Review

Microglia-Associated Neuroinflammation in Alzheimer's Disease

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Review

Microglia-Associated Neuroinflammation in Alzheimer's Disease

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Abstract: Background: Neuroinflammation has long been implicated in the progression of amyloid beta (Aβ) accumulation and the decline of cognitive function in Alzheimer's disease (AD). Currently, many transcription factors, downstream signaling pathways, and molecular mechanisms that regulate the polarization of microglia have been explored. Furthermore, microglia may also exert a complex role in AD through the transformation of Aβ plaques or debris clearance, reflected in Aβ phagocytosis. One of the mediators of neuroinflammation in AD is the activated microglia. Therefore, the regulation of microglial function may be the key to successfully treating AD. Methods: This is a review article. PubMed, Embase, Scopus, and research meeting abstracts were searched up to 2024 for studies of microglia and neuroinflammation in Alzheimer's Disease. Systematic information retrieval was performed and appropriate studies were isolated based on important information available in the studies. The information from each of the articles was understood and extracted to form a database. Results: The similar neuropathological results between several animals and AD cases show the possibility to implement microglia-related changes as an earlier diagnostic marker for AD in humans. The gene sets identified in various transcriptomic studies further foster this avenue of research by offering potential targets for therapeutic development. Multiple studies suggest that microglia-associated neuroinflammation at a special stage could also be protective, and therefore, intervention should be delicate so that a beneficial response is retained. Conclusion: The phenotype balance between A1 (toxic) and A2 (safe) microglial phenotypes to toxic illness in AD has become a hot research topic at present. Substantial evidence, both in vitro and in vivo, has suggested that the loss of the normal A2 phenotype and the activation of toxic A1 microglia contribute to neurodegeneration in AD. Promoting or restoring the polarization of microglia towards the A2 phenotype may thus represent an effective therapeutic strategy for ameliorating neuroinflammation and progressive neurocognitive impairments.

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1. Introduction

The most prevalent kind of dementia is AD, whose incidence is expected to nearly quadruple globally and nearly double in Europe by 2050 [1]. The primary pathogenic characteristic of AD is thought to be brain atrophy, which is marked by the buildup of amyloid plaques and neuronal fibrillary tangles as well as the loss of neurons and synapses. Over the past few decades, drug discovery and clinical development have been challenged with failures, and today, some AD-related costs exceed the costs associated with cancer, cardiovascular diseases, and dementia [2,3]. The leading plaque hypothesis speculates that Aß plaques result in the hyperphosphorylation of Tau, white matter damage, and AD pathogenesis. However, amyloid-based targets have repeatedly failed in clinical trials, as recently reviewed. In part, the controversial outcomes might be due to the downstream Tau-based pathways being considered, though many questions related to Tau and its role in neurodegeneration in patients remain unanswered [4,5]. In recent years, it has become clear that neuroinflammation also plays a crucial role in the progression of the illness. High levels of long-term inflammation act as a driver for entanglement with AD [6,7]. Introduction to AD is the most

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commonly observed neurodegenerative condition, characterized by impairments in memory, language, decision-making, and behavioral changes. The histopathological hallmarks of AD include extracellular beta (Aß) plaques and the intracellular accumulation of hyperphosphorylated Tau protein, which form neurofibrillary tangles (NFT). The disturbing rapid rise in the worldwide incidence and prevalence of AD has been linked to an aging population, and AD is now the sixth-leading cause of death in the United States, with approximately 5.7 million Americans diagnosed with AD. Without effective treatments, the number of AD patients is anticipated to soar to 14 million people by 2050, with an annual cost of over 1 trillion US dollars [8–10].

