cytokine levels. Additionally, *Trem2* haploinsufficiency exacerbated tau pathology in P301S mice.[29] *Trem2* KO led to escalated hippocampal and cerebral cortex p-tau levels in 6-month-old hTau mice, with kinase dysregulation surfacing as early as 3 months.[17] Moreover, tau hyperphosphorylation and aggregation were heightened in 12-month-old THY-Tau22 mice upon *Trem2* deficiency.[37] These findings suggest early kinase dysregulation in hTau;*Trem2*$^{-/-}$ mice instigating worsened tauopathy. Notably, this aggravated tauopathy correlated with microglial subactivation, as evidenced by the smaller ramification index in Tau22;*Trem2*$^{-/-}$ mice at 12 months,[37] aligning with observations in hTau mice.[17] This connection implies a link between reduced microgliosis in *Trem2*-deficient animals and exacerbated tauopathy in aging subjects.

Conversely, Dr. Leyns'[18] research indicated that p-tau accumulation and tau solubility exhibited no significant changes in PS19; *Trem2*$^{-/-}$ mice relative to PS19 mice.[18] Dr. Lee's findings corroborated this stance, revealing that *Trem2* deletion amplified tau pathology in the TauPS2APP model but exerted no influence in the P301Lhomo model.[27] This implies that microglial TREM2 activity may constrain the extent to which Aβ pathology contributes to tau phosphorylation, aggregation, and propagation.[27] Such insight aligns with observations in 4-month-old 5XFAD mice, where p-tau levels in proximity to plaques significantly increased in the absence of *Trem2*.[34] These revelations underscore TREM2's pivotal role in hindering a crucial facet of Aβ-facilitated tau pathology.

Interestingly, AT8 staining of p-tau in the hippocampus was reduced in PS19;*Trem2*^{R47H} mice compared to PS19; *Trem2*^{CV} mice at 3 months, before overt tau pathology onset. Subsequently, at 9 months, the increase in p-tau was significantly curtailed in PS19;*Trem2*^{R47H} mice compared to PS19;*Trem2*^{CV} mice, indicating a distinct impact of the TREM2 R47H variant on tau pathology.[48] While this study arrives at a different conclusion, it is important to acknowledge that the unique *Trem2*^{CV} mice employed might have introduced new factors into the model, contributing to these disparate findings.

Influence of TREM2 on the inflammatory response

TREM2 displayed a mild repressing effect on CNS inflammation under both basal and lipopolysaccharide (LPS)-stimulated conditions [Supplementary Table 6, http://links.lww.com/CM9/B880].[24] Notably, several transcripts, including *Treml1*, *Ctsk*, *Mmp9*, *Lcn2*, and *S100a8*, exhibited alterations in *Trem2*$^{-/-}$ mice compared to WT mice under basal conditions. Further variations were observed in lipopolysaccharide (LPS)-treated *Trem2*$^{-/-}$ mice relative to WT mice, encompassing changes in *Treml1*, *Avp*, *Ccl19*, *Acp5*, and *Mmp9*.[24] Nonetheless, *in vivo* LPS challenge indicated a statistically significant reduction in proinflammatory cytokines such as IL-1, IL-6, and TNF-α in *Trem2*^{R47H} mice, revealing distinct roles of the TREM2 R47H variant compared to *Trem2* knockout.[54]

Divergent effects of TREM2 on inflammation were observed in the context of Aβ pathology. TREM2 overexpression yielded neuroinflammation suppression, reflected in reduced TNF-α, IL-1β, and IL-6 expression in 9-month-old APPPS1 mice following TREM2 upregulation.[11] Furthermore, hippocampal levels of inflammatory factors (IL-6 and TNF-α) in *Trem2*$^{+/-}$ and *Trem2*$^{-/-}$ groups surpassed those in 4-month-old APPPS1-21 mice, with these outcomes remaining gene-dose independent.[45] However, Velocigene-targeted *Trem2* deficiency yielded reduced IL-1 and IL-6, coupled with increased chitinase-like 3/Ym1 and resistin B–like/Fizz1 in 4-month-old APPPS1-21 mice.[21] Dr. Zhou's[59] insights hinted at the potential mediation role of the Toll-like receptor 4 (TLR4)/TREM2 signaling axis, bridging AD and inflammation. Subsequent studies aligned with this notion, revealing that TREM2 activation in IL-4-treated AD mice led to the attenuation of the caspase recruitment domain protein 9(CARD9)-TLR4 pathway. This highlighted TREM2's potential anti-inflammatory effect, suppressing TLR4-mediated pro-inflammatory responses.[60]

