MDPI

Review

Microglia-Associated Neuroinflammation in Alzheimer's Disease and Its Therapeutic Potential

Siddharth Shah [1],* and Hritvik Jain [2]

1   Department of Neurosurgery, University of Florida, Gainesville, FL 32608, USA
2   Department of Internal Medicine, All India Institute of Medical Sciencies, Jodhpur 342005, India; hritvikjain2001@gmail.com
*   Correspondence: siddharth.dr99@gmail.com

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). The phenotype balance between A1 (toxic) and A2 (safe) microglial phenotypes to toxic illness in AD has become a hot research topic at present. Currently, many transcription factors, downstream signaling pathways, and molecular mechanisms that regulate the polarization of microglia are being 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 paper 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 of implementing 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. 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. Conclusions: 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. 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.

Keywords: microglia; Alzheimer's disease; neurosurgery; neurology; neuroglia

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 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 [2,3]. 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 [4,5]. 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 [5,6]. 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 [7,8]. The histopathological hallmarks of AD include extracellular beta (Aß) plaques and the intracellular accumulation of hyperphosphorylated Tau protein, which form neurofibrillary tangles (NFTs) [9,10].

The most documented cytological and molecular signs typical of AD include the activation of pro-inflammatory microglia associated with senile Aβ plaques, the extracellular deposition of these peptides, neurofibrillary tangles into living neurons, and dystrophic dendritic and synaptic structures. There are also several mutations in the microglial equipping factors that were identified in amyloid-overproducing mice, which determines the role of microglia 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 rarely examined. 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 [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 number 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 microglia in the system of AD therapy [17]. 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, the tumor necrosis factor, and interferon-gamma and chemokines) to recruit other cells like microglia, astrocytes, and T-cells to the site of inflammation [18]. Furthermore, complement protein activation is an important link between the brain and immune system activation. Microglia play a role in AD neurodegeneration by regulating synaptic activity and releasing harmful chemicals. Comprehending the function of microglia in Alzheimer's disease is essential for creating therapies that work. The role of microglia in AD is thoroughly summarized in this article, along with the pertinent mutant genes, subtypes of microglia, phagocytic function, inflammatory response, and neurodegeneration. It also covers current advancements in creating therapies that target AD microglia. To completely comprehend the processes by which microglia contribute to AD and to create fresh approaches for treating this crippling condition, further study is required.

Search Strategy

The literature search method involved searching PubMed, Embase, Scopus, and research meeting abstracts using relevant keywords to identify English literature publications, including full texts, concerning human subject matter from its inception until May 2024. The search terms used were "microglia", "neuroinflammation", "Alzheimer's Disease", "AD", "Therapeutic", and "Neurodegeneration". A comprehensive review was then performed on various studies, including observational studies, Case–Control studies, cohort studies, clinical trials, meta-analyses, and reviews.

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, continuously scanning the microenvironment to detect pathogen-derived signals promptly [23,24].

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 the 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 the 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 the 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 the 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 and Its Role in Neurological Homeostasis

Is it possible to positively activate microglial responses to protect the brain in acute, chronic, and progressive situations that are commonly thought to involve and even trigger neurodegenerative sequelae? The extent to which microglia exacerbate cognitive impairment is not well understood [31]. It becomes more obvious, therefore, that classically activated states result when the microglial involvement in an inflammatory response is increased beyond what is required. As they have always done throughout life, these states represent damage responses specific to the CNS milieu, which exists independently of

conventional inflammatory initiators. Reactive conditions like this can result in increased pay, reduced synaptic density, excess soluble NFTs, and an overrepresentation of neuroinflammation. Cognitive functions may suffer as a result of this decrease in synapse density. Aggressive inflammatory threats worsen these neurological loads during continuous crises. Essentially, this phenomenon is because central commerce may be hampered by chaos to the greatest extent possible [32]. Research investment focused on preventing the excessive chronic activation of microglia without considering what demonstrable stimuli can be echoed using directed polarization and subsequent protective maintenance seems like driving a car while learning about its function with only the intention of understanding failure [33]. This finding is in contrast to the ongoing knowledge that the informed clockwork existence of microglia maintaining homeostasis is the goal. Future technology investors are also pleased with the abundance of precise information obtained by having large-scale talks with tiny molecules deep into unfathomable dark space. Any future goal should logically focus as much on discussion gestation from seasoned expertise related to particular cell responses [34]. By preventing the systematic breakdown as satisfied cell automation works toward revalued male functioning, each will successfully permit the broader homeostatic demand. The brain's indigenous immune cells are called microglia. They make up around 10–15% of the cells in the adult brain, are essential for preserving tissue homeostasis, and support the immune system's reaction to infection or damage [35]. Almost all neurobiologists agree that it is important to thoroughly record and analyze the possible role of microglia in the modifications observed in experimental paradigms. Ongoing microglia research advances our understanding of the natural microglial function (NMF) in a variety of host responses, including behavior, plasticity, aging, and illness, in the context of the CNS's nonneuronal cell population [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 pro-inflammatory 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 receptors (CD200Rs), and the 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, although 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 pro-inflammatory 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 an Aβ-dependent Tau deposition showed that TREM2 regularly triggered microglia and exacerbated leukodystrophy 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 pro-inflammatory 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 NFT 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, the Wnt-3a activation in primary microglia may encourage microglia to enter the pro-inflammatory state of Alzheimer's disease [47,48]. Moreover, the intraperitoneal injection of exogenous interfering substances, such as lipopolysaccharides (LPSs), 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 their 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	Microglial Phenotype
APP/PS1 mice	TLR2	TLR2 activation inhibition results in increased Aβ accumulation, compromised recognition, and elevated neuroinflammation [51]	M1
AD-TLR2KO	TLR2	Neurobehavioral function deteriorates, and white matter damage is exacerbated by TLR2 genetic deletion [52]	M1
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]	M1
TLR4w AD mice and TLR4m AD mice	TLR4	Microglia activation and upregulation-control of cytokines reliant on TLR4 [54]	M1
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]	M1
NALP3-deficient mice	NLRP3	Involved in tissue proteinase B release and lysosomal degradation; triggers inflammation and tissue damage in AD [56]	M1
APP/PS1 mice	NLRP3	Encouragement of M2 phenotype conversion in microglia and decrease in Aβ deposition [57]	M1
TREM2-WT) or TREM2-R47H	TREM2	Minimization of Aβ seeding and suppression of microglia linked to illness [58]	M2
TREM2 KO and WT C57BL/6J	TREM2	Tau transport, dispersion, and seeding via microglial cell exosomes are enhanced by TREM2 loss [59]	M2
Primary astrocytes and microglia	CD200	Prevents the glutamate toxicity response and microglial activation caused by meth [60]	M2
CD200 +/+ and CD200 −/− mice	CD200	MPTP experimental mouse model [61]	M2
C57BL/6 mice	CD32	Induce pro-inflammatory signaling [62]	M2

By secreting pro-inflammatory chemicals, the M1 microglial phenotype causes neuroinflammation and consequent neuronal injury. The associated pathways that are engaged in this process include the Janus Kinase/Signal Transducer and Activator of Transcription (JAK/STAT) pathway, Nuclear Factor-kappa B (NF-κB), and toll-like receptors (TLRs). However, the M2 phenotype of microglia secretes substances that reduce inflammation, which has the effect of protecting the nervous system. This feature is regulated by many signaling pathways, such as the Notch system, PI3K/AKT, AMPK, Adenosine Monophosphate-Activated Protein Kinase, and Peroxisome Proliferator-Activated Receptor Gamma (PPAR-γ) [62,63].