The most documented cytological and molecular signs typical of AD include the activation of pro-inflammatory microglia associated with senile Aβ plaques, extracellular deposition of these peptides, neurofibrillary tangles into living neurons, and dystrophic dendritic and synaptic structures. There are also a number of mutations in the microglial equipping factors that were identified in amyloid-overproducing mice, which determines the role of microglial in the Aβ clearance system in the brain [11,12]. They are mainly involved in Aβ catabolism, TNF release, oxidative stress, and neurofilament breakdown. It is known that Aβ phagocytosis is managed mainly by CD11b, CD68, ApoE, and PPARɣ receptors. Associations between microglia and other AD-induced pathogenetic markers, especially those associated with σ receptors, are examined rarely. Although neuroinflammation occurs in the final stage of this pathology, microglial activation can cause an inflammatory response, leading to severe neurodegeneration with Aβ [13,14]. A significant number of studies have reported that inflammation is associated with the severity of such lesions in humans and animal models. AD is a chronic and frequently terminal disease of the human central nervous system (CNS) and the leading cause of dementia worldwide. The two main pathological features of this disease are the presence of beta-amyloid (Aβ) plaques in the brain and neurofibrillary tangles (NFTs) originating from the hyperphosphorylation of tau [15,16]. However, recently, much data have been published showing that pro-inflammatory microglia were also present in various brain areas affected by amyloidosis, which suggests that neuroinflammation is also an essential component of AD-associated pathology. Despite a large amount of studies on neuroinflammation in AD, the data obtained indicate both a pathological exacerbation of pro-inflammatory conditions and the need for the potential beneficial role of microglial in the system of AD therapy [17,18].

2. Pathophysiology and Neuroinflammatory Mechanisms

In response, infiltrated peripheral immune cells follow similar activation patterns of microglia and begin to produce immune signals, amplify the immune response, dismantle the damaged tissue, and help maintain the structural and functional integrity of the brain. Thereafter, anti-inflammatory signals are produced to temper the pathological process, engaging the resolution and repair phases [19,20]. Remarkable progress has been made in these consequences of gene expression analysis, which may help us identify specific modification patterns and corresponding function changes. However, failure of the resolution phase can cause overproduced pro-inflammatory substances to spread further from the original damaged site, promoting widespread synaptic or cytotoxic neurodegenerative changes, cytokine production, pathological protein accumulation, mitochondrial dysfunction, and reduced phagocytic capacity, amplifying the detrimental impact of protective responses and making them compatible with the pathogenesis and progression of neurodegenerative disorders [21,22]. Microglia account for 10 to 15% of the total cells of the brain and they play a crucial role in brain development, homeostasis, plasticity, and repair. In normal conditions, microglia exhibit a ramified and long motile resting phenotype, which continuously scan the microenvironment to promptly detect pathogen-derived signals [23]. When activated by pathogens or other endogenous signals, these cells rapidly change their cell body and retract their processes, becoming amoeboid and releasing pro-inflammatory molecules (cytokines and chemotactic factors, such as interleukin-1, interleukin-6, tumor necrosis factor, and interferon-gamma and chemokines) to recruit other cells like microglia, astrocytes, and T-cells to the site of inflammation [24]. Furthermore, complement protein activation is an important link between the brain and immune system activation.

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3. Role of Microglia in Neuroinflammation

In addition to the pathological M1-like type, the homeostatic signature of microglia is often downregulated as well, resulting in dysregulation of anti-inflammatory M2-like microglia. Under lipopolysaccharide (LPS) stimulation and amyloid burden conditions, M2 markers like TREM2, CD206 and IGF-1 diminish progressively, altering the function of microglia in apoptosis and neuron survival. In a transgenic AD mouse model, Oliveira and colleagues found mRNA expression of TNF-α to be more than 2-fold higher in the over-activated microglia than in the anti-inflammatory microglia [25]. However, the gene transcription of M2-like molecules including CNTF, IGF-1 and TGFB1 remains unchanged in the anti-inflammatory microglia. Strikingly, knocking down TREM2 expression in microglia and tau propagation process pleads for the crucial role of the M2-like type [26]. Its absence leads to substantial injury exacerbation in the prefrontal cortex, hippocampus and amygdala. Moreover, a specific mutation in TREM2 like R47M has been found to limit amyloid plaque clearance in AD [27]. As the resident immune cell in the central nervous system, microglia perform a wide spectrum of physiological activities to ensure the normal function of the neural network. They contribute not only to the axon outgrowth and synaptic pruning during neurodevelopment, but also to apoptosis regulation and cytokine drainage in the healthy brain. In most neurodegenerative diseases including AD, microglia become over-activated and acquire a phenotype distinct from the anti-inflammatory microglia [28]. The conversion process from homeostatic to activated microglia in response to biotic and abiotic insults has been conceptualized as M1/M2 activation. Upon primary phagocytic role, M1-like microglia release high levels of cytotoxic factors including ROS and NO which are toxic to the surrounding neurons. Moreover, their excessive secretion of pro-inflammatory mediators like IL-1β, IL-6, TNF-α and TGF-β will further stimulate the over-activation of nearby microglia, astrocytes and microvascular endothelial cells [29,30]. Consequently, the vicious cycle between microglia and their neural microenvironment accelerates the disease progression.