A complex interplay emerged in the tau model. TREM2 overexpression in P301S mice reduced the level of several transcripts, including *Tnf-α*, *Il-1β*, and *Il-6*, while elevating microglial M2 phenotype markers like *Arg1*, *Retnla*, *Il-4*, and *Il-10*.[19] This suggests that changes in neuroinflammatory factors may stem from reactive microgliosis. Conversely, the absence of *Trem2* in TauPS2APP mice resulted in higher proinflammatory cytokine levels, including TNF-α, IL-1α, IL-1β, and IL-6.[27] Moreover, *Trem2* haploinsufficiency exacerbated inflammation in tau pathology, evident through increased expression of proinflammatory cytokines TNF-α and IL-1α in 8- to 9-month-old P301S;*Trem2*$^{+/-}$ mice.[29] However, the absence of *Trem2* in 6-month-old PS19 mice yielded decreased expression of inflammatory genes like IL-1β, IL-1α, and TNF-α.[48] No significant disparities were detected in mRNA and protein levels of anti- or pro-inflammation between 6-month hTau;*Trem2*$^{-/-}$ mice and hTau mice.[48]

In summary, diverse studies suggest that TREM2 variably modulates inflammation in amyloid and tau pathology scenarios. Furthermore, the causal relationship between increased inflammatory states and heightened tau

pathology in *Trem2* mouse models remains elusive, warranting further investigation.

Discussion

Our comprehensive systematic review has synthesized findings from *Trem2* mouse models, aiming to elucidate the multifaceted role of TREM2 in AD and address key questions. However, the diverse inquiries posed yielded inconsistent responses, prompting consideration of several intriguing facets.

First, disparities in targeting strategies for constructing mouse models may underlie the observed discrepancies. Remarkably, various *Trem2*$^{-/-}$ models exhibited distinct downstream effects on TREML1 expression. Notably, Velocigene *Trem2*$^{-/-}$ mice displayed over 300-fold elevation in TREML1 expression under basal conditions compared to controls.[24] This aberrant TREML1 upregulation was absent in brain tissues from the Colonna lab or CRISPR/Cas9 *Trem2*$^{-/-}$ models. Furthermore, removal of the floxed neomycin cassette entirely abrogated TREML1 expression in Velocigene *Trem2*$^{-/-}$ mice.[24] This phenomenon was attributed to residual elements within the Velocigene targeting construct, potentially driving downstream gene expression at the endogenous locus. Intriguingly, mounting evidence links elevated TREML1 levels in the brain with reduced AD risk in humans, hinting at a possible protective role in the disease. Additionally, TREML1's potential anti-inflammatory role complicates matters. Given this, in influence of TREML1 complicates the attribution of effects solely to *Trem2*$^{-/-}$ in the Velocigene *Trem2*$^{-/-}$ model. Thus, to avoid misinterpretation, caution is essential when employing Velocigene *Trem2*$^{-/-}$ mice in future studies.

Second, our review highlights that *Trem2* haploinsufficiency and complete *Trem2* loss demonstrated gene- and dose-independent results, implying the existence of compensatory mechanisms.[29] Furthermore, contrasting effects observed between *Trem2*^{R47H} and *Trem2*$^{-/-}$ models on AD pathology and neuroinflammation likely stem from distinct mechanisms. One plausible explanation is that the TREM2 R47H variant disrupts TREM2 expression when endogenous regulatory mechanisms remain intact. Notably, *Trem2* RNA levels were significantly reduced by 42% in *Trem2*$^{+/R47H}$ mice compared to *Trem2*$^{+/+}$ mice, akin to levels observed in *Trem2*$^{+/-}$ mice.[25] Consequently, special consideration should be extended to the *Trem2*^{R47H} mouse model when extrapolating findings to pathological processes in AD patients. Furthermore, verification of these findings in AD patients is imperative.

