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The Characteristics and Function of Disease-Associated Microglia Related to Alzheimer's Disease

Ruining Zhang

School of Medicine, Shanghai Jiaotong University, Shanghai, China
nicole-20240303@outlook.com

Abstract. Microglia is the brain's innate immune cells that is closely related to various neurodegenerative diseases including Alzheimer's disease (AD). Traditional nomenclature has characterized microglia polarization by binary M1/M2 frameworks. But recent attention has shifted to a newly defined activated microglial state called disease-associated microglia (DAM). Studies have found these DAM to exhibit opposing effects on AD pathogenesis, participating in both inflammatory and protective processes in the brain. This review explores the definition of DAM and their complicated molecular and functional features in AD progression. It also addresses recent findings on TREM2 in mediating DAM activation and polarization. Finally, we will briefly mention common therapeutic targets based on DAM to cure AD.

Keywords: Alzheimer's disease, microglia, TREM2, neurodegeneration, therapy

1. Introduction

Alzheimer's disease (AD) is a progressive and irreversible neurodegenerative disease that is the primary cause of dementia worldwide, placing great challenges on global health conditions [1, 2]. To answer the question of what exactly is AD, several key pathological hallmarks must be mentioned. These hallmarks were previously concluded by researches, including the extracellular deposition of amyloid-beta (Aβ) plaques and the intracellular aggregation of hyperphosphorylated tau proteins, which will form neurofibrillary tangles (NFTs) [3]. Statistics revealed the incidence of AD to double every five years after the age of 65, with the average disease duration ranging from 8 to 10 years [4]. This long-lasting course of disease raises economic burdens worldwide and impairs people's quality of life. Consequently, the growing epidemiological burden, along with the lack of successful curing options drive ongoing and innovative efforts of research across various fields, ranging from basic molecular mechanisms to preclinical interventions and the development of novel therapeutic strategies [5].

In this content, a set of parenchymal residents referred to as microglia exhibit prominent significance in the development and maintenance of the central nervous system (CNS). Such brain residents were previously defined as a subset of phagocytes. Yet this perspective is greatly widened by advancing experiments up to date. It is now believed that microglia are highly versatile cells capable of adapting both morphologically and functionally to its surrounding environment [6]. Microglia play a critical and multifaceted role in the pathogenesis and progression of AD, mediating

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both detrimental neuroinflammatory responses and potentially beneficial amyloid-beta (Aβ) clearance and synaptic support [7]. Understanding the intricate interactions between microglia and the core pathological hallmarks of AD—Aβ plaques and tau protein tangles—is crucial in facilitating effective therapeutic interventions [8].

While microglia as the brain's resident immune cells is significant in maintaining the homeostasis of the central nervous system (CNS), their activation state shifts significantly in AD and other similar neurodegenerative disorders. Using comprehensive single-cell RNA analysis of AD mouse model, Keren-Shaul et al. first described a novel subset of microglia associated with neurodegenerative diseases, defined as DAM, which was characterized by a unique gene expression signature distinct from homeostatic microglia [9]. Emergence of DAM as critical players in the pathophysiological processes of AD have announced themselves potential targets for therapeutic designing. Further investigations are urgently needed to unravel the molecular pathways of DAM transition and activation, as well as their interactions with critical pathologic hallmarks of AD. Here, we will discuss the unique definition of DAM as opposed to traditional nomenclature based on microglial function and its geographical and functional characteristics in Alzheimer’s disease.

2. DAM: beyond M1 and M2 polarization

Early 2000s saw a rise in immunological studies aiming to classify microphages based on findings using in vitro models. A model describing two opposing states of macrophage activation was depicted: M1 as the classic activated pro-inflammatory and potentially neurotoxic state, and M2, an alternative activated state usually considered anti-inflammatory or neuroprotective [10, 11]. Associated with this M1/M2 phenotyping, the term M0 was used to reflect a homeostatic or resting state of microglia related to TGF-β signaling [12]. These quiescent microglia roam the CNS, constantly extending and retracting their processes to monitor neural tissue for damage, pathogens, or abnormal protein aggregates, which when sensed, stimulate a M0 transition to either M1 or M2, induced by different cytokines stimuli [13, 14].