3.1. Microglia: Definition and Functions

Are there ways in which microglial responses can be positively engaged to protect the brain in acute, chronic, and progressive states consensually conceived to involve and even initiate neurodegenerative sequelae? It seems not entirely clear that the mere presence of microglia potentiate cognitive dysfunction [31]. However, it seems more clear that when microglial participation in what is obviously an inflammatory reaction is heightened beyond what is necessary, in classically activated states reflecting injury responses unique to the CNS milieu that resides separately from traditional inflammatory initiators as it continually has throughout life, such reactive states may overrepresentation of neuroinflammation, excess soluble NFTs, increased pTau, and decreased synaptic density leading to a reduction in cognitive functions paramount to neurological burdens during ongoing crises in essence exacerbated by aggressive inflammatory threat as much as disorder can contribute to central commerce hindering maximum efficacy [32]. An ongoing knowledge that informed clockwork existence of microglia maintaining homeostasis is the goal, but research investment directed at countering only excessive chronic activation of microglia without regard to what demonstrable stimuli can be echoed by means of directed polarization and subsequent protective maintenance seems like driving a car whilst learning about its function with only the intention of understanding failure [33]. That investors in the technology of the future are simultaneously well in excellent supply of exacting information gained by taking conversations at large with small molecules located deep within microglial dark space. It only seems logical any future purpose should be directed as much towards conversation gestation from experienced wisdom attendant to specific cell responses [34]. Each will effectively enable the larger homeostatic need, abrogating systematic breakdown as contented cell automation toward revalued functionality masculine. Microglia are the resident immune cells of the brain. They compose about 10-15% of the cells in the adult brain, play a crucial role in maintaining tissue homeostasis, and contribute to immune responses during infection or injury [35]. Vocal for essentially all neurobiologists are confrontations to carefully document and interpret the potential participation of microglia in changes

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seen in experimental paradigms. Ongoing microglia research contributes to our understanding of natural microglial function (NMF) in the spectrum of host responses in contexts such as behavior, plasticity, aging, and disease, in the community of other nonneuronal cells of the CNS [36].

3.2. Activation of Microglia in Alzheimer's Disease

Research has indicated that the control of the microglial phenotype is mostly dependent on the interaction between chemicals produced by the surrounding cells and pattern recognition receptors (PRRs) [37]. To affect the microglial phenotype in AD, these PRRs may detect Aβ, other damage-associated molecular patterns (DAMPs), or pathogen-associated molecular patterns (PAMPs) [38]. When microglia are activated, they respond more readily to different stimuli that cause inflammation or harm. The signaling through PRRs may cause an inflammatory response and proinflammatory cytokine secretion once the microglia have sensed the DAMPs and PAMPs through toll-like receptors (TLRs), retinoic acid-inducible gene-I (RIG-I)-like receptors (RLRs), nucleotide-binding oligomerization domain (NOD)-like receptors (NLRs), or other PRRs [39]. These stimulated microglia are commonly referred to as disease-associated microglia (DAM). Furthermore, it has been demonstrated that microglia are activated by Aβ binding, specifically to TLR4. Scavenger receptors (SRs), TLRs, triggering receptors in myeloid cells 2 (TREM-2), CD14, CD47, Fcγ receptors (FcηRs), CD200 receptor (CD200R), and receptor for advanced glycation end products (RAGE) are the primary receptors produced by activated microglia [40–42]. To be more precise, fAβ-stimulated microglial activation requires CD14, TLR2, and TLR4, albeit it is yet unknown what molecular pathways control this activation. Nevertheless, the prolonged stimulation of TLR2 and TLR4 in microglia may trigger the release of Aβ, which makes this persistent activation of microglia harmful [43]. The maintenance of microglial metabolism appears to depend on TREM2 signaling, and TREM2 impairment affects microglial migration, phagocytosis, and survival. Furthermore, TREM2's modest activation has been demonstrated to have anti-inflammatory properties by preventing the proinflammatory response triggered by TLR4 receptors [44]. TREM2's function in the inflammatory process is still up for debate, though. For instance, AD-Tau injections into amyloidosis-affected mice's brains to cause Aβ-dependent Tau deposition shown that TREM2 regularly triggered microglia and exacerbated neurodystrophy and Tau pathology. Moreover, fibrils, APPS, and other Aβ peptides are also strong microglia activators [45]. In AD pathogenesis, the PRRs bind to various forms of Aβ with varying affinities to start glial cell activation, which leads to an increase in the number of microglia and ultimately their density [46]. Additionally, Aβ may bind to the surface of microglia and activate NF-KB-dependent pathways that in turn activate the pathways of extracellular signal-regulated kinase (ERK) and mitogen-activated protein kinase (MAPK), which in turn induce the production of proinflammatory genes. In the postmortem brain of AD patients, even after the Aβ plaque growth ends, the density of microglia is increased linearly and positively correlated with NFTs burden, as consistently observed in the non-amnesic AD variant of primary progressive aphasia, according to an autopsy study of the temporal neocortex in 15 control subjects without dementia and 91 AD patients. Contrary to previous research, Wnt-3a activation in primary microglia may encourage microglia to enter the proinflammatory state of Alzheimer's disease [47,48]. Moreover, the intraperitoneal injection of exogenous interfering substances, such as lipopolysaccharides (LPS), in 5×FAD and APP23 mice results in the hyperresponsiveness of the microglia around the thick core plaque. The activation of microglia triggered by inflammation, which is caused by overactivated microglia, has garnered growing attention to investigate the molecular mechanisms governing the microglial phenotypic differences due to its important biological value [49,50]. Table 1 summarizes the microglia receptors associated with AD.