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. The 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]. A large number of inflammation-related genes were found to have differential expressions 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 [67,68]. The findings may also guide us to maintain remyelination in the brain parenchymal the way they do. 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 [69,70].

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. Regarding 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 state [73,74]. 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 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 the 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 on 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 also aids in the progression of AD pathophysiology and will help develop tailor-made treatment strategies for AD [79,80].

5.1. Suppression of the Microglial Priming

Several 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 the CSF of AD patients [83]. The importance of distinct subsets of microglia, in particular, disease-associated microglia (DAM), in the development of AD has been highlighted by several research investigations [84–86]. Microglial depletion is based on the hypothesis that certain activated microglia, including DAM, may enhance AD pathogenesis by many means, including promoting Aβ plaque formation, enhancing neuroinflammation, and perhaps impacting tau pathology. DAMs are believed to have significant effects on the health and function of neurons [87]. They are distinguished by a distinct transcriptional profile and are frequently observed near amyloid plaques. As a result, it has been suggested that treatment approaches ought to focus on specifically targeting these DAMs and be more disease-specific [88].

5.2. Suppression of the Inflammatory Reaction

The CNS's physiological processes of 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 [89]. While the dissociation 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 [90]. Evidence suggests that NF-κB activation enhances Aβ processing and BACE1 production, which is likely a unique molecular mechanism controlling the course of AD [91]. It has been found that the reduction in the Aβ burden requires the suppression of NF-κB activation by polyphenols, antioxidants, and non-steroidal anti-inflammatory medications (NSAIDs) [92]. 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 [93]. Tanshinone I is used to inhibit the synthesis and expression of several pro-inflammatory M1 mediators, therefore 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 [94]. Purinergic receptor antagonists can control extracellular ATP levels, which are involved in the NLRP3 inflammasome's activation and the subsequent release of cytokines that promote inflammation. By blocking the activation of IL-1β and IL-18,

two essential cytokines in the inflammasome pathway, caspase-1 inhibitors reduce inflammation [95]. By blocking NLRP3's activation, oligomerization, or interactions with other inflammasome components, direct inhibitors of the protein can stop the inflammasome from assembling and thus suppress inflammatory signals. These treatment approaches may lessen neuroinflammation, mitigate neuronal loss, and slow the advancement of AD [96]. However, further pre-clinical and clinical research is necessary to ascertain the safety and effectiveness of these medications as well as to fully understand the possible adverse effects and long-term implications of targeting certain inflammasome components. Our capacity to create novel, tailored therapeutics for AD that reduce side effects and optimize therapeutic potential will only increase as we continue to expand our knowledge of the molecular processes and interactions within the inflammasome pathway.

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 [96].

5.4. Investigating TREM-2: Regulating Microglial Activation as an AD Treatment Approach

The Triggering Receptor Expressed on Myeloid Cells 2 (TREM-2) is a cell surface-bound protein that belongs to the myeloid cells that are primarily present in the central nervous system microglia. The TREM-2 is known to be important in controlling the activity of microglia during inflammation, infection, or neurodegenerative disease [97]. Following the activation by diverse ligands like lipids and apoptotic cells, the TREM-2 inhibits inflammatory pathways while promoting microglia's survival, multiplication, and albino phagocytosis. It should be noted that this protein is also important for the maintenance of normal conditions of the brain since it aids in the clearance of cellular debris and the management of inflammatory response [98]. The TREM-2 in inflammatory response due to neurodegeneration has been of interest most particularly in the case of diseases such as Alzheimer's primary focus. Research has shown that polymorphisms in the TREM-2 gene increase susceptibility towards Alzheimer's disease, thus reinforcing the credibility of the gene. It therapeutically philanthropizes to the enhancement of neurodegeneration by switching TREM-2 activation to favor non-hurtful microglial responses over inflammatory responses, which proves beneficial in retarding neurodegeneration [98,99].

TREM-2-dependent actions can encourage plaque compaction and lessen the plaque-associated neuritic pathology, even though they could not be able to considerably lower the amount of amyloid plaque in mouse models. The TREM-2 has thus become the main treatment target for AD, and scientists are working on ways to selectively modify it in order to produce the desired results [97]. In rodent and cellular models, disease-associated TREM-2 mutations can cause the loss of function, suggesting that improving the TREM-2 function may be advantageous. Higher TREM-2 levels may have protective benefits against the advancement of AD, according to indirect evidence from individuals with the condition. Early in the illness, higher amounts of the soluble TREM-2 (sTREM-2) in cerebrospinal fluid (CSF) have been seen in many independent cohorts. This finding suggests that the sTREM-2 may be a marker for full-length TREM2-mediated signaling [98]. Up to five years prior to the expected year of start, people with dominant hereditary AD and moderate cognitive impairment have been found to have elevated sTREM-2 levels. Nevertheless, sTREM-2 and amyloid deposition did not correlate, indicating that tau-related cellular disease may cause the TREM-2 expression to rise. Additionally, studies have shown that sTREM-2 levels increase in both humans and animals as a result of physiological aging, with TREM-2-dependent increases in microglial nodules in mice. One intriguing