Additionally, our review suggests a context-dependent nature for TREM2's involvement in AD progression. It appears to be condition-triggered, activated by factors such as brain injury, aging, Aβ, and tau pathology. Basally, TREM2's impact is limited; however, under stimulus, its role becomes disease progression-dependent within the AD context. Its influence varies, ameliorating early disease and exacerbating advanced stages. Reduced TREM2 function impairs microglial response to Aβ deposition, enhances Aβ-induced local neurotoxicity, and intensifies Aβ-triggered tau seeding and propagation. Though TREM2 signaling guards against Aβ-associated cerebral changes, its role may differ in primary tauopathies. AD-associated TREM2 variants amplify AD risk by accentuating Aβ-mediated local toxicity and facilitating tau seeding and spread during early disease phases. However, in advanced stages of the disease and in primary tauopathies with extensive tau pathology, AD-linked TREM2 variants might attenuate tau-mediated synapse loss through reduced microglial synapse phagocytosis. These observations align with a dual-hit hypothesis, where *Trem2* deficiency in microglia preserves normal function but falters when challenged by aging or pathological conditions, such as tauopathy. Hence, it is pivotal to delve further into these initiating factors and their impacts on the disease trajectory. Furthermore, forthcoming studies utilizing conditional *Trem2*$^{-/-}$ mice for temporally controlled *Trem2* depletion, circumventing developmental stages, should hold enhanced insights into TREM2's temporal role during aging and various disease phases.

Comprehending the ligands of TREM2 is pivotal for unraveling its signaling and function. The extracellular domain of TREM2 directly binds to diverse entities, including Aβ[58] and zwitterionic lipids such as LPS and lipoteichoic acids (LTAs),[61] as well as high-density and low-density lipoproteins (HDLs and LDLs) and several apolipoproteins.[62] Among these, APOE stands out as a well-established TREM2 ligand.[36] Notably, lipid dysmetabolism has been identified in *Trem2*$^{-/-}$ mouse models, suggesting that investigating the intricate interplay between lipid metabolism and TREM2 holds promise for future research directions.

Prominent voices within the AD research community have underscored the necessity to transcend reductionist viewpoints and the linear amyloid cascade paradigm. A more holistic comprehension of the disease demands studies that address its intricate cellular context, encompassing the evolving interactions among diverse cell types as the disease unfolds across time and tissues. Fascinatingly, TREM2 may play a pivotal role in the early phase of AD pathogenesis, encompassing the amyloid-induced tau spreading that precedes the tau-linked neurodegeneration stage. In the progression of AD, Aβ aggregation and accumulation in the neocortex extend over 15–25 years before the onset of symptoms, while tau pathology emerges only a few years before cognitive decline. Accordingly, we posit that TREM2-activated microglia engage in Aβ phagocytosis during early disease stages, restraining Aβ-facilitated tau pathology and synaptic phagocytosis during the advanced disease phase. The integration of TREM2 into the AD pathogenesis narrative necessitates further exploration, as it appears to disrupt the Aβ-tau cascade. Investigating this complex interplay over time and across various tissues is imperative, emphasizing the significance of assessing the effects of disease-associated and risk genes on the broader brain network to comprehend causality and develop effective interventions.

In conclusion, this study raises profound questions regarding the therapeutic targeting of TREM2 to address AD. Harnessing antibodies or drugs to stimulate the TREM2

pathway holds promise as a therapeutic strategy for impeding or ameliorating AD progression. However, this review underscores the intricate nature of employing TREM2 as a therapeutic target for AD. Progressing ahead, the identification and establishment of an optimal therapeutic window is paramount. Close monitoring of neurodegenerative stages and AD-relate biomarkers will aid in discerning when to stimulate or inhibit the TREM2 pathway.