Table 1. Microglia receptors associated with Alzheimer's disease (AD).

Model system	Receptor	Role in AD pathogenesis
APP/PS1 mice	TLR2	TLR2 activation inhibition results in increased Aβ accumulation, compromised recognition, and elevated neuroinflammation [51]

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AD-TLR2KO	TLR2	Neurobehavioral function deteriorates and white matter damage is exacerbated by TLR2 genetic deletion [52]
TLR4M Tg mice	TLR4	In comparison to TLR4W Tg mice, TLR4 mutations lower the Ab-induced IL-1b, CCL3, and CCL4 expressions in monocytes; Aβ deposition and soluble Aβ42 are increased in the brains of TLR4M Tg mice, and IL-1b, CCL3, and CCL4 expressions are decreased in cognitive function and the hippocampus [53]
TLR4w AD mice and TLR4m AD mice	TLR4	Microglia activation and upregulation-control of cytokines reliant on TLR4 [54]
Human neurons	NLRP1	By activating Casp1 and Casp6, NLRP1 inflammasomes, which are expressed in human central nervous system neurons, contribute to axonal degradation and cognitive impairment [55]
NALP3-deficient mice	NLRP3	Involved in tissue proteinase B release and lysosomal degradation; triggers inflammation and tissue damage in AD [56]
APP/PS1 mice	NLRP3	Encouragement of M2 phenotype conversion in microglia and decrease in Aβ deposition [57]
TREM2-WT) or TREM2-R47H	TREM2	Minimization of Aβ seeding and suppression of microglia linked to illness [58]
TREM2 KO and WT C57BL/6J	TREM2	Tau transport, dispersion, and seeding via microglial cell exosomes are enhanced by TREM2 loss [59]
Primary astrocytes and microglia	CD200	Prevents the glutamate toxicity response and microglial activation caused by meth [60]
CD200 +/+ and CD200 −/− mice	CD200	MPTP experimental mouse model [61]
C57BL/6 mice	CD32	Induce proinflammatory signaling [62]