approach to creating potent treatment approaches for AD is to modify TREM-2 activity [99]. Antibody stimulation improves microglial chemotaxis, clustering near Aβ plaques, and the phagocytosis of cellular debris, perhaps aiding in the clearance of Aβ plaques, according to research on mouse TREM-2. Nevertheless, studies using an anti-mouse TREM-2 antibody that obstructs cell-autonomous signaling and competes for ligand binding showed that the TREM-2 antagonism markedly deteriorated the course of experimental autoimmune encephalomyelitis (EAE) [100]. There are now three viable methods for adjusting TREM-2 activity. A pair of companies have discovered antibodies that improve TREM-2 signaling via crosslinking, while the third strategy tries to stop ADAM family proteases from losing the extracellular domain. One interesting antibody clone, 4D9, efficiently blocks the shedding of the soluble TREM-2 by binding to an epitope that is just 12 amino acids N-terminal to the TREM-2 protein. According to in vitro biochemical experiments, 4D9 can prevent the TREM-2 stalk peptide from being cleaved, which activates DAP12/phosphorylation/Syk signaling—a critical step in downstream signaling. Studies have shown that, when 4D9 is given peripherally at large dosages, it effectively binds the sTREM-2 in the CSF, indicating that it can interact with the target in the CNS in vivo [101]. Research has evaluated how Aβ accumulation in transgenic AD mice models is impacted by 4D9 and AL002a/c, a humanized monoclonal IgG1 antibody that binds to TREM-2 and initiates the TREM-2 signaling pathway. Remarkably, neither 4D9 nor AL002c improved the microglia's ability to cluster around amyloid plaques [102]. In conclusion, whereas the antibodies in the AL002 family have many characteristics in common, their approaches to Aβ clearance and microglial clustering are different. Although the exact causes of these variations are unknown, variations in the mice models or dosage paradigms used in these investigations may be the reason. Figure 1 summarizes the TREM-2 activation.
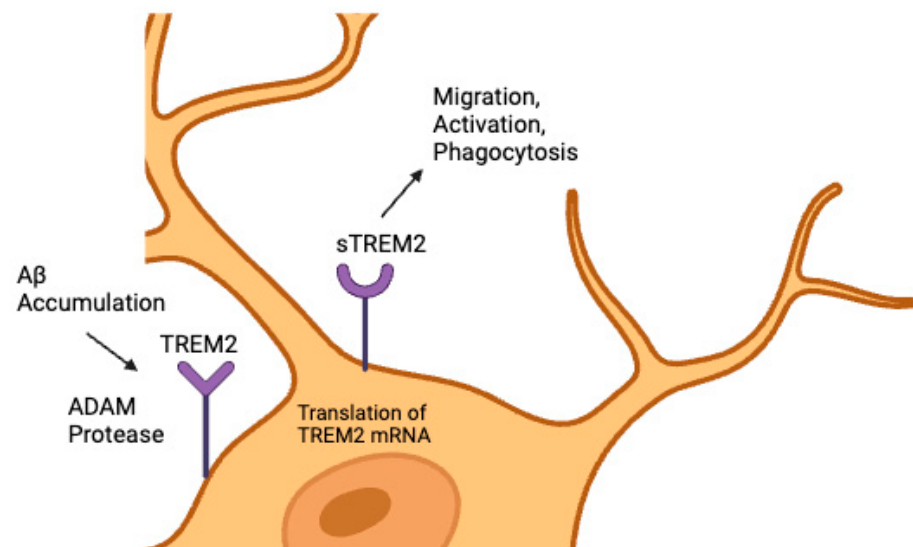

Figure 1. Activation of microglia by sTREM-2.

6. Conclusions 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 action 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 the poor NREM rapid-sleep spindle expression in the frontal cortex, even before the demonstration of positive β-amyloid pathology. This finding suggests that AD should have been diagnosed sooner. Targets for both the diagnosis and treatment of AD include the inhibition of microglia activation and the related pro-inflammatory 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 functions 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 pro-inflammatory phenotype of microglia in the early stages of the disease. The lack of common criteria for characterizing microglial phenotypes and functional states is a prominent constraint of current research that might cause discrepancies in the literature and impede the development of targeted therapeutics. Moreover, a lot of research focuses on distinct facets of microglial biology, which could not adequately convey the intricate interactions between different microglial roles in the setting of AD. To obtain the best possible treatment results, the planning and execution of clinical trials that particularly target microglial pathways should take into account variables including illness stage, genetic background, and unique patient features.

It is clear that microglia play a significant role in the pathophysiology of AD, and the development of successful treatment approaches will depend on a greater knowledge of their varied roles and interactions with other brain biological components. Nevertheless, despite tremendous advancements in recent years, there are still a great deal of unanswered questions about the biology of microglia, particularly about their heterogeneity, their methods of action, and the interactions between different signaling pathways. Subsequent studies ought to persist in deciphering the intricacies of microglial biology, study the fundamental molecular pathways that propel their multifarious tasks, and examine the possibility of regulating microglial activity to impede or reverse the advancement of sickness. Furthermore, to fully realize the promise of therapeutics targeting microglia for the prevention, treatment, and ultimate cure of AD, it will be imperative to overcome the present gaps in our knowledge of microglial biology and function. By working together, these initiatives will capitalize on the potential of microglia-targeted therapies for AD and usher in a new age of precision medicine.