M1 polarization is potentially mediated by pathogens, damage-associated molecular patterns (DAMPs), or pro-inflammatory cytokines (IFN-γ, TNF-α, LPS), after which, these M1 produce reactive oxygen species (ROS), nitric oxide (NO), and pro-inflammatory cytokines such as interleukin (IL)-1β, IL-16 and chemokines, including the C-C motif chemokine ligand 2 (CCL2), to allow protection against injurious stimuli and recruitment of removal cells to clear pathological agents [15, 16]. Although M1 polarization is seemingly a neuron-protective mechanism against pathogens, prolonged neuroinflammation may result in neurotoxicity, leading to neurodegeneration [17]. In contrast, diverse M2 microglia are induced by anti-inflammatory cytokines (IL-4, IL-10, IL-13) before immunocomplexes ligate their Fc receptors, followed by activation of peroxisome proliferator-activated receptor gamma (PPARγ) by fatty acids and liver X receptor (LXR) by oxysterols [18, 19]. M2 promote resolution of inflammation by secreting neurotrophic factors (BDNF, NT, GDNF) and enhancing synaptic remodeling with growth factors (IGF-1, FGF, CSF1), as well as removing cellular debris and apoptotic cells [16].

While the M1/M2 classification has served as a useful framework for characterizing microglial polarization in vitro, accumulating evidence have also suggested this binary paradigm to oversimplify the dynamic and heterogeneous nature of microglial activation in vivo. For instance, the M1 and M2 dichotomy does not take into consideration myeloid that are senescent or proliferating [20, 21]. High-resolution single-cell transcriptomic analyses together with functional characterization studies have uncovered that microglia adopt a spectrum of intermediate or mixed activation states in physiological and pathological conditions. These diverse activation profiles are

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likely the result of their spatial and temporal interactions with microenvironmental signals. Such context-dependent functional adaptations cannot be fully described by traditional M1/M2 categorization [22-25]. This shift in understanding draws attention to the need for more subtle frameworks that better account for the functional diversity of microglia in either health or disease states, such as multi-dimensional polarization states or disease-specific microglial subtypes.

With the use of single-cell transcriptomics, studies have identified Disease-associated microglia (DAM) as a unique activated state manifesting distinct transcriptional and functional traits that can react to AD pathology [9]. DAM was initially discovered in a mouse model carrying five AD-related mutations known as 5XFAD mice [26]. Further investigations have drawn more attention to these newly recognized microglia subtypes by justifying similar expression patterns in other AD murine models as well as in human AD patients [27]. DAM features change dynamically according to environmental cues like amyloid-β plaques and tau pathology, which allow them to step outside the classical M1/M2 paradigm. Molecular analysis of DAM reviewed that these cells retain the expression of core microglial markers like Iba1, Cst3, and Hexb, but downregulate homeostatic genes such as P2ry12, P2ry13, Cx3cr1, CD33, and Tmem119 [12]. At the same time, DAM presents coordinated upregulation of multiple gene clusters, especially those encoding APOE, TREM2, SPP1, and other components of lysosomal, phagocytic, and lipid metabolic pathways. These changes in expression include several well-known AD risk genes (Apoe, Ctsd, Lpl, Tyrobp, Trem2), suggesting these microglial alterations to both result from and contribute to AD progression through impaired protein clearance and dysregulated lipid metabolism [28, 29].

Since microglial polarization is highly dependent on their interactions with the surrounding microenvironment, studies on DAM in varied environmental stimuli may help construct a better understanding of their characteristics. Further researches must also focus on DAM in other neurodegenerative diseases, as similar molecular expression patterns have been observed across various conditions including AD, Amyotrophic lateral sclerosis (ALS) and Multiple sclerosis (MS) [9, 22, 30, 31].

