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REVIEW ARTICLE

Microglia and Astrocytes in Alzheimer's Disease: Implications for Therapy

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Abstract: ***Background*:** Alzheimer's disease (AD) is a complex neurodegenerative disorder characterized by the progressive loss of neurons, which typically leads to severe impairments in cognitive functions including memory and learning. Key pathological features of this disease include the deposition of highly insoluble amyloid β peptides and the formation of neurofibrillary tangles (NFTs) in the brain. Mounting evidence also implicates sustained glial-mediated inflammation as a major contributor of the neurodegenerative processes and cognitive deficits observed in AD.

***Methods*:** This paper provides an overview of findings from both human and animal studies investigating the role of microglia and astrocytes in AD, and discusses potential avenues for therapeutic intervention.

***Results*:** Glial-mediated inflammation is a 'double-edged sword', performing both detrimental and beneficial functions in AD. Despite tremendous effort in elucidating the molecular and cellular mechanisms underlying AD pathology, to date, there is no treatment that could prevent or cure this disease. Current treatments are only useful in slowing down the progression of AD and helping patients manage some of their behavioral and cognitive symptoms.

***Conclusion*:** A better understanding of the role of microglia and astrocytes in the regulation of AD pathology is needed as this could pave the way for new therapeutic strategies.

Keywords: Alzheimer's disease, astrocytes, cytokines, glial cells, inflammation, microglia.

1. INTRODUCTION

Alzheimer's disease (AD) is the leading cause of dementia in the elderly population, affecting approximately 24 million people worldwide [1]. First described by Alois Alzheimer in the early 20th century, AD is characterized by severe cognitive deficits including memory loss and language impairment, leading to increasing dependence in everyday life [2]. Neuropsychiatric symptoms such as depression, apathy and hallucinations are also frequently observed in the AD population, thus imposing even heavier burdens on affected individuals and families [3]. However, even if there are indubitably psychiatric symptoms in AD, this disease is more commonly characterized as a neurological or neurodegenerative disorder inasmuch as its key pathological hallmarks include neuronal loss and cellular dysfunction [4]. The amyloid cascade hypothesis, which was formulated in 1992, posits that the main pathological event leading to neuronal loss and dementia in AD is the formation of β-amyloid (Aβ) in the brain, which ultimately leads to the deposition of extracellular amyloid plaques [5]. The production of Aβ is the result of the proteolytic cleavage of β-amyloid precursor protein (APP) by two enzymes: Beta-secretase 1 (BACE1) and γ-secretase [6]. In addition to exerting detrimental effects to surrounding neurons, the accumulation of Aβ in the brain can lead to a series of events including the hyperphosphorylation of the microtubule-associated protein tau and the formation of neurofibrillary tangles (NFTs), both of which highly contribute to the neurodegenerative processes in AD [7, 8].

Over the past few years, the amyloid cascade hypothesis has been the prevailing concept for explaining AD pathogenesis. However, several lines of investigation are now supporting the view that inflammation may be the key neuropathological event leading to neurodegeneration in AD. Indeed, a number of studies have observed elevated cytokine levels in the brain of individuals with AD [9, 10] and animal models of the disease [11-13]. There is also abundant evidence showing that activation of glial cells, including microglia and astrocytes, plays an important role in eliciting the inflammatory signalling pathway involved in neurodegeneration [14, 15]. Also noteworthy are studies showing that reactive astrocytes and microglia are particularly found in high number near senile plaques of individuals with AD [16-18], suggesting a role for these immune cells in the pathogenesis of AD. However, despite significant progress in research, whether the glial-mediated inflammatory response observed in AD is a consequence or a cause of neurodegeneration is still a subject of debate.

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Given the high burden of AD to the affected individual and to the society in terms of the ensued health care costs, a better understanding of the pathophysiological mechanisms of this disorder is urgently needed as this could help promote the development of new therapeutic strategies. The overarching aim of this paper is to provide a thorough overview of the contribution of microglia and astrocytes in inflammation and AD pathogenesis by illustrating key findings from animal and human studies. Potential avenues for therapeutic interventions are also discussed.

2. MICROGLIA DURING HEALTHY AND INFLAMMATORY CONDITIONS

Microglia are resident macrophages that represent approximately 10% of all the cells in the central nervous system (CNS) [19]. Being one of the first immune cells that get immunologically active during an inflammatory reaction, they constitute the first line of cellular defence against invading pathogens and other types of brain injury [20]. Despite being extensively studied, their true origin remains a subject of debate. Early evidence suggested that microglia differentiate in