References

1. Zhang, X.-X.; Tian, Y.; Wang, Z.-T.; Ma, Y.-H.; Tan, L.; Yu, J.-T. The Epidemiology of Alzheimer's Disease Modifiable Risk Factors and Prevention. *J. Prev. Alzheimer's Dis.* **2021**, *8*, 313–321. [CrossRef] [PubMed]
2. Alzheimer's Association Report. 2023 Alzheimer's disease facts and figures. *Alzheimer's Dement. J. Alzheimer's Assoc.* **2023**, *19*, 1598–1695. [CrossRef] [PubMed]
3. Knapskog, A.-B.; Engedal, K.; Selbæk, G.; Øksengård, A.-R. Alzheimers sykdom—diagnostikk og behandling [Alzheimer's Disease—Diagnosis and Treatment]. *Tidsskr. Den Nor. Laegeforening: Tidsskr. Prakt. Med. Ny Raekke* **2021**, *141*. [CrossRef]
4. Ávila-Villanueva, M.; Gómez-Ramírez, J.; Ávila, J.; Fernández-Blázquez, M.A. Loneliness as Risk Factor for Alzheimer's disease. *Curr. Aging Sci.* **2022**, *15*, 266–293. [CrossRef]
5. Weber, C.; Dilthey, A.; Finzer, P. The role of microbiome-host interactions in the development of Alzheimer's disease. *Front. Cell. Infect. Microbiol.* **2023**, *13*, 1151021. [CrossRef]
6. García-Osta, A.; Dong, J.; Moreno-Aliaga, M.J.; Ramirez, M.J. p27, The Cell Cycle and Alzheimer's Disease. *Int. J. Mol. Sci.* **2022**, *23*, 1211. [CrossRef]
7. Zhao, J.; Huai, J. Role of primary aging hallmarks in Alzheimer's disease. *Theranostics* **2023**, *13*, 197–230. [CrossRef]
8. Friedli, M.J.; Inestrosa, N.C. Huperzine A and Its Neuroprotective Molecular Signaling in Alzheimer's Disease. *Molecules* **2021**, *26*, 6531. [CrossRef]
9. del Campo, M.; Vermunt, L.; Peeters, C.F.W.; Sieben, A.; Hok-A-Hin, Y.S.; Lleó, A.; Alcolea, D.; van Nee, M.; Engelborghs, S.; van Alphen, J.L.; et al. CSF proteome profiling reveals biomarkers to discriminate dementia with Lewy bodies from Alzheimer's disease. *Nat. Commun.* **2023**, *14*, 5635. [CrossRef]
10. Toups, K.; Hathaway, A.; Gordon, D.; Chung, H.; Raji, C.; Boyd, A.; Hill, B.D.; Hausman-Cohen, S.; Attarha, M.; Chwa, W.J.; et al. Precision Medicine Approach to Alzheimer's Disease: Successful Pilot Project. *J. Alzheimer's Dis.* **2022**, *88*, 1411–1421. [CrossRef]
11. Guzman-Martinez, L.; Calfío, C.; Farias, G.A.; Vilches, C.; Prieto, R.; Maccioni, R.B. New Frontiers in the Prevention, Diagnosis, and Treatment of Alzheimer's Disease. *J. Alzheimer's Dis.* **2021**, *82*, S51–S63. [CrossRef]
12. Jia, J.; Zhang, Y.; Shi, Y.; Yin, X.; Wang, S.; Li, Y.; Zhao, T.; Liu, W.; Zhou, A.; Jia, L. A 19-Year-Old Adolescent with Probable Alzheimer's Disease. *J. Alzheimer's Dis.* **2023**, *91*, 915–922. [CrossRef]
13. Tecalco–Cruz, A.C.; Pedraza-Chaverri, J.; Briones-Herrera, A.; Cruz-Ramos, E.; López–Canovas, L.; Zepeda–Cervantes, J. Protein degradation-associated mechanisms that are affected in Alzheimer's disease. *Mol. Cell. Biochem.* **2022**, *477*, 915–925. [CrossRef]
14. Dubois, B.; von Arnim, C.A.F.; Burnie, N.; Bozeat, S.; Cummings, J. Biomarkers in Alzheimer's disease: Role in early and differential diagnosis and recognition of atypical variants. *Alzheimer's Res. Ther.* **2023**, *15*, 175. [CrossRef]
15. Gustavsson, A.; Norton, N.; Fast, T.; Frölich, L.; Georges, J.; Holzapfel, D.; Kirabali, T.; Krolak-Salmon, P.; Rossini, P.M.; Ferretti, M.T.; et al. Global estimates on the number of persons across the Alzheimer's disease continuum. *Alzheimer's Dement.* **2022**, *19*, 658–670. [CrossRef]
16. De Sousa, R.A.L.; Improta-Caria, A.C. Regulation of microRNAs in Alzheimer's disease, type 2 diabetes, and aerobic exercise training. *Metab. Brain Dis.* **2022**, *37*, 559–580. [CrossRef]
17. Lane, D.J.; Metselaar, B.; Greenough, M.; Bush, A.I.; Ayton, S.J. Ferroptosis and NRF2: An emerging battlefield in the neurodegeneration of Alzheimer's disease. *Essays Biochem.* **2021**, *65*, 925–940. [CrossRef]
18. Yang, H.; Luo, Y.; Hu, Q.; Tian, X.; Wen, H. Benefits in Alzheimer's Disease of Sensory and Multisensory Stimulation. *J. Alzheimer's Dis.* **2021**, *82*, 463–484. [CrossRef]
19. Hampel, H.; Hardy, J.; Blennow, K.; Chen, C.; Perry, G.; Kim, S.H.; Villemagne, V.L.; Aisen, P.; Vendruscolo, M.; Iwatsubo, T.; et al. The Amyloid-beta Pathway in Alzheimer's Disease. *Mol. Psychiatry* **2021**, *26*, 5481–5503. [CrossRef]
20. Dhapola, R.; Hota, S.S.; Sarma, P.; Bhattacharyya, A.; Medhi, B.; Reddy, D.H. Recent advances in molecular pathways and therapeutic implications targeting neuroinflammation for Alzheimer's disease. *Inflammopharmacology* **2021**, *29*, 1669–1681. [CrossRef]
21. Song, T.; Song, X.; Zhu, C.; Patrick, R.; Skurla, M.; Santangelo, I.; Green, M.; Harper, D.; Ren, B.; Forester, B.P.; et al. Mitochondrial dysfunction, oxidative stress, neuroinflammation, and metabolic alterations in the progression of Alzheimer's disease: A meta-analysis of in vivo magnetic resonance spectroscopy studies. *Ageing Res. Rev.* **2021**, *72*, 101503. [CrossRef]
22. Teleanu, D.M.; Niculescu, A.-G.; Lungu, I.I.; Radu, C.I.; Vladâcenco, O.; Roza, E.; Costăchescu, B.; Grumezescu, A.M.; Teleanu, R.I. An Overview of Oxidative Stress, Neuroinflammation, and Neurodegenerative Diseases. *Int. J. Mol. Sci.* **2022**, *23*, 5938. [CrossRef]
23. Wang, C.; Chen, S.; Guo, H.; Jiang, H.; Liu, H.; Fu, H.; Wang, D. Forsythoside A Mitigates Alzheimer's-like Pathology by Inhibiting Ferroptosis-mediated Neuroinflammation via Nrf2/GPX4 Axis Activation. *Int. J. Biol. Sci.* **2022**, *18*, 2075–2090. [CrossRef]
24. Chausse, B.; Kakimoto, P.A.; Kann, O. Microglia and lipids: How metabolism controls brain innate immunity. *Semin. Cell Dev. Biol.* **2020**, *112*, 137–144. [CrossRef]
25. Pan, R.-Y.; He, L.; Zhang, J.; Liu, X.; Liao, Y.; Gao, J.; Liao, Y.; Yan, Y.; Li, Q.; Zhou, X.; et al. Positive feedback regulation of microglial glucose metabolism by histone H4 lysine 12 lactylation in Alzheimer's disease. *Cell Metab.* **2022**, *34*, 634–648.e6. [CrossRef]
26. Merighi, S.; Nigro, M.; Travagli, A.; Gessi, S. Microglia and Alzheimer's Disease. *Int. J. Mol. Sci.* **2022**, *23*, 12990. [CrossRef]
27. Thakur, S.; Dhapola, R.; Sarma, P.; Medhi, B.; Reddy, D.H. Neuroinflammation in Alzheimer's Disease: Current Progress in Molecular Signaling and Therapeutics. *Inflammation* **2022**, *46*, 1–17. [CrossRef]