3. TREM2-dependent DAM activation dynamics: a potential rescue to AD pathology

A set of triggering receptor expressed on myeloid cells 2 (TREM2) abundantly found on activated microglia have caught the attention of DAM researches since rare allelic variants of R47H in TREM2 conferred 3- to 4-fold increased risk of sporadic AD incidence in mice, with human R47H mutations transferred into 5XFAD conveying similar impaired microglia function [27, 32-34]. Results have identified the switch of microglia from a homeostatic state to DAM in AD to progress through two distinct but sequential molecular phases: an initial TREM2-independent triggering phase followed by TREM2-dependent functional maturation, with theories claiming stage 1 to be the prerequisite of stage 2 [29]. The first phase involves detection of pathological stimuli (Aβ aggregates, neuronal debris) through pattern recognition receptors (TLRs, CD36) leading to decreased regulation of homeostatic markers (P2RY12, CX3CR1, TMEM119) and enhancement of early response genes (Apoe, SPP1, CST7), initiating microglial migration toward amyloid plaques while maintaining limited phagocytic capacity [35, 36]. Yet, the basic molecular mechanisms of step 1 are still not clear. The subsequent TREM2-dependent phase, activated by sustained exposure to lipid-associated damage signals, drives complete transcriptional reprogramming characterized by upregulated lysosomal (CTSD, HEXB), phagocytic (TYROBP), and lipid metabolism (LPL, LIPA) pathways, resulting in the fully differentiated DAM phenotype with enlarged amoeboid morphology and enhanced but often dysfunctional phagocytic activity—a transformation strongly linked to AD genetic risk loci and representing a maladaptive response to chronic neurodegeneration [37-39].

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Nonetheless, the actual role of TREM2 in the transition from step 1 to step 2 is not fully understood, though researchers have hypothesized TREM2's proliferative function to act through β-catenin, PI3K, and mTOR pathways [40-42].

TREM2 interacts with diverse ligands, including phospholipids, sulfatides, and apolipoproteins such as APOE, as well as lipoprotein particles (e.g., HDL and LDL). Since these ligands are often exposed on apoptotic or damaged cell surface, it may be inferred that TREM2 act as a crucial step in mediating phagocytosis, cellular clearance and homeostasis [43]. Other studies have identified TREM2 to be capable of ligating APOE, both of which are major genetic risk factors for late onset AD [44-47]. To evaluate the characteristics of TREM2-APOE binding, one comprehensive biolayer interferometry analysis concluded that their engagement is likely mediated by protein instead of lipidation [48]. Because APOE have several isoforms, differences in affinity indicated that APOE4 generally ligate stronger than APOE3 and APOE2 [48, 49]. And since APOE4 exacerbates amyloid plaques deposition in brain, this difference in TREM2 binding affinity may be a reason why DAM exhibit opposing and complicated results on AD pathology [50-53].

After TREM2 was bind by ligands, downstream signals and molecular pathways were then examined by investigators. They have reached a consensus stating DAM engulfment of Aβ to be achieved through engagement of both spleen tyrosine kinase (SYK)-dependent and SYK-independent signaling pathways. Further structural and functional analyses confirmed that apart from lipoproteins such as APOE, TREM2 directly binds to oligomeric amyloid-beta (oAβ) and other Aβ aggregates, initiating microglial migration towards Aβ plaques and subsequent phagocytosis [54, 55]. Notably, APOE lipidation can improve the efficiency of Aβ uptake by microglial through enhancing its binding to TREM2, as well as promoting the ligation of Aβ and APOE, low-density lipoprotein (LDL) or clusters [47].. Upon ligand binding, TREM2 recruits SYK through its adaptor protein DAP12, which will then initiate downstream signaling cascades that promote microglial activation, phagocytosis, and plaque encapsulation. SYK-dependent pathways are critical for triggering key inflammatory and cytoskeletal remodeling processes, facilitating microglial migration toward Aβ deposits and their subsequent containment. However, TREM2 also mediates Aβ responses independently of SYK, likely through alternative signaling intermediates such as PI3K/AKT or MAPK pathways, which regulate microglial survival, metabolic reprogramming, and cytokine production. These SYK-independent mechanisms may help maintain homeostasis of microglial function even under circumstances where SYK signaling is disrupted [56].