Funding

This work was supported by grants from National Natural Science Foundation of China (Nos. 82220108009, 81970996, and 82201568), National Key Research and Development Program of China (No. 2022YFC3602600), STI2030-Major Projects (No. 2021ZD0201801), Young Elite Scientists Sponsorship Program by CAST (No. 2021QNRC001), Beijing Hospitals Authority Innovation Studio of Young Staff Funding Support (No. 202118), and Beijing Nova Program (No. Z211100002121051).

Conflicts of interest

None.

References

1. Rong Z, Cheng B, Zhong L, Ye X, Li X, Jia L, *et al*. Activation of FAK/Rac1/Cdc42-GTPase signaling ameliorates impaired microglial migration response to Aβ(42) in triggering receptor expressed on myeloid cells 2 loss-of-function murine models. FASEB J 2020;34:10984–10997. doi: 10.1096/fj.202000550RR.
2. Serrano-Pozo A, Frosch MP, Masliah E, Hyman BT. Neuropathological alterations in Alzheimer disease. Cold Spring Harb Perspect Med 2011;1:a006189. doi: 10.1101/cshperspect.a006189.
3. Itagaki S, McGeer PL, Akiyama H, Zhu S, Selkoe D. Relationship of microglia and astrocytes to amyloid deposits of Alzheimer disease. J Neuroimmunol 1989;24:173–182. doi: 10.1016/0165-5728(89)90115-x.
4. Jia L, Quan M, Fu Y, Zhao T, Li Y, Wei C, *et al*. Dementia in China: Epidemiology, clinical management, and research advances. Lancet Neurol 2020;19:81–92. doi: 10.1016/S1474-4422(19)30290-X.
5. Strittmatter WJ, Saunders AM, Schmechel D, Pericak-Vance M, Enghild J, Salvesen GS, *et al*. Apolipoprotein E: High-avidity binding to beta-amyloid and increased frequency of type 4 allele in late-onset familial Alzheimer disease. Proc Natl Acad Sci USA 1993;90:1977–1981. doi: 10.1073/pnas.90.5.1977.
6. Pan G, King A, Wu F, Simpson-Yap S, Woodhouse A, Phipps A, *et al*. The potential roles of genetic factors in predicting ageing-related cognitive change and Alzheimer's disease. Ageing Res Rev 2021;70:101402. doi: 10.1016/j.arr.2021.101402.
7. Efthymiou AG, Goate AM. Late onset Alzheimer's disease genetics implicates microglial pathways in disease risk. Mol Neurodegener 2017;12:43. doi: 10.1186/s13024-017-0184-x.
8. Guerreiro R, Wojtas A, Bras J, Carrasquillo M, Rogaeva E, Majounie E, *et al*. TREM2 variants in Alzheimer's disease. N Engl J Med 2013;368:117–127. doi: 10.1056/NEJMoa1211851.
9. Jonsson T, Stefansson H, Steinberg S, Jonsdottir I, Jonsson PV, Snaedal J, *et al*. Variant of TREM2 associated with the risk of Alzheimer's disease. N Engl J Med 2013;368:107–116. doi: 10.1056/NEJMoa1211103.
10. Daws MR, Lanier LL, Seaman WE, Ryan JC. Cloning and characterization of a novel mouse myeloid DAP12-associated receptor family. Eur J Immunol 2001;31:783–791. doi: 10.1002/1521-4141(200103)31:3<783:aid-immu783>3.0.co;2-u.
11. Jiang T, Tan L, Zhu XC, Zhang QQ, Cao L, Tan MS, *et al*. Upregulation of TREM2 ameliorates neuropathology and rescues spatial cognitive impairment in a transgenic mouse model of Alzheimer's disease. Neuropsychopharmacology 2014;39:2949–2962. doi: 10.1038/npp.2014.164.
12. Gawish R, Martins R, Böhm B, Wimberger T, Sharif O, Lakovits K, *et al*. Triggering receptor expressed on myeloid cells-2 fine-tunes inflammatory responses in murine Gram-negative sepsis. FASEB J 2015;29:1247–1257. doi: 10.1096/fj.14-260067.
13. Kobayashi M, Konishi H, Sayo A, Takai T, Kiyama H. TREM2/DAP12 signal elicits proinflammatory response in microglia and exacerbates neuropathic pain. J Neurosci 2016;36:11138–11150. doi: 10.1523/JNEUROSCI.1238-16.2016.
14. Wang Y, Cella M, Mallinson K, Ulrich JD, Young KL, Robinette ML, *et al*. TREM2 lipid sensing sustains the microglial response in an Alzheimer's disease model. Cell 2015;160:1061–1071. doi: 10.1016/j.cell.2015.01.049.
