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Dual Role of TREM2 in 5xFAD Alzheimer's Disease Mouse Models: Implications for Targeting Strategies

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Abstract:

This review explores the dual role of TREM2 (Triggered Receptor Expressed on Myeloid cells 2) in the 5xFAD Alzheimer's disease (AD) mouse model and its potential implications for targeted therapeutic strategies. TREM2, a key regulator of microglia, exhibits complex dual effects of neuroprotection and neurotoxicity in AD pathogenesis. In recent years, with deepening insights into AD pathogenesis, TREM2's roles in Aβ clearance, metabolic homeostasis maintenance, and inflammatory regulation have garnered increasing attention. However, TREM2 may exhibit diametrically opposed functions across different disease stages and activation states, posing challenges for targeted therapies. This paper systematically elucidates TREM2's protective role in the 5xFAD model (e.g., promoting Aβ clearance, maintaining neuronal function) alongside its potential harmful effects (e.g., driving pathological inflammation), and analyzes the mechanisms underlying its dual roles (e.g., disease stage dependency, activation level dependency). Based on existing research, this paper further summarizes the challenges facing TREM2-targeted therapies and explores novel strategies for precisely regulating TREM2 function, providing theoretical foundations and directions for future AD treatments.

Keywords: TREM2; 5xFAD model; Alzheimer's disease; microglia; targeted therapy.

1. Background:

Alzheimer's disease (AD) is the most prevalent neurodegenerative disorder in contemporary society. Its hallmark pathological features include senile plaques formed by β-amyloid (Aβ) deposition, neurofibrillary tangles resulting from hyperphosphorylated tau protein, and persistent chronic neuroinflammation[4][5][10] . Within the complex AD pathological network, the innate immune system, particularly the brain's resident immune cells microglia, play a pivotal role. They serve not only as Aβ scavengers but also as major sources of inflammatory cytokines, and the precise regulation of their functional state decisively impacts neuronal survival and synaptic plasticity[55] .

Among the numerous molecules regulating microglial function, Triggering Receptor Expressed on Myeloid cells 2 (TREM2) has garnered significant attention in recent years. Human genetic studies indicate that rare coding mutations in TREM2 (e.g., R47H) represent a strong risk factor for late-onset AD, with an effect comparable to the APOE ε4 allele. This directly positions innate immune dysregulation at the core of AD pathogenesis. As a key immune receptor on the surface of microglia, TREM2 profoundly influences the pathological progression of AD by regulating cellular phagocytosis, metabolism, proliferation, and survival. In preclinical studies, particularly in the 5xFAD transgenic mouse model capable of simulating early and rapid Aβ deposition in AD, targeting TREM2 has been regarded as a highly promising therapeutic strategy[18].

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However, as research deepens, the role of TREM2 in AD reveals astonishing complexity, far beyond simple categorizations of "protective" or "harmful." Substantial evidence indicates that TREM2 function exhibits significant context-dependence. For instance, in 5xFAD mice, TREM2 deletion or loss-of-function mutations (e.g., R47H) typically impair microglial phagocytosis and clearance of Aβ plaques, leading to increased plaque burden and exacerbated neurotoxicity—demonstrating its neuroprotective aspect[35] . Paradoxically, however, other studies suggest TREM2-dependent microglial activation may drive pathological inflammation and even exacerbate synaptic damage and tau pathology under specific conditions, exhibiting potential neurotoxicity.[23][42] . This "dual role" places TREM2-targeted therapies in a dilemma: should its function be agonized or antagonized?

In my view, the critical scientific question in this field now is: 'How can we integrate these seemingly contradictory findings to understand the underlying mechanisms behind TREM2's dual role? 'Does its functional switch follow specific patterns related to disease stage, activation level, or cell specificity? Answering these questions is crucial for transforming TREM2 from a promising target into a safe and effective therapeutic strategy. Therefore, this review aims to systematically examine the dual evidence of neuroprotection and neurotoxicity exhibited by TREM2 in the classic AD mouse model 5xFAD, delving into the context-dependent mechanisms of its action. Building on this foundation, we will further explore how these insights from basic research provide critical theoretical underpinnings and developmental directions for future precision strategies in TREM2-targeted therapies—including intervention timing, dose control, and patient stratification.