4. Neuroinflammatory Signaling Pathways in Alzheimer's Disease

The neuroinflammatory hypothesis that long-term microglial-mediated sterile inflammation plays a key role in the pathogenesis of neurodegenerative diseases has become increasingly convincing. Continuous and excessive production of neurotoxic molecules such as cytokines and chemokines could have disastrous effects [63]. Initial alterations in the specificity and concentration of endogenous molecules activate astrocytes and microglia. Consequently, microglia could amplify the inflammation cascade and switch from their beneficial and defensive effects, leading to chronic and irreversible neuronal damage [63]. In fact, a large number of inflammation-related genes were found to have a differential expression and functional responses in people with AD, suggesting that the risk of AD is likely to be attributed to the cumulative effects of multiple genotypes connected to the immune response [64,65]. Considering that virtually all AD lesions involve an immune response, it is critical to explore the neuroinflammatory signaling pathways in AD, which will provide insight into subcellular and functional alterations in the brain under neuroinflammatory conditions [66]. Thus, the purpose of this review is to provide a comprehensive picture of the microglia-mediated innate immune signaling pathways as a guide for driving the study of therapeutic strategies to regulate the neuroinflammatory response and prevent AD [67]. The findings may also guide us to maintain remyelination in the brain parenchymal the way they do. In neurodegenerative diseases such as AD, chronic inflammation in the brain and increased expression of pro-inflammatory factors are associated with the brain's innate immune cells: microglia [68]. Microglia are important innate immune system cells in the central nervous system (CNS). Neuronal and CNS-constituted cell abnormalities and death can activate microglia. Activated microglia can secrete inflammatory factors,

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including chemokines and pro-/anti-inflammatory cytokines. Normally, microglia protect the brain by eliminating waste materials and dead or dying nerve cells. However, in response to acute and trauma-induced brain injury, extensive overreaction of microglia and excessive release of inflammatory factors can damage healthy cells and cause a neurological deficit [69]. Describing the neuroinflammatory signaling pathways could contribute to a comprehensive understanding of how brain stress or injury alters microglial functioning and to the development of potential targets for controlling microglial overactivation and breaking the dormant state, thus offering therapeutic solutions for neurodegenerative or brain stress-associated diseases [70].

5. Therapeutic Approaches Targeting Microglia and Neuroinflammation

The continuous failure of therapeutic attempts in AD as a result of the complexity of underlying multimechanistic pathways is made obvious by the additive detrimental effect of targeting trigger-activated microglia only in a solitary way. In regard to the clinical staging of AD, the chronological intervention of microglia arrest and inhibition differentially requires applied techniques that meet the particular requirements of the AD stage [71]. The later stage of blocking detrimental microglia effects may be beneficial in terms of recovery and interaction with the very toxic deposit substance, as long as the presence of plaques inhibits synaptic function or facilitates other mediator pathways such as tau hyperphosphorylation [72]. The resulting over-protective environment directly leads to neurodegenerative events and ultimate cognitive function. This summary focuses on the paradoxical role of reactive microglia in AD since these cells possess both protective and harmful properties in the progression of the AD disease state [73]. Any therapeutic experimental strategy to regulate or modulate the interaction of amyloid beta and microglia should consider such complex pathways. Concerning neuroprotection, rebellious microglia in turn directly contribute to systemic neuroinflammation or cells from different lineages that are involved in multiorgan organ failure. Therefore, novel approaches to a selective therapy must be adequately considered well before an effective therapeutic regime is applied [75]. AD is a chronic age-related neurodegenerative condition characterized by an accumulation of extracellular amyloid plaques, composed of fibrillar β-amyloid (Aβ) peptide, in specific brain regions. An imbalance between the production of toxic aggregates and their clearance leads to a protracted retention of Aβ fibers, and their accumulation around neurons may cause cellular impairment, neuroinflammation, and eventually cell death [76,77]. To date, there are no effective therapies that halt or reverse progressive memory loss or brain dysfunction in AD. This review will focus on the involvement of microglia in AD pathology and the influence of microglia activation towards Aβ and tau neuropathology [78]. The current therapeutic strategies targeting microglia and controlling neuroinflammation in the AD brain will be summarized, including both classical and alternative treatments focused on Aβ degradation, anti-inflammatory strategies or immunomodulation, and cell therapies. Confronting the paradoxical role of microglia to protect neurons but also aid in the progression of AD pathophysiology will help develop tailor-made treatment strategies in AD [79,80].

5.1. Suppression of the Microglial Priming

A number of variables, such as age, systemic inflammation, or stress, can create imbalances in the central nervous system (CNS), which can trigger the formation of microglia and make them more susceptible to and reactive to inflammatory stimuli [81]. Therefore, blocking pre-disease microglial priming may be a useful therapy approach for AD. Research has demonstrated that middle-aged AD patients who are obese and insulin resistant are more likely to cause inflammation, but statins have a preventive effect against this damage by delaying the growth of microglia [82]. Moreover, it has been demonstrated that folic acid and omega-3 fatty acid supplements can intervene in neuroinflammation and lower the degree of inflammation in the blood and CSF fluid of AD patients [83].