15. Yuan P, Condello C, Keene CD, Wang Y, Bird TD, Paul SM, *et al*. TREM2 haplodeficiency in mice and humans impairs the microglia barrier function leading to decreased amyloid compaction and severe axonal dystrophy. Neuron 2016;90:724–739. doi: 10.1016/j.neuron.2016.05.003.
16. Jay TR, Hirsch AM, Broihier ML, Miller CM, Neilson LE, Ransohoff RM, *et al*. Disease progression-dependent effects of TREM2 deficiency in a mouse model of Alzheimer's disease. J Neurosci 2017;37:637–647. doi: 10.1523/JNEUROSCI.2110-16.2016.
17. Bemiller SM, McCray TJ, Allan K, Formica SV, Xu G, Wilson G, *et al*. TREM2 deficiency exacerbates tau pathology through dysregulated kinase signaling in a mouse model of tauopathy. Mol Neurodegener 2017;12:74. doi: 10.1186/s13024-017-0216-6.
18. Leyns CEG, Ulrich JD, Finn MB, Stewart FR, Koscal LJ, Remolina Serrano J, *et al*. TREM2 deficiency attenuates neuroinflammation and protects against neurodegeneration in a mouse model of tauopathy. Proc Natl Acad Sci U S A 2017;114:11524–11529. doi: 10.1073/pnas.1710311114.
19. Jiang T, Zhang YD, Chen Q, Gao Q, Zhu XC, Zhou JS, *et al*. TREM2 modifies microglial phenotype and provides neuroprotection in P301S tau transgenic mice. Neuropharmacology 2016;105:196–206. doi: 10.1016/j.neuropharm.2016.01.028.
20. Lee CYD, Daggett A, Gu X, Jiang LL, Langfelder P, Li X, *et al*. Elevated TREM2 gene dosage reprograms microglia responsivity and ameliorates pathological phenotypes in Alzheimer's disease models. Neuron 2018;97:1032–1048.e5. doi: 10.1016/j.neuron.2018.02.002.
21. Jay TR, Miller CM, Cheng PJ, Graham LC, Bemiller S, Broihier ML, *et al*. TREM2 deficiency eliminates TREM2+ inflammatory macrophages and ameliorates pathology in Alzheimer's disease mouse models. J Exp Med 2015;212:287–295. doi: 10.1084/jem.20142322.
22. Carbajosa G, Malki K, Lawless N, Wang H, Ryder JW, Wozniak E, *et al*. Loss of Trem2 in microglia leads to widespread disruption of cell coexpression networks in mouse brain. Neurobiol Aging 2018;69:151–166. doi: 10.1016/j.neurobiolaging.2018.04.019.
23. Zheng H, Jia L, Liu CC, Rong Z, Zhong L, Yang L, *et al*. TREM2 promotes microglial survival by activating Wnt/β-catenin pathway. J Neurosci 2017;37:1772–1784. doi: 10.1523/JNEUROSCI.2459-16.2017.
24. Kang SS, Kurti A, Baker KE, Liu CC, Colonna M, Ulrich JD, *et al*. Behavioral and transcriptomic analysis of Trem2-null mice: Not all knockout mice are created equal. Hum Mol Genet 2018;27:211–223. doi: 10.1093/hmg/ddx366.
25. Cheng-Hathaway PJ, Reed-Geaghan EG, Jay TR, Casali BT, Bemiller SM, Puntambekar SS, *et al*. The Trem2 R47H variant confers loss-of-function-like phenotypes in Alzheimer's disease. Mol Neurodegener 2018;13:29. doi: 10.1186/s13024-018-0262-8.
26. Meilandt WJ, Ngu H, Gogineni A, Lalehzadeh G, Lee SH, Srinivasan K, *et al*. Trem2 deletion reduces late-stage amyloid plaque accumulation, elevates the Aβ42:Aβ40 ratio, and exacerbates axonal dystrophy and dendritic spine loss in the PS2APP Alzheimer's mouse model. J Neurosci 2020;40:1956–1974. doi: 10.1523/JNEUROSCI.1871-19.2019.
27. Lee SH, Meilandt WJ, Xie L, Gandham VD, Ngu H, Barck KH, *et al*. Trem2 restrains the enhancement of tau accumulation and neurodegeneration by β-amyloid pathology. Neuron 2021;109:1283–1301.e6. doi: 10.1016/j.neuron.2021.02.010.
28. von Saucken VE, Jay TR, Landreth GE. The effect of amyloid on microglia-neuron interactions before plaque onset occurs independently of TREM2 in a mouse model of Alzheimer's disease. Neurobiol Dis 2020;145:105072. doi: 10.1016/j.nbd.2020.105072.
29. Sayed FA, Telpoukhovskaia M, Kodama L, Li Y, Zhou Y, Le D, *et al*. Differential effects of partial and complete loss of TREM2 on