2. Biological Functions of TREM2 and Research Context in AD

2.1 Structure, Ligands, and Downstream Signaling Pathways (e.g., DAP12/SYK) of TREM2

TREM2 is a transmembrane receptor expressed on myeloid cells, featuring an extracellular immunoglobulin-like domain, a transmembrane domain, and an intracellular tail. TREM2 activates downstream signaling pathways upon ligand binding. DAP12 (DNAX Activator Protein 12), acting as a key adaptor protein, recruits and activates SYK (Spleen Tyrosine Kinase) via its immunoreceptor tyrosine-containing motif (ITAM), thereby initiating intracellular signaling cascades[20]. In the context of Alzheimer's disease (AD), TREM2 ligands include amyloid-β (Aβ) oligomers and apoptotic neuronal debris. Binding of these ligands triggers the DAP12/SYK pathway, regulating inflammatory responses and phagocytic functions in microglia[18]. Studies indicate that the TREM2-R47H mutant exhibits signaling defects in AD mouse models, leading to altered downstream gene expression. For instance, in 5xFAD/Trem2R47H mice, glial cells show diminished responses to plaques, highlighting the importance of TREM2 structural integrity for its signaling pathway function[21] . Furthermore, spatial transcriptomics analysis revealed that TREM2 mutations independently affect neuronal expression of BDNF and Ntrk2, irrespective of amyloid pathology, further underscoring the central role of the TREM2-DAP12/SYK axis in AD pathology[22] .

2.2 TREM2-Mediated Microglial Functions: Phagocytosis, Migration, Metabolic Reprogramming, and Survival

TREM2 plays multiple roles in microglial function, including phagocytosis, migration, metabolic reprogramming, and cell survival. In AD, TREM2-dependent microglia become activated and aggregate around amyloid plaques, clearing Aβ through phagocytosis and thereby reducing pathological burden. For example, in the 5xFAD mouse model, TREM2 overexpression enhances microglial phagocytic capacity and reduces plaque burden, whereas the TREM2-R47H mutation impairs phagocytosis and diminishes plaque-associated microglial reactivity[21]8]) . Regarding migration, TREM2 promotes microglial movement toward lesion sites. However, in Trem2-/- mice, monocyte-derived macrophages (MDMs) exert cognitive-enhancing effects via TREM2-independent pathways, highlighting TREM2's specificity in cell migration[23] . Regarding metabolic reprogramming, TREM2 modulates glial energy metabolism to adapt to the AD environment. In TREM2-R47H mutant models, glia exhibit suppressed inflammatory responses and unique interferon-related gene profiles, indicating altered metabolic pathways. Regarding survival functions, TREM2 signaling supports microglial survival under stress conditions, whereas mutants cause functional loss and increased axonal injury—as evidenced by synaptic loss and elevated neurofilament light chain levels in Trem2R47H NSS mice[24] .

2.3 Genetic Association of TREM2 in AD and Its Expression Dynamics

The genetic association of TREM2 with AD has been extensively studied, with the R47H missense mutation emerging as a strong risk factor for late-onset AD. This mutation causes partial or complete loss of TREM2 function, impairing microglial responses to amyloid plaques[25]. In human AD, glial reactivity is diminished in TREM2 carriers (e.g., R47H and R62H) compared to non-carriers, indicating TREM2's necessity in AD pathology[6]. Regarding expression dynamics, TREM2 exhibits age- and disease-dependent changes in AD mouse models and humans[2]. For example, in 5xFAD/Trem2R47H mice, reduced TREM2 expression during early disease stages (4 months) impaired glial-plaque interactions and suppressed inflammation, whereas late stages (12 months) exhibited distinct interferon signatures and persistent tissue damage.Single-cell RNA sequencing reveals that TREM2-dependent disease-associated

microglia (DAM) are activated in AD, but species-specific differences exist between humans and mice, with human AD microglia exhibiting an IRF8-driven reactive phenotype[6] . Furthermore, metabolomic analyses demonstrate that TREM2 mutations impact serum and brain metabolites, such as reduced glycerophospholipids in APOE ε4 carriers, further underscoring the critical role of TREM2 expression dynamics in AD pathological progression[8][12][26] .