28. Sun, N.; Victor, M.B.; Park, Y.P.; Xiong, X.; Ni Scannail, A.; Leary, N.; Prosper, S.; Viswanathan, S.; Luna, X.; Boix, C.A.; et al. Human microglial state dynamics in Alzheimer's disease progression. *Cell* **2023**, *186*, 4386–4403.e29. [CrossRef]

29. Al-Ghraiybah, N.F.; Wang, J.; Alkhalifa, A.E.; Roberts, A.B.; Raj, R.; Yang, E.; Kaddoumi, A. Glial Cell-Mediated Neuroinflammation in Alzheimer's Disease. *Int. J. Mol. Sci.* **2022**, *23*, 10572. [CrossRef]

30. Rajesh, Y.; Kanneganti, T.-D. Innate Immune Cell Death in Neuroinflammation and Alzheimer's Disease. *Cells* **2022**, *11*, 1885. [CrossRef]

31. Jorfi, M.; Maaser-Hecker, A.; Tanzi, R.E. The neuroimmune axis of Alzheimer's disease. *Genome Med.* **2023**, *15*, 6. [CrossRef] [PubMed]

32. Wang, M.; Zhang, H.; Liang, J.; Huang, J.; Chen, N. Exercise suppresses neuroinflammation for alleviating Alzheimer's disease. *J. Neuroinflammation* **2023**, *20*, 76. [CrossRef] [PubMed]

33. Scheffler, K.; Stenzel, J.; Krohn, M.; Lange, C.; Hofrichter, J.; Schumacher, T.; Brüning, T.; Plath, A.S.; Walker, L.; Pahnke, J. Determination of spatial and temporal distribution of microglia by 230nm-high-resolution, high-throughput automated analysis reveals different amyloid plaque populations in an APP/PS1 mouse model of Alzheimer's disease. *Curr. Alzheimer. Res.* **2011**, *8*, 781–788. [CrossRef] [PubMed] [PubMed Central]

34. Hansen, D.V.; Hanson, J.E.; Sheng, M. Microglia in Alzheimer's disease. *J. Cell Biol.* **2017**, *217*, 459–472. [CrossRef] [PubMed]

35. Qin, Q.; Teng, Z.; Liu, C.; Li, Q.; Yin, Y.; Tang, Y. TREM2, microglia, and Alzheimer's disease. *Mech. Ageing Dev.* **2021**, *195*, 111438. [CrossRef]

36. Sarlus, H.; Heneka, M.T. Microglia in Alzheimer's disease. *J. Clin. Investig.* **2017**, *127*, 3240–3249. [CrossRef]

37. Baik, S.H.; Kang, S.; Lee, W.; Choi, H.; Chung, S.; Kim, J.-I.; Mook-Jung, I. A Breakdown in Metabolic Reprogramming Causes Microglia Dysfunction in Alzheimer's Disease. *Cell Metab.* **2019**, *30*, 493–507.e6. [CrossRef]

38. Singh, D. Astrocytic and microglial cells as the modulators of neuroinflammation in Alzheimer's disease. *J. Neuroinflammation* **2022**, *19*, 206. [CrossRef]

39. Li, Y.; Xia, X.; Wang, Y.; Zheng, J.C. Mitochondrial dysfunction in microglia: A novel perspective for pathogenesis of Alzheimer's disease. *J. Neuroinflammation* **2022**, *19*, 248. [CrossRef]

40. Crapser, J.D.; Spangenberg, E.E.; Barahona, R.A.; Arreola, M.A.; Hohsfield, L.A.; Green, K.N. Microglia facilitate loss of perineuronal nets in the Alzheimer's disease brain. *EBioMedicine* **2020**, *58*, 102919. [CrossRef]

41. Andronie-Cioara, F.L.; Ardelean, A.I.; Nistor-Cseppento, C.D.; Jurcau, A.; Jurcau, M.C.; Pascalau, N.; Marcu, F. Molecular Mechanisms of Neuroinflammation in Aging and Alzheimer's Disease Progression. *Int. J. Mol. Sci.* **2023**, *24*, 1869. [CrossRef] [PubMed]

42. Gerrits, E.; Brouwer, N.; Kooistra, S.M.; Woodbury, M.E.; Vermeiren, Y.; Lambourne, M.; Mulder, J.; Kummer, M.; Möller, T.; Biber, K.; et al. Distinct amyloid-β and tau-associated microglia profiles in Alzheimer's disease. *Acta Neuropathol.* **2021**, *141*, 681–696. [CrossRef] [PubMed]

43. Rangaraju, S.; Dammer, E.B.; Raza, S.A.; Rathakrishnan, P.; Xiao, H.; Gao, T.; Duong, D.M.; Pennington, M.W.; Lah, J.J.; Seyfried, N.T.; et al. Identification and therapeutic modulation of a pro-inflammatory subset of disease-associated-microglia in Alzheimer's disease. *Mol. Neurodegener.* **2018**, *13*, 24. [CrossRef] [PubMed]

44. Fassler, M.; Rappaport, M.S.; Cuño, C.B.; George, J. Engagement of TREM2 by a novel monoclonal antibody induces activation of microglia and improves cognitive function in Alzheimer's disease models. *J. Neuroinflammation* **2021**, *18*, 1–18. [CrossRef] [PubMed]

45. Chen, H.; Guo, Z.; Sun, Y.; Dai, X. The immunometabolic reprogramming of microglia in Alzheimer's disease. *Neurochem. Int.* **2023**, *171*, 105614. [CrossRef] [PubMed]

46. Zhao, X.; Sun, J.; Xiong, L.; She, L.; Li, L.; Tang, H.; Zeng, Y.; Chen, F.; Han, X.; Ye, S.; et al. β-amyloid binds to microglia Dectin-1 to induce inflammatory response in the pathogenesis of Alzheimer's disease. *Int. J. Biol. Sci.* **2023**, *19*, 3249–3265. [CrossRef]

47. Sangineto, M.; Ciarnelli, M.; Cassano, T.; Radesco, A.; Moola, A.; Bukke, V.N.; Romano, A.; Villani, R.; Kanwal, H.; Capitanio, N.; et al. Metabolic reprogramming in inflammatory microglia indicates a potential way of targeting inflammation in Alzheimer's disease. *Redox Biol.* **2023**, *66*, 102846. [CrossRef]

48. Medrano-Jiménez, E.; Meza-Sosa, K.F.; A Urbán-Aragón, J.; Secundino, I.; Pedraza-Alva, G.; Pérez-Martínez, L. Microglial activation in Alzheimer's disease: The role of flavonoids and microRNAs. *J. Leukoc. Biol.* **2022**, *112*, 47–77. [CrossRef]