microglial injury response and tauopathy. Proc Natl Acad Sci USA 2018;115:10172–10177. doi: 10.1073/pnas.1811411115.
30. Jay TR, von Saucken VE, Muñoz B, Codocedo JF, Atwood BK, Lamb BT, *et al*. TREM2 is required for microglial instruction of astrocytic synaptic engulfment in neurodevelopment. Glia 2019;67:1873–1892. doi: 10.1002/glia.23664.
31. Stoiljkovic M, Gutierrez KO, Kelley C, Horvath TL, Hajós M. TREM2 deficiency disrupts network oscillations leading to epileptic activity and aggravates amyloid-β-related hippocampal pathophysiology in mice. J Alzheimers Dis 2022;88:837–847. doi: 10.3233/JAD-210041.
32. Griciuc A, Patel S, Federico AN, Choi SH, Innes BJ, Oram MK, *et al*. TREM2 acts downstream of CD33 in modulating microglial pathology in Alzheimer's disease. Neuron 2019;103:820–835.e7. doi: 10.1016/j.neuron.2019.06.010.
33. Ulland TK, Song WM, Huang SC, Ulrich JD, Sergushichev A, Beatty WL, *et al*. TREM2 maintains microglial metabolic fitness in Alzheimer's disease. Cell 2017;170:649–663.e13. doi: 10.1016/j.cell.2017.07.023.
34. Wang Y, Ulland TK, Ulrich JD, Song W, Tzaferis JA, Hole JT, *et al*. TREM2-mediated early microglial response limits diffusion and toxicity of amyloid plaques. J Exp Med 2016;213:667–675. doi: 10.1084/jem.20151948.
35. Turnbull IR, Gilfillan S, Cella M, Aoshi T, Miller M, Piccio L, *et al*. Cutting edge: TREM-2 attenuates macrophage activation. J Immunol 2006;177:3520–3524. doi: 10.4049/jimmunol.177.6.3520.
36. Parhizkar S, Arzberger T, Brendel M, Kleinberger G, Deussing M, Focke C, *et al*. Loss of TREM2 function increases amyloid seeding but reduces plaque-associated ApoE. Nat Neurosci 2019;22:191–204. doi: 10.1038/s41593-018-0296-9.
37. Vautheny A, Duwat C, Aurégan G, Joséphine C, Hérard AS, Jan C, *et al*. THY-Tau22 mouse model accumulates more tauopathy at late stage of the disease in response to microglia deactivation through TREM2 deficiency. Neurobiol Dis 2021;155:105398. doi: 10.1016/j.nbd.2021.105398.
38. Keren-Shaul H, Spinrad A, Weiner A, Matcovitch-Natan O, Dvir-Szternfeld R, Ulland TK, *et al*. A unique microglia type associated with restricting development of Alzheimer's disease. Cell 2017;169:1276–1290.e17. doi: 10.1016/j.cell.2017.05.018.
39. Qu W, Li L. Loss of TREM2 confers resilience to synaptic and cognitive impairment in aged mice. J Neurosci 2020;40:9552–9563. doi: 10.1523/JNEUROSCI.2193-20.2020.
40. Krasemann S, Madore C, Cialic R, Baufeld C, Calcagno N, El Fatimy R, *et al*. The TREM2-APOE pathway drives the transcriptional phenotype of dysfunctional microglia in neurodegenerative diseases. Immunity 2017;47:566–581.e9. doi: 10.1016/j.immuni.2017.08.008.