3. Characteristics of 5xFAD Mouse Model and Its Value in TREM2 Research

3.1 Pathological Phenotype of 5xFAD Mice: Rapid and Significant Aβ Deposition with Neuroinflammation

The 5xFAD transgenic mouse model is currently one of the most important models for studying the pathological mechanisms of Alzheimer's disease (AD). Its most prominent feature is the rapid and significant accumulation of β-amyloid (Aβ) plaques accompanied by neuroinflammation. This model overexpresses five familial AD mutations (Swedish, Florida, London, etc.) in the human APP and PSEN1 genes, leading to Aβ plaque deposition as early as 2 months of age, accompanied by glial cell activation and synaptic dysfunction[28][29][33] . Concurrently, A β deposition in these mice predominantly localizes to the cerebral cortex and hippocampus, primarily as soluble Aβ1-42, closely mirroring the pathological features observed in human AD patients. Furthermore, this model exhibits pronounced neuroinflammatory responses, including activation of microglia and astrocytes, alongside upregulation of inflammatory cytokines such as IL-1β and TNF-α[31] . These pathological alterations provide an ideal platform for investigating TREM2's role in Aβ clearance and neuroinflammation regulation. For instance, in the 5xFAD background, TREM2 deficiency or mutations (e.g., R47H) significantly impair microglial phagocytosis and clearance of Aβ plaques, leading to increased plaque burden and exacerbated neurotoxicity[27][30].

3.2 Advantages and Limitations of This Model in TREM2 Function Studies

The 5xFAD mouse model offers unique advantages for TREM2 research but also presents certain limitations. Its strengths are primarily reflected in the following aspects: First, the rapid and reproducible progression of Aβ pathology in 5xFAD mice facilitates the assessment of TREM2's temporal regulation of microglial function within a short timeframe. For instance, studies reveal that the TREM2-R47H mutation in 5xFAD mice impairs microglial plaque phagocytosis, accompanied by synaptic damage and cognitive decline[8][21] . Second, this model permits investigation of TREM2-dependent or -independent immunoregulatory pathways via gene editing or pharmacological interventions (e.g., PD-L1 blockade). For example, myeloid-derived macrophages (MDMs) in TREM2-deficient 5xFAD mice still improve cognition via non-TREM2-dependent pathways, suggesting avenues for novel immunotherapies[32] . However, this model has limitations: 1) its aggressive Aβ pathology does not fully mirror the slow progression of human AD; 2) The TREM2-R47H mutation's phenotype in mouse models may be influenced by background genes or splicing variants. For instance, reduced protein expression in certain Trem2R47H models due to cryptic splicing can confound functional analyses. Thus, model specificity must be carefully considered when interpreting experimental results[34][6] .

4. Neuroprotective Role of TREM2 in 5xFAD Models

4.1 Promoting Aβ Clearance and Enhancing Plaque Encirclement: Mechanisms and Experimental Evidence

TREM2 exhibits significant plaque clearance in the 5xFAD model by regulating microglial phagocytosis of Aβ. Studies indicate that TREM2 knockout leads to increased Aβ deposition in the brains of 5xFAD mice, accompanied by neuronal loss and cognitive deterioration. Conversely, pharmacologically activating CARD9, a downstream signaling molecule of TREM2, significantly promotes Aβ plaque clearance[35] . Single-cell transcriptomic analysis further reveals that TREM2 deficiency alters the phagocytic capacity of microglia toward Aβ, manifested as abnormal expression of genes related to lipid metabolism (e.g., Fth1, Pcsk1n)[17]18])([6 . Furthermore, CNS overexpression of TREM2 via hematopoietic stem cell transplantation reduced Aβ aggregation and improved memory function, providing direct evidence for TREM2-targeting therapeutic strategies[36] .