49. Lepiarz-Raba, I.; Gbadamosi, I.; Florea, R.; Paolicelli, R.C.; Jawaid, A. Metabolic regulation of microglial phagocytosis: Implications for Alzheimer's disease therapeutics. *Transl. Neurodegener.* **2023**, *12*, 48. [CrossRef]

50. Frigerio, C.S.; Wolfs, L.; Fattorelli, N.; Thrupp, N.; Voytyuk, I.; Schmidt, I.; Mancuso, R.; Chen, W.-T.; Woodbury, M.E.; Srivastava, G.; et al. The Major Risk Factors for Alzheimer's Disease: Age, Sex, and Genes Modulate the Microglia Response to Aβ Plaques. *Cell Rep.* **2019**, *27*, 1293–1306.e6. [CrossRef]

51. McDonald, C.L.; Hennessy, E.; Rubio-Araiz, A.; Keogh, B.; McCormack, W.; McGuirk, P.; Reilly, M.; Lynch, M.A. Inhibiting TLR2 activation attenuates amyloid accumulation and glial activation in a mouse model of Alzheimer's disease. *Brain, Behav. Immun.* **2016**, *58*, 191–200. [CrossRef] [PubMed]

52. Zhou, C.; Sun, X.; Hu, Y.; Song, J.; Dong, S.; Kong, D.; Wang, Y.; Hua, X.; Han, J.; Zhou, Y.; et al. Genomic deletion of TLR2 induces aggravated white matter damage and deteriorated neurobehavioral functions in mouse models of Alzheimer's disease. *Aging* **2019**, *11*, 7257–7273. [CrossRef] [PubMed]

53. Jin, J.-J.; Kim, H.-D.; Maxwell, J.A.; Li, L.; Fukuchi, K.-I. Toll-like receptor 4-dependent upregulation of cytokines in a transgenic mouse model of Alzheimer's disease. *J. Neuroinflammation* **2008**, *5*, 23. [CrossRef] [PubMed]

54. Song, M.; Jin, J.; Lim, J.-E.; Kou, J.; Pattanayak, A.; A Rehman, J.; Kim, H.-D.; Tahara, K.; Lalonde, R.; Fukuchi, K.-I. TLR4 mutation reduces microglial activation, increases Aβ deposits and exacerbates cognitive deficits in a mouse model of Alzheimer's disease. *J. Neuroinflammation* **2011**, *8*, 92. [CrossRef]

55. Kaushal, V.; Dye, R.; Pakavathkumar, P.; Foveau, B.; Flores, J.; Hyman, B.; Ghetti, B.; Koller, B.H.; LeBlanc, A.C. Neuronal NLRP1 inflammasome activation of caspase-1 coordinately regulates inflammatory interleukin-1-beta production and axonal degeneration-associated caspase-6 activation. *Cell Death Differ.* **2015**, *22*, 1676–1686. [CrossRef]

56. Halle, A.; Hornung, V.; Petzold, G.C.; Stewart, C.R.; Monks, B.G.; Reinheckel, T.; Fitzgerald, K.A.; Latz, E.; Moore, K.J.; Golenbock, D.T. The NALP3 inflammasome is involved in the innate immune response to amyloid-β. *Nat. Immunol.* **2008**, *9*, 857–865. [CrossRef]

57. Heneka, M.T.; Kummer, M.P.; Stutz, A.; Delekate, A.; Schwartz, S.; Vieira-Saecker, A.; Griep, A.; Axt, D.; Remus, A.; Tzeng, T.-C.; et al. NLRP3 is activated in Alzheimer's disease and contributes to pathology in APP/PS1 mice. *Nature* **2013**, *493*, 674–678. [CrossRef]

58. Milner, M.T.; Maddugoda, M.; Götz, J.; Burgener, S.S.; Schroder, K. The NLRP3 inflammasome triggers sterile neuroinflammation and Alzheimer's disease. *Curr. Opin. Immunol.* **2020**, *68*, 116–124. [CrossRef]

59. Barczuk, J.; Siwecka, N.; Lusa, W.; Rozpędek-Kamińska, W.; Kucharska, E.; Majsterek, I. Targeting NLRP3-mediated neuroinflammation in Alzheimer's Disease Treatment. *Int. J. Mol. Sci.* **2022**, *23*, 8979. [CrossRef]

60. Bravo, J.; Ribeiro, I.; Terceiro, A.F.; Andrade, E.B.; Portugal, C.C.; Lopes, I.M.; Azevedo, M.M.; Sousa, M.; Lopes, C.D.F.; Lobo, A.C.; et al. Neuron–microglia contact-dependent mechanisms attenuate methamphetamine-induced microglia reactivity and enhance neuronal plasticity. *Cells* **2022**, *11*, 355. [CrossRef]

61. Rabaneda-Lombarte, N.; Serratosa, J.; Bové, J.; Vila, M.; Saura, J.; Solà, C. The CD200R1 microglial inhibitory receptor as a therapeutic target in the MPTP model of Parkinson's disease. *J. Neuroinflammation* **2021**, *18*, 88. [CrossRef] [PubMed]

62. Liu, L.; Liu, X.; Zhao, J.; Yan, F.; Wang, R.; Wen, S.; Wang, L.; Luo, Y.; Ji, X. Brain-selective mild hypothermia promotes long-term white matter integrity after ischemic stroke in mice. *CNS Neurosci. Ther.* **2018**, *24*, 1275–1285. [CrossRef] [PubMed]

63. Hou, Y.; Wei, Y.; Lautrup, S.; Yang, B.; Wang, Y.; Cordonnier, S.; Mattson, M.P.; Croteau, D.L.; Bohr, V.A. NAD$^+$ supplementation reduces neuroinflammation and cell senescence in a transgenic mouse model of Alzheimer's disease via cGAS–STING. *Proc. Natl. Acad. Sci. USA* **2021**, *118*, e2011226118. [CrossRef] [PubMed]

64. Govindarajulu, M.; Ramesh, S.; Beasley, M.; Lynn, G.; Wallace, C.; Labeau, S.; Pathak, S.; Nadar, R.; Moore, T.; Dhanasekaran, M. Role of cGAS–Sting Signaling in Alzheimer's Disease. *Int. J. Mol. Sci.* **2023**, *24*, 8151. [CrossRef] [PubMed]

65. Wang, Y.; Lin, Y.; Wang, L.; Zhan, H.; Luo, X.; Zeng, Y.; Wu, W.; Zhang, X.; Wang, F. TREM2 ameliorates neuroinflammatory response and cognitive impairment via PI3K/AKT/FoxO3a signaling pathway in Alzheimer's disease mice. *Aging* **2020**, *12*, 20862–20879. [CrossRef]