41. Ulrich JD, Finn MB, Wang Y, Shen A, Mahan TE, Jiang H, *et al*. Altered microglial response to Aβ plaques in APPPS1-21 mice heterozygous for TREM2. Mol Neurodegener 2014;9:20. doi: 10.1186/1750-1326-9-20.
42. Zhou Y, Song WM, Andhey PS, Swain A, Levy T, Miller KR, *et al*. Human and mouse single-nucleus transcriptomics reveal TREM2-dependent and TREM2-independent cellular responses in Alzheimer's disease. Nat Med 2020;26:131–142. doi: 10.1038/s41591-019-0695-9.
43. Jadhav VS, Lin PBC, Pennington T, Di Prisco GV, Jannu AJ, Xu G, *et al*. Trem2 Y38C mutation and loss of Trem2 impairs neuronal synapses in adult mice. Mol Neurodegener 2020;15:62. doi: 10.1186/s13024-020-00409-0.
44. Fitz NF, Wolfe CM, Playso BE, Biedrzycki RJ, Lu Y, Nam KN, *et al*. Trem2 deficiency differentially affects phenotype and transcriptome of human APOE3 and APOE4 mice. Mol Neurodegener 2020;15:41. doi: 10.1186/s13024-020-00394-4.
45. Cui X, Qiao J, Liu S, Wu M, Gu W. Mechanism of TREM2/DAP12 complex affecting β-amyloid plaque deposition in Alzheimer's disease modeled mice through mediating inflammatory response. Brain Res Bull 2021;166:21–28. doi: 10.1016/j.brainresbull.2020.10.006.
46. Sheng L, Chen M, Cai K, Song Y, Yu D, Zhang H. Microglial Trem2 induces synaptic impairment at early stage and prevents amyloidosis at late stage in APP/PS1 mice. FASEB J 2019;33:10425–10442. doi: 10.1096/fj.201900527R.
47. Fitz NF, Nam KN, Wolfe CM, Letronne F, Playso BE, Iordanova BE, *et al*. Phospholipids of APOE lipoproteins activate microglia in an isoform-specific manner in preclinical models of Alzheimer's disease. Nat Commun 2021;12:3416. doi: 10.1038/s41467-021-23762-0.
48. Gratuze M, Leyns CE, Sauerbeck AD, St-Pierre MK, Xiong M, Kim N, *et al*. Impact of TREM2R47H variant on tau pathology-induced gliosis and neurodegeneration. J Clin Invest 2020;130:4954–4968. doi: 10.1172/JCI138179.
49. Song WM, Joshita S, Zhou Y, Ulland TK, Gilfillan S, Colonna M. Humanized TREM2 mice reveal microglia-intrinsic and -extrinsic effects of R47H polymorphism. J Exp Med 2018;215:745–760. doi: 10.1084/jem.20171529.
50. Claes C, Danhash EP, Hasselmann J, Chadarevian JP, Shabestari SK, England WE, *et al*. Plaque-associated human microglia accumulate lipid droplets in a chimeric model of Alzheimer's disease. Mol Neurodegener 2021;16:50. doi: 10.1186/s13024-021-00473-0.
51. Yang Y, Wu X, Qu X, Wang X, Luo C, Li L, *et al*. The effect of triggering receptor expressed by myeloid cells 2 modified bone marrow mesenchymal stem cells on Alzheimer's disease-mouse model. Ann Clin Lab Sci 2019;49:23–30.
52. McQuade A, Kang YJ, Hasselmann J, Jairaman A, Sotelo A, Coburn M, *et al*. Gene expression and functional deficits underlie TREM2-knockout microglia responses in human models of Alzheimer's disease. Nat Commun 2020;11:5370. doi: 10.1038/s41467-020-19227-5.