4.2 Maintaining Glial Cell Metabolic Homeostasis and Survival Capacity

TREM2 maintains microglial homeostasis by regulating energy metabolism pathways, such as the FXR/RXR and LXR/RXR signaling pathways. Metabolomics studies revealed significant lipid metabolism disorders in the brains of 5xFAD mice, particularly abnormalities in glycerophospholipid and sphingolipid metabolism, which TREM2 activation partially reversed. In TREM2 knockout models, microglia exhibited mitochondrial dysfunction and increased oxidative stress, leading to impaired phagocytic capacity. Notably, treatment with the TREM2 ligand LSL60101 upregulates Trem2 gene expression while reducing levels of the microglial activation marker Iba-1, indicating that TREM2 enhances microglial survival and function by maintaining metabolic homeostasis[17][18][37] .

4.3 Alleviating Synaptic Toxicity and Enhancing Synaptic Plasticity

The neuroprotective effects of TREM2 also manifest

in the maintenance of synaptic structure. In the 5xFAD model, TREM2 activation significantly increases the expression of postsynaptic density protein 95 (PSD95) and synaptophysin, suggesting its ability to mitigate Aβ-mediated synaptic toxicity[38] . Mechanistically, TREM2 indirectly protects synaptic function by suppressing neuroinflammation (e.g., reducing GFAP-positive astrocytic reactivity) and decreasing tau hyperphosphorylation[18][39][40] . Behavioral studies confirm that the TREM2 agonist LSL60101, when combined with donepezil, significantly improves cognitive deficits and social behavioral abnormalities in 5xFAD mice. This effect is closely associated with the restoration of synaptic plasticity[41].

5. Neurotoxic Role of TREM2 in the 5xFAD Model

5.1 Driving Disease-Associated Microglia (DAM) Phenotype and Pro-inflammatory Factor Release

In the 5xFAD mouse model, TREM2 significantly promotes the phenotypic transition to disease-associated microglia (DAM) by regulating microglial activation status. Studies indicate that TREM2 deficiency reduces microglial phagocytic capacity toward Aβ plaques while enhancing the release of proinflammatory factors (e.g., IL-1β, TNF-α)[23] . Single-cell RNA sequencing data further revealed that in hippocampal microglia of 5xFAD and TREM2 knockout (T2KO) mice, expression of inflammation-related genes (e.g., Ttr, Fth1) was significantly upregulated and closely associated with activation of acute phase response signaling pathways (e.g., FXR/RXR, LXR/RXR pathways). This pro-inflammatory microenvironment may exacerbate neuroinflammation, thereby accelerating AD pathology progression[42] .

5.2 Glial Dysfunction and Neuronal Injury

TREM2 dysfunction disrupts microglial homeostasis, manifesting as abnormal synaptic pruning and neuronal injury. In the 5xFAD model, TREM2-deficient microglia fail to efficiently clear Aβ deposits while releasing neurotoxic substances (e.g., reactive oxygen species) that directly damage surrounding neurons. Experimental evidence indicates that hematopoietic stem cell transplantation overexpressing TREM2 significantly reduces Aβ aggregation and improves cognitive function in 5xFAD mice. This effect correlates with a shift in the microglial phenotype toward anti-inflammatory properties, evidenced by decreased Iba-1 levels and upregulation of Trem2 expression. Furthermore, recovery of synaptic markers (e.g., PSD95, synaptin) further confirms TREM2's role in protecting neurons by regulating microglial function[12][21][38] .

5.3 Potential Mechanisms That May Exacerbate Pathological Progression (e.g., Association with Tau Pathology)

The neurotoxic effects of TREM2 may synergistically exacerbate AD pathology through multiple mechanisms. First, TREM2 deficiency promotes abnormal phosphorylation of tau protein, consistent with the worsening tau pathology observed in the 5xFAD model. Second, metabolomic analysis revealed dysregulation of glycerophospholipid and sphingolipid metabolism in 5xFAD mouse brains, while TREM2 may influence Aβ-Tau interactions by regulating lipid metabolism (e.g., APOE4-associated pathways)[8][12][13][43] . Furthermore, the association between TREM2 and the CARD9 signaling pathway suggests it may indirectly promote tau pathology through innate immune responses (e.g., complement activation)[35] . These findings provide a mechanistic explanation for TREM2's "double-edged sword" role in AD, where its dysfunction may simultaneously drive a vicious cycle of both Aβ and tau pathology.