A crucial role of the TREM2-DAM axis is the phagocytosis and clearance of Aβ plaques, which is a critical process in Alzheimer's disease pathogenesis. TREM2 signaling enhances microglial capacity to recognize, engulf, and degrade Aβ deposits like oligomeric Aβ (oAβ) and fibrillar plaques. Studies demonstrated that TREM2 upregulation accelerates amyloid reduction in AD mouse models, while its deficiency or dysfunction leads to impaired plaque clearance and increased Aβ burden [40, 57-61]. A key mechanism underlying this process involves TREM2-mediated recognition of externalized phosphatidylserine (ePtdSer), an "eat-me" signal exposed by dystrophic neurons surrounding Aβ plaques. Microglia migrate toward these plaques via TREM2-dependent pathways, where TREM2-ePtdSer interactions promote efficient Aβ phagocytosis [62, 63]. Conversely, impaired TREM2 function, such as in the AD-associated R47H variant, disrupts its binding to ePtdSer, compromising microglial engulfment of Aβ debris and exacerbating plaque accumulation [64]. Intriguingly, in addition to engulfing plaques which after enveloped can stay stable for weeks, works have also demonstrated DAM to be capable of condensing or compacting these Aβ fibrils [65]. These results have shown TREM2 as a pivotal regulator of DAM-mediated Aβ clearance, with therapeutic implications for enhancing microglial phagocytic function in AD.

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Beyond its critical role in Aβ phagocytosis, TREM2 signaling engages in a broad spectrum of microglial responses to amyloid pathology, including proliferation, migration, lifespan, and metabolic reprogramming [57, 66]. TREM2-mediated survival signaling sustains microglial populations at lesion sites and their continued engagement in plaque clearance and inflammatory modulation. Also, it is involved in brain homeostasis maintenance by recognizing and clearing apoptotic neurons with cellular debris, a process particularly essential in AD, where neuronal death is a prominent pathological feature [67-70]. These findings collectively underscore that functional TREM2 on disease-associated microglia is crucial for mitigating the consequences of neuronal apoptosis in AD by ensuring timely removal of cellular debris and limiting neurotoxic inflammatory cascades that could exacerbate neurodegeneration.

4. Are DAM beneficial, detrimental, or both

Apart from TREM2, multiple molecular mechanisms regulate DAM activity. An AD risk factor known as transmembrane receptor CD33 is downregulated 3-fold during DAM activation. The rs3865444C polymorphism in its promoter region increases CD33 expression and AD risk, whereas loss-of-function variants (rs3865444A and rs12459419T) that disrupt CD33 splicing are protective [71, 72]. These findings highlight the suppression of CD33 function to importantly mitigate AD pathology. Similarly, another AD-associated receptor named MS4A6A is 4-fold downregulated in DAM. Notably, MS4A6A expression are elevated in all of its risk variants, suggesting that impaired downregulation in microglia may contribute to dysfunctional DAM [73]. Additionally, genes that downregulated during the homeostatic-to-DAM transition such as protective mutations in BIN1, PICALM, and PLCG2, further support the role of DAM-associated gene suppression in neuroprotection [74-76]. These examples reveal a striking pattern: loss-of-function mutations in DAM-upregulated genes are positively correlated with an increased risk of Alzheimer's disease, while gain-of-function mutations in DAM-downregulated genes heighten susceptibility to AD. These findings seem to point to the hypothesis that these disease- related myeloid cells serve as a protective response against AD pathology as a form of innate immunity [29].