53. Jiang T, Tan L, Zhu XC, Zhou JS, Cao L, Tan MS, *et al*. Silencing of TREM2 exacerbates tau pathology, neurodegenerative changes, and spatial learning deficits in P301S tau transgenic mice. Neurobiol Aging 2015;36:3176–3186. doi: 10.1016/j.neurobiolaging.2015.08.019.
54. Cheng Q, Danao J, Talreja S, Wen P, Yin J, Sun N, *et al*. TREM2-activating antibodies abrogate the negative pleiotropic effects of the Alzheimer's disease variant Trem2(R47H) on murine myeloid cell function. J Biol Chem 2018;293:12620–12633. doi: 10.1074/jbc.RA118.001848.
55. Preuss C, Pandey R, Piazza E, Fine A, Uyar A, Perumal T, *et al*. A novel systems biology approach to evaluate mouse models of late-onset Alzheimer's disease. Mol Neurodegener 2020;15:67. doi: 10.1186/s13024-020-00412-5.
56. Ellwanger DC, Wang S, Brioschi S, Shao Z, Green L, Case R, *et al*. Prior activation state shapes the microglia response to antihuman TREM2 in a mouse model of Alzheimer's disease. Proc Natl Acad Sci U S A 2021;118:e2017742118. doi: 10.1073/pnas.2017742118.
57. Frank S, Burbach GJ, Bonin M, Walter M, Streit W, Bechmann I, *et al*. TREM2 is upregulated in amyloid plaque-associated microglia in aged APP23 transgenic mice. Glia 2008;56:1438–1447. doi: 10.1002/glia.20710.
58. Zhao Y, Wu X, Li X, Jiang LL, Gui X, Liu Y, *et al*. TREM2 is a receptor for beta-amyloid that mediates microglial function. Neuron 2018;97:1023–1031.e7. doi: 10.1016/j.neuron.2018.01.031.
59. Zhou J, Yu W, Zhang M, Tian X, Li Y, Lü Y. Imbalance of microglial TLR4/TREM2 in LPS-treated APP/PS1 transgenic mice: A potential link between Alzheimer's disease and systemic inflammation. Neurochem Res 2019;44:1138–1151. doi: 10.1007/s11064-019-02748-x.
60. Qin Z, Gu M, Zhou J, Zhang W, Zhao N, Lü Y, *et al*. Triggering receptor expressed on myeloid cells 2 activation downregulates toll-like receptor 4 expression and ameliorates cognitive impairment in the Aβ1-42 -induced Alzheimer's disease mouse model. Synapse 2020;74:e22161. doi: 10.1002/syn.22161.
61. Kawabori M, Kacimi R, Kauppinen T, Calosing C, Kim JY, Hsieh CL, *et al*. Triggering receptor expressed on myeloid cells 2 (TREM2) deficiency attenuates phagocytic activities of microglia and exacerbates ischemic damage in experimental stroke. J Neurosci 2015;35:3384–3396. doi: 10.1523/JNEUROSCI.2620-14.2015.
62. Hakola HP. Neuropsychiatric and genetic aspects of a new hereditary disease characterized by progressive dementia and lipomembranous polycystic osteodysplasia. Acta Psychiatr Scand Suppl 1972;232:1–173.

How to cite this article: Yin YS, Yang HC, Li RY, Wu GS, Qin Q, Tang Y. A systematic review of the role of TREM2 in Alzheimer's disease. Chin Med J 2024;137:1684–1694. doi: 10.1097/CM9.0000000000003000