6. Integrative Analysis of Dual Roles: Contradiction and Unity

6.1 Disease Stage Dependence: The Hypothesis of Early Protection and Late Harmfulness

The dual role of TREM2 in Alzheimer's disease (AD) exhibits distinct disease stage dependency. In early AD, TREM2 exerts neuroprotective effects by promoting phagocytosis and clearance of Aβ plaques by microglia. Studies indicate that in 5xFAD/-TREM2-R47H mice at 4 months of age, partial TREM2 dysfunction leads to reduced glial-plaque interaction, accompanied by suppressed inflammation but increased axonal injury, suggesting that insufficient early TREM2 activation may accelerate neurodegeneration[18] . However, in the late disease stage (12 months), the same model regained the ability of microglia to interact with plaques. Yet, persistently elevated neurofilament light chain (NfL) levels and synaptic loss indicate that TREM2 dysfunction may become detrimental.[44][48] . This dynamic shift parallels observations in atherosclerosis research—where TREM2 promotes lipid uptake (increasing lesion volume) in early plaques while enhancing macrophage survival to stabilize plaques in later stages[17] . This stage dependency suggests TREM2-targeted therapies require precise timing of intervention.

6.2 The "Golden Range" Hypothesis of Activation Level: Moderate Activation is Beneficial, Excessive Activation is Harmful

TREM2 function exhibits a classic "U-shaped curve" characteristic. In the 5xFAD mouse model, both complete TREM2 deficiency (TREM2-/−) and haploinsufficiency (TREM2+/−) result in impaired microglial response to Aβ plaques. However, the latter exhibits a unique disease-associated microglial (DAM) gene expression profile intermediate between wild-type and knockout mice. Notably, the TREM2-R47H variant exhibits enhanced NLRP3 inflammasome activation in vitro but fails to improve cognitive deficits in vivo, suggesting that overactivation may trigger harmful inflammatory responses[45][46] . Single-cell RNA

sequencing further revealed that the TREM2 agonist antibody hT2AB restored TREM2-R47H mouse cell cycle and interferon-responsive microglial subpopulations, whereas excessive activation in wild-type mice led to gender-differentiated response saturation[47] . Collectively, these data support the existence of a TREM2 activation "sweet spot," whose boundaries may be determined by microenvironmental ligand concentrations and feedback regulation of downstream signaling pathways (e.g., the IL-1β/IL-1RN axis)[23] .

6.3 Impact of Experimental Variables on Results (Genetic Manipulation Methods, Mouse Age, etc.)

Contradictory conclusions regarding TREM2 function across laboratories may stem from methodological differences. First, genetic manipulation methods significantly influence phenotypes: traditional TREM2-R47H models exhibit reduced protein expression due to alternative splicing, whereas TREM2-R47H NSS models maintain normal expression levels yet display age-dependent phenotypes. Second, mouse age is a critical variable—4-month-old TREM2-R47H NSS mice exhibit synaptic protection, whereas 12-month-old mice show LTP deficits[48] . Moreover, background strain differences cannot be overlooked: in the 5xFAD background, TREM2 overexpression reduced plaque burden but failed to improve cognition, while the benefits of CD33 knockout were completely lost in TREM2-deficient mice, demonstrating genetic background modulation[49] . Spatial transcriptomics further revealed that TREM2-R47H independently upregulates the cortical neuronal BDNF/TrkB pathway irrespective of Aβ pathology. This cell-type-specific effect may be obscured in whole-tissue analyses[15][22] . These factors underscore the necessity for stringent experimental controls and multi-omics approaches to decipher cell-specific responses when interpreting TREM2 studies.