However, further investigations have found DAM more sophisticated than previously thought. In terms of Aβ phagocytosis and tau pathology, TREM2-dependent microglial activation seems to have opposed effects. Some studies state that TREM2 deficiency seems to eliminate plaque-associated CD45hiLyC+ myeloid cells, resulting in reduced neuroinflammation and AD pathology [77, 78]. While other studies found enriched processes on TREM2-expressing microglia that extend specifically to Aβ plaques, claiming that these processes allow DAM to mediate Aβ condensation into amyloid deposits. Indeed, microglial activation via the NLRP3 inflammasome has been shown to promote Aβ accumulation through triggering a distinct inflammatory cascade that results in IL-1β release and generation of ASC specks. These large polymeric complexes bind directly to Aβ plaque cores, accelerating plaque deposition [79-81]. These findings indicate that microglial recognition of Aβ may paradoxically enhance its accumulation, creating a feed-forward loop in AD pathogenesis. Targeting the dual role of TREM2-DAM, recent research discovered that TREM2 deficiency initially reduced amyloid pathology in young APP/PS1-21 mice, before paradoxically exacerbating amyloid deposition at later disease stages. Furthermore, TREM2 loss impaired plaque-associated myeloid cell accumulation in aged mice by suppressing their local proliferation [82].

Compared with Aβ, the influence of TREM2-dependent DAM on pure tau-mediated neurodegeneration, which characterizes later AD stages, remains less clear, with conflicting findings depending on the different mouse model and specific environmental context. Enhancing TREM2 expression is discovered to modestly alleviate soluble phosphorylated tau protein levels in a PS19

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tauopathy mouse model [83]. Additional TREM2 agonism with a monoclonal antibody is also capable of attenuating tau-related-pathology and neurodegeneration, suggesting that active TREM2 signaling can mitigate tau-related damage [84]. Other researches also indicate that TREM2 deficiency can exacerbate tau pathology, accelerating both hyperphosphorylation and accumulation of tau protein in humanized tauopathy mouse models, likely spreading tau proteins through microglial exosomes [85, 86]. Conversely, some findings suggest that TREM2 deficiency might attenuate tau accumulation or spreading. One study found that the TREM2 R47H variant or germline knockout of Trem2 can reduce microglial proliferation within ranges of Aβ plaques and facilitate the depositing and spreading of tau aggregates, indicating a role for TREM2 in limiting peri-plaque tau pathologies [87]. While studies examining TREM2's role in pure tau pathology have yielded inconsistent results, research on Aβ-induced tau spreading has consistently demonstrated that TREM2-dependent DAM activation plays a crucial protective role. Specifically, TREM2 signaling appears essential for delaying amyloid β-mediated propagation of tau pathology [88]. This protective function is further supported by evidence showing that TREM2 deficiency in amyloid/tau double-transgenic mouse models exacerbates tauopathy, concluding microglial TREM2 to be significant in mitigating Aβ-driven tau pathogenesis [81]. Thus, theories have proposed the role of TREM2-dependent microglial activation in AD to be complex and possibly stage-dependent. Aβ may trigger a neuroprotective DAM phenotype switching that limits both amyloid fibril deposition and tauopathy in early disease progression, while at later stages, chronic inflammation and TREM2 overactivation could drive DAM dysfunction and transformation to a neurotoxic (pro-inflammatory) state, exacerbating disease progression [16, 89-91].