66. Hampel, H.; Caraci, F.; Cuello, A.C.; Caruso, G.; Nisticò, R.; Corbo, M.; Baldacci, F.; Toschi, N.; Garaci, F.; Chiesa, P.A.; et al. A Path Toward Precision Medicine for Neuroinflammatory Mechanisms in Alzheimer's Disease. *Front. Immunol.* **2020**, *11*, 456. [CrossRef]

67. Uddin, S.; Kabir, T.; Jalouli, M.; Rahman, A.; Jeandet, P.; Behl, T.; Alexiou, A.; Albadrani, G.M.; Abdel-Daim, M.M.; Perveen, A.; et al. Neuroinflammatory Signaling in the Pathogenesis of Alzheimer's Disease. *Curr. Neuropharmacol.* **2022**, *20*, 126–146. [CrossRef]

68. Czapski, G.A.; Strosznajder, J.B. Glutamate and GABA in Microglia-Neuron Cross-Talk in Alzheimer's Disease. *Int. J. Mol. Sci.* **2021**, *22*, 11677. [CrossRef]

69. Chen, Y.; Yu, Y. Tau and neuroinflammation in Alzheimer's disease: Interplay mechanisms and clinical translation. *J. Neuroinflammation* **2023**, *20*, 165. [CrossRef]

70. Chen, C.; Liao, J.; Xia, Y.; Liu, X.; Jones, R.; Haran, J.; McCormick, B.; Sampson, T.R.; Alam, A.; Ye, K. Gut microbiota regulate Alzheimer's disease pathologies and cognitive disorders via PUFA-associated neuroinflammation. *Gut* **2022**, *71*, 2233–2252. [CrossRef]

71. Li, Y.; Macyczko, J.R.; Liu, C.-C.; Bu, G. ApoE4 reduction: An emerging and promising therapeutic strategy for Alzheimer's disease. *Neurobiol. Aging* **2022**, *115*, 20–28. [CrossRef] [PubMed]

72. Griciuc, A.; Federico, A.N.; Natasan, J.; Forte, A.M.; McGinty, D.; Nguyen, H.; Volak, A.; LeRoy, S.; Gandhi, S.; Lerner, E.P.; et al. Gene therapy for Alzheimer's disease targeting CD33 reduces amyloid beta accumulation and neuroinflammation. *Hum. Mol. Genet.* **2020**, *29*, 2920–2935. [CrossRef] [PubMed]

73. Yang, J.; Wise, L.; Fukuchi, K.-I. TLR4 Cross-Talk With NLRP3 Inflammasome and Complement Signaling Pathways in Alzheimer's Disease. *Front. Immunol.* **2020**, *11*, 724. [CrossRef]

74. Catorce, M.N.; Gevorkian, G. LPS-induced Murine Neuroinflammation Model: Main Features and Suitability for Pre-clinical Assessment of Nutraceuticals. *Curr. Neuropharmacol.* **2016**, *14*, 155–164. [CrossRef] [PubMed]

75. Chou, V.; Pearse, R.V.; Aylward, A.J.; Ashour, N.; Taga, M.; Terzioglu, G.; Fujita, M.; Fancher, S.B.; Sigalov, A.; Benoit, C.R.; et al. INPP5D regulates inflammasome activation in human microglia. *Nat. Commun.* **2023**, *14*, 7552. [CrossRef] [PubMed]

76. Boza-Serrano, A.; Ruiz, R.; Sanchez-Varo, R.; García-Revilla, J.; Yang, Y.; Jimenez-Ferrer, I.; Paulus, A.; Wennström, M.; Vilalta, A.; Allendorf, D.; et al. Galectin-3, a novel endogenous TREM2 ligand, detrimentally regulates inflammatory response in Alzheimer's disease. *Acta Neuropathol.* **2019**, *138*, 251–273. [CrossRef] [PubMed]

77. Jain, S.; Singh, R.; Paliwal, S.; Sharma, S. Targeting Neuroinflammation as Disease Modifying Approach to Alzheimer's Disease: Potential and Challenges. *Mini-Reviews Med. Chem.* **2023**, *23*, 2097–2116. [CrossRef]

78. Lopes, J.R.; Zhang, X.; Mayrink, J.; Tatematsu, B.K.; Guo, L.; LeServe, D.S.; Abou-El-Hassan, H.; Rong, F.; Dalton, M.J.; Oliveira, M.G.; et al. Nasal administration of anti-CD3 monoclonal antibody ameliorates disease in a mouse model of Alzheimer's disease. *Proc. Natl. Acad. Sci. USA* **2023**, *120*, e2309221120. [CrossRef]

79. Bronzuoli, M.R.; Iacomino, A.; Steardo, L.; Scuderi, C. Targeting neuroinflammation in Alzheimer's disease. *J. Inflamm. Res.* **2016**, *9*, 199–208. [CrossRef]

80. Shi, J.; Huang, S. Comparative Insight into Microglia/Macrophages-Associated Pathways in Glioblastoma and Alzheimer's Disease. *Int. J. Mol. Sci.* **2023**, *25*, 16. [CrossRef]

81. Dias, H.I.; Brown, C.L.; Polidori, M.C.; Lip, G.Y.; Griffiths, H.R. LDL-lipids from patients with hypercholesterolaemia and Alzheimer's disease are inflammatory to microvascular endothelial cells: Mitigation by statin intervention. *Clin. Sci.* **2015**, *129*, 1195–1206. [CrossRef] [PubMed]

82. Verdile, G.; Keane, K.N.; Cruzat, V.F.; Medic, S.; Sabale, M.; Rowles, J.; Wijesekara, N.; Martins, R.N.; Fraser, P.E.; Newsholme, P. Inflammation and oxidative stress: The molecular connectivity between insulin resistance, obesity, and Alzheimer's disease. *Mediat. Inflamm.* **2015**, *2015*, 105828. [CrossRef] [PubMed]

83. Chen, H.; Liu, S.; Ji, L.; Wu, T.; Ji, Y.; Zhou, Y.; Zheng, M.; Zhang, M.; Xu, W.; Huang, G. Folic acid supplementation mitigates Alzheimer's disease by reducing inflammation: A randomized controlled trial. *Mediat. Inflamm.* **2016**, *2016*, 9512146. [CrossRef] [PubMed]