7. Potential Strategies, Challenges, and Implications for TREM2-Targeted Therapy

7.1 Current Primary Strategies: TREM2 Agonists/Antagonists and Signaling Pathway Modulation

Current TREM2-targeted therapeutic strategies primarily focus on developing agonists or antagonists to modulate its downstream signaling pathways. Research indicates that TREM2 plays a critical role in Alzheimer's disease (AD) by regulating microglial phagocytosis of amyloid plaques and inflammatory responses. For instance, in the 5xFAD mouse model, TREM2 overexpression reduces plaque burden and improves cognitive function, whereas the R47H mutation causes partial functional loss manifested as impaired plaque-associated microglial reprogramming[6][7] . Agonist strategies aim to enhance TREM2 activity, such as by binding TREM2 with antibodies or small-molecule drugs (e.g., FDA-approved Carpipramine, Clocapramine) to stabilize its conformation and promote signaling[51] . Antagonists are used to suppress excessive inflammatory responses; for instance, targeting TREM2 in the tumor microenvironment reverses immunosuppression[52] . However, TREM2's complex regulatory mechanisms—such as its interaction with the TLR4/NF-κB pathway—require precise intervention to avoid off-target effects or signaling pathway imbalances[23][50] .

7.2 Core Insights from the 5xFAD Model: Critical Importance of Therapeutic Time Window and Dose Precision

The 5xFAD mouse model reveals the time-window and dose-dependent critical roles of TREM2 intervention. Studies show that administering TREM2 agonists in the early disease stage (e.g., 4 months of age) significantly reduces plaque burden and dendritic atrophy, whereas late-stage intervention (12 months) yields limited effects and may exacerbate synaptic damage due to chronic inflammation. For example, Trem2R47H NSS mice exhibited impaired microglia-plaque interactions and suppressed inflammation in early stages, but developed a distinct interferon-related gene signature and synaptic loss in later stages[48] . Furthermore, inappropriate dosing may induce paradoxical effects: low-dose agonists may fail to activate microglia, while high doses may cause excessive inflammation or off-target toxicity[23] . These data underscore that clinical translation requires dynamic monitoring of treatment response using biomarkers (e.g., plasma NfL levels) and individualized protocol adjustments based on disease staging[44][48] .

7.3 Key Challenges in Clinical Translation (e.g., biomarker development, blood-brain barrier penetration, and patient stratification)

The clinical translation of TREM2-targeted therapies faces multiple challenges. First, biomarker development requires breakthroughs: although TREM2, Axl, and galectin-3 correlate with pathological progression in AD mouse models, their dynamic changes and specificity in human AD remain to be validated[53] . Second, blood-brain barrier (BBB) permeability remains a major bottleneck limiting drug delivery. For instance, the antibody AL002 may have demonstrated limited efficacy in the INVOKE-2 trial due to insufficient BBB penetration. Small-molecule drugs (such as Pimozide identified through virtual screening) or nanocarrier technologies may offer potential solutions[54] . Finally, patient stratification must account for genetic heterogeneity: TREM2 R47H carriers exhibit markedly different microglial reactivity compared to wild-type patients, and APOE ε4 status may further modulate treatment response[8][12][13] . Future studies should integrate multi-omics data (e.g., single-cell spatial transcriptomics) to refine patient subtyping and explore synergistic effects of combination therapies (e.g., TREM2 agonists with Aβ-clearing antibodies).

8. Conclusions

From an expert perspective, the dual role of TREM2 in the 5xFAD Alzheimer's disease (AD) mouse model reveals its complex dynamics in disease progression. As an initial defense against Aβ pathology, TREM2 demonstrates neuroprotective potential in early stages by promoting microglial clearance of Aβ plaques; however, under specific conditions, it may transition into a driver of chronic inflammation, exacerbating neurodegeneration. This context-dependent behavior underscores the dynamic nature of TREM2 function rather than a simple binary opposition.

Balancing perspectives and findings across studies reveals that while some support TREM2 activation as a therapeutic strategy, others caution against its potential risks—such as excessive activation triggering harmful inflammatory responses. This divergence stems from variations in experimental conditions, disease stages, and models—such as time-dependent changes observed in the 5xFAD model. Consequently, future TREM2-targeted therapies must transcend simple activation or inhibition, evolving into a "fine-tuning art" that precisely calibrates intervention timing, dosage, and patient context. This demands integrating multi-omics data with clinical observations to unravel TREM2's dynamic immunoregulatory mechanisms in AD.

Collectively, TREM2 research offers novel avenues for precision immunotherapy in AD, yet its success hinges on profound insights into functional dynamics. By integrating basic research with clinical practice, we may develop personalized intervention strategies to ultimately improve outcomes for AD patients.

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