Another defining feature of neurodegenerative and neuroinflammatory disorders is synaptic loss due to neuronal damage, disrupting microglia-neuron axis and provoking a heterogenous microglial reaction [92]. Studies indicate that neuronal hyperexcitability in initial stages of AD promotes synaptic dysfunction, with disease-associated microglia exacerbating this condition through phagocytic activity [62]. Evidence have revealed that synaptic engulfment by DAMs is mediated by key molecules known as “eat-me” signals such as complement complex or component C1q and CX3CR1-CX3CL1 axis. These signals will mark those synapses that need removal. Later, microglia expressing complement receptors will engulf these tagged synapses [93-96]. Opposed to “eat-me” molecules, “don’t eat me” signals are also critical in regulating synaptic pruning. Their expression levels are often down-regulated in neurodegenerative diseases. Signal regulatory protein α (SIRPα) is one example of these signals that recognizes clusters of differentiation 47 (CD47) [97]. Its reduced microglial expression in AD impairs CD47 signaling and leads to enhanced phagocytosis of synapses [98]. This abnormal clearance and pruning worsens synaptic pathology and aggravates cognitive decline in AD [99].

5. DAM as potential therapeutic targets of AD

As we mentioned above, the various and diverse properties of DAM make them ideal targets in treating Alzheimer’s disease as well as other neurodegenerative disorders. Currently, many pharmacological and molecular drugs were designed to modulate DAM activity and function. One novel drug is minocycline which is a tetracycline derivative that has anti-inflammatory properties. This drug has shown promising effects in enhancing microglial activation, which is hypothesized to work through suppressing pro-inflammatory cytokines [100]. Apart from this, the discovery of AD-related TREM2 risk variants suggested that regulating TREM2 function could be a possible therapeutic strategy [47]. Though adverse side-effects are still not quite clear, experiments using agonistic TREM2 antibodies have presented their abilities in preventing the shedding and

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crosslinking of cell-surface TREM2 [58, 61, 101-103]. Another group of experiments have focused on interfering with lipid metabolism from a dietary point of view. Several preclinical trials have confirmed that ω-3 polyunsaturated fatty acid (PUFA) supplements, such as docosahexaenoic acid (DHA) and eicosapentaenoic acid (EPA), are capable of alleviating AD pathology in postmenopausal women and older adults with mild cognitive impairment [104, 105].

While targeting DAM has shown great prospects in AD therapy, we still know little about the fundamental molecular characteristics of DAM. To perfect out therapeutic strategies, future researches may need to design drugs that target DAM or AD more precisely. For instance, drugs that promote anti-inflammatory DAM activation while inhibiting their counterparts, or antibodies that target AD-specific DAMs without altering other microglia. Likewise, it is also important to study DAM in different neurodegenerative disorders to visualize their differences. Apart from designing treatment targets, DAM may work as early diagnostic markers or prognostic indicators. Finally, it is necessary to describe in vivo DAM networks to better understand their role within the AD microenvironment to construct fundamental basis for further investigations.

6. Concluding remarks

In mediating Alzheimer's disease pathogenesis, disease-associated microglia have outgrown the traditional M1/M2 polarization framework to reveal a more dynamically-regulated activation state. Their unique transcriptional feature marked by downregulation of homeostatic genes and upregulation of phagocytic, lysosomal, and lipid metabolic pathways, make them both neuroprotective and neuroinflammatory.

Contributing to the complexity of microglial responses to AD pathology, the TREM2-dependent activation of DAM occurs in two sequential phases. TREM2's interaction with APOE and Aβ mediates its role in Aβ clearance, tau propagation and microglial survival. However, DAM function is double-edged: while they contribute to Aβ clearance and limit tau pathology in early stages, chronic activation may drive neuroinflammatory cascades and exacerbate neurodegeneration in advanced disease.

In such aspects, DAM represent a potential and promising therapeutic target for AD through pharmacological and molecular approaches, as well as modulating related lipid metabolisms. These measurements hold great potential for slowing disease progression and improving cognitive outcomes. Key questions remain, including the molecular triggers of the initial TREM2-independent phase, the stage-specific shifts in DAM function, and the impact of genetic variability (e.g., APOE isoforms, TREM2 variants) on their plasticity. Addressing these questions could unlock therapeutic avenues—such as targeted modulation of DAM-specific pathways—to enhance protective functions while dampening neurotoxicity. Further research into DAM dynamics, signaling networks, and genetic regulators will be critical to translating these insights into effective treatments for AD.

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