84. Keren-Shaul, H.; Spinrad, A.; Weiner, A.; Matcovitch-Natan, O.; Dvir-Szternfeld, R.; Ulland, T.K.; David, E.; Baruch, K.; Lara-Astaiso, D.; Toth, B.; et al. A unique microglia type associated with restricting development of Alzheimer's disease. *Cell* **2017**, *169*, 1276–1290.e17. [CrossRef]

85. Kim, A.; García-García, E.; Straccia, M.; Comella-Bolla, A.; Miguez, A.; Masana, M.; Alberch, J.; Canals, J.M.; Rodríguez, M.J. Reduced fractalkine levels lead to striatal synaptic plasticity deficits in Huntington's disease. *Front. Cell. Neurosci.* **2020**, *14*, 163. [CrossRef]

86. Kleinberger, G.; Brendel, M.; Mracsko, E.; Wefers, B.; Groeneweg, L.; Xiang, X.; Focke, C.; Deußing, M.; Suárez-Calvet, M.; Mazaheri, F.; et al. The FTD-like syndrome causing TREM2 T66M mutation impairs microglia function, brain perfusion, and glucose metabolism. *EMBO J.* **2017**, *36*, 1837–1853. [CrossRef]

87. Kober, D.L.; Alexander-Brett, J.M.; Karch, C.M.; Cruchaga, C.; Colonna, M.; Holtzman, M.J.; Brett, T.J.; States, U. Neurodegenerative disease mutations in TREM2 reveal a functional surface and distinct loss-of-function mechanisms. *eLife* **2016**, *5*, e20391. [CrossRef]

88. Koenigsknecht, J.; Landreth, G. Microglial phagocytosis of fibrillar β-Amyloid through a β$_1$Integrin-dependent mechanism. *J. Neurosci.* **2004**, *24*, 9838–9846. [CrossRef]

89. Kounatidis, I.; Ligoxygakis, P. *Drosophila* as a model system to unravel the layers of innate immunity to infection. *Open Biol.* **2012**, *2*, 120075. [CrossRef]

90. Jones, S.V.; Kounatidis, I. Nuclear factor-kappa b and Alzheimer disease, unifying genetic and environmental risk Factors from cell to humans. *Front. Immunol.* **2017**, *8*, 1805. [CrossRef]

91. Shi, Z.; Hong, Y.; Zhang, K.; Wang, J.; Zheng, L.; Zhang, Z.; Hu, Z.; Han, X.; Han, Y.; Chen, T.; et al. BAG-1M co-activates BACE1 transcription through NF-κB and accelerates Aβ production and memory deficit in Alzheimer's disease mouse model. *Biochim. Biophys. Acta (BBA)-Mol. Basis Dis.* **2017**, *1863*, 2398–2407. [CrossRef]

92. Kong, F.; Jiang, X.; Wang, R.; Zhai, S.; Zhang, Y.; Wang, D. Forsythoside B attenuates memory impairment and neuroinflammation via inhibition on NF-κb signaling in Alzheimer's disease. *J. Neuroinflammation* **2020**, *17*, 305. [CrossRef] [PubMed]

93. Wang, C.; Fan, L.; Khawaja, R.R.; Liu, B.; Zhan, L.; Kodama, L.; Chin, M.; Li, Y.; Le, D.; Zhou, Y.; et al. Microglial NF-κB drives tau spreading and toxicity in a mouse model of tauopathy. *Nat. Commun.* **2022**, *13*, 1969. [CrossRef] [PubMed]

94. Vaccari, J.P.d.R.; Dietrich, W.D.; Keane, R.W. Activation and regulation of cellular inflammasomes: Gaps in our knowledge for central nervous system injury. *J. Cereb. Blood Flow Metab.* **2014**, *34*, 369–375. [CrossRef] [PubMed]

95. Hamelin, L.; Lagarde, J.; Dorothée, G.; Leroy, C.; Labit, M.; Comley, R.A.; de Souza, L.C.; Corne, H.; Dauphinot, L.; Bertoux, M.; et al. Early and protective microglial activation in Alzheimer's disease: A prospective study using[18]F-DPA-714 PET imaging. *Brain* **2016**, *139*, 1252–1264. [CrossRef] [PubMed]

96. Esmaeili, M.A.; Yadav, S.; Gupta, R.K.; Waggoner, G.R.; Deloach, A.; Calingasan, N.Y.; Beal, M.F.; Kiaei, M. Preferential PPAR-α activation reduces neuroinflammation, and blocks neurodegeneration in vivo. *Hum. Mol. Genet.* **2015**, *25*, 317–327. [CrossRef]

97. Wang, Y.; Ulland, T.K.; Ulrich, J.D.; Song, W.; Tzaferis, J.A.; Hole, J.T.; Yuan, P.; Mahan, T.E.; Shi, Y.; Gilfillan, S.; et al. TREM2-mediated early microglial response limits diffusion and toxicity of amyloid plaques. *J. Exp. Med.* **2016**, *213*, 667–675. [CrossRef]

98. Wang, Y.-J.; Monteagudo, A.; Downey, M.A.; Ashton-Rickardt, P.G.; Elmaleh, D.R. Cromolyn inhibits the secretion of inflammatory cytokines by human microglia (HMC3). *Sci. Rep.* **2021**, *11*, 8054. [CrossRef]

99. Wang, Y.-T.T.; A Pascoal, T.; Therriault, J.; Kang, M.S.; Benedet, A.L.; Savard, M.; Tissot, C.; Lussier, F.Z.; Arias, J.F.; Mathotaarachchi, S.; et al. Interactive rather than independent effect of *APOE* and sex potentiates tau deposition in women. *Brain Commun.* **2021**, *3*, fcab126. [CrossRef]

100. Webster, S.D.; Park, M.; I Fonseca, M.; Tenner, A.J. Structural and functional evidence for microglial expression of C1qRP, the C1q receptor that enhances phagocytosis. *J. Leukoc. Biol.* **2000**, *67*, 109–116. [CrossRef]

101. Weigand, A.J.; Thomas, K.R.; Bangen, K.J.; Eglit, G.M.; Delano-Wood, L.; Gilbert, P.E.; Brickman, A.M.; Bondi, M.W.; Initiative, F.T.A.D.N. APOE interacts with tau PET to influence memory independently of amyloid PET in older adults without dementia. *Alzheimer's Dement.* **2020**, *17*, 61–69. [CrossRef] [PubMed]

102. Weller, R.O.; Subash, M.; Preston, S.D.; Mazanti, I.; Carare, R.O. SYMPOSIUM: Clearance of Aβ from the Brain in Alzheimer's Disease: Perivascular Drainage of amyloid-β peptides from the brain and its failure in cerebral amyloid angiopathy and Alzheimer's disease. *Brain Pathol.* **2008**, *18*, 253–266. [CrossRef] [PubMed]