5.2. Suppression of the Inflammatory Reaction

The CNS's physiological processes pertaining to signaling, cognition, and memory have been linked to the factor NF-κB. AD patients may experience CNS impairment as a result of this factor being triggered by oxidative stress, neuroinflammation, and other causes [84]. While the dissociation

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of IκB from the dimer may trigger the NF-κB influx into the nucleus, the production of ROS triggers the enzymatic activities of IKKb to phosphorylate the heterodimer of NF-κB, which is an inhibitor of kappaB (IκB), leading to its degradation via the ubiquitin-proteasome pathway [85]. Evidence suggests that NF-κB activation enhances Aβ processing and BACE1 production, which is likely a unique molecular mechanism controlling the course of AD [86]. It has been found that the reduction of the Aβ burden requires the suppression of NF-κB activation by polyphenols, antioxidants, and non-steroidal anti-inflammatory medications (NSAIDs) [87]. For example, forsythia B regulates neuroinflammation in APP/PS1 mice, effectively improving cognitive function, lowering the accumulation of tau and Aβ, and attenuating glial cell activation in the hippocampus [88]. Tanshinone I is used to inhibit the synthesis and expression of several proinflammatory M1 mediators, so suppressing the LPS-induced activation of NF-κB in microglia. Similarly, by inhibiting the NF-kB signaling pathway, primary microglia may produce less pathogenic tau, which would restore the microglia's autophagy deficiency and lessen the neurotoxic response [89].

5.3. Control of Microglia's Phenotypic Alterations

In the early stages of Alzheimer's disease, microglia remove toxic damage to sustain neuronal activity. Interference with microglia's activation may prolong the anti-inflammatory action of these cells. In the mouse model of AD, treatment with PPAR-γ activators, such as pioglitazone and rosiglitazone, could cause microglia to exhibit an anti-inflammatory phenotype with phagocytosis, which is likely connected to the phagocytosis of amyloid deposits. Alternatively, activated PPPAR-γ could suppress the inflammatory response[90,91].

6. Conclusion and Future Directions

The phenotype balance between A1 (toxic) and A2 (safe) microglial phenotypes to toxic illness in AD has become a hot research topic at present. Substantial evidence, both in vitro and in vivo, has suggested that the loss of the normal A2 phenotype and the activation of toxic A1 microglia contribute to neurodegeneration in AD. Promoting or restoring the polarization of microglia towards the A2 phenotype may thus represent an effective therapeutic strategy for ameliorating neuroinflammation and progressive neurocognitive impairments. In view of the limited number of studies now available, we propose future directions and caveats for establishing the A2 classification of microglia. The parental population of microglia is the myeloid-monocytic lineage. These cells are of particular interest because of their phenotypic heterogeneity and functional plasticity in response to changes in the microenvironment. Accumulating evidence has suggested that microglial cells play a key role in AD. Our understanding of microglia function in AD pathogenesis has changed over time. Initially, microglia were thought to contribute to AD pathology by releasing a variety of toxic substances, including proteases, inflammatory cytokines, and reactive oxygen and nitrogen species. More recent work, however, has suggested that this is not their only role in the pathogenesis of AD. In fact, it is now thought that this myeloid cell population becomes dysfunctional late in the disease process and can no longer perform its physiological functions and regulatory interactions, including the phagocytosis of amyloidogenic proteins. These opposing roles of microglia in AD pathology have made therapeutic strategies targeting AD difficult. Increased microglial activity is linked to poor NREM rapid-sleep spindle expression in the frontal cortex, even before to the demonstration of positive β-amyloid pathology. This suggests that AD should have been diagnosed sooner. Targets for both diagnosis and treatment of AD include the inhibition of microglia activation and the related proinflammatory mediators. It will be crucial to investigate the cause of the microglia activation seen in the early stages of AD because different microglia phenotypes have different functions. These include the anti-inflammatory M2 phenotype, which aims to remove Aβ and shield neurons, and the M1 phenotype, which causes neuronal damage. Treatment for AD may be as effective as possible if it focuses on the proinflammatory phenotype of microglia in the early stages of the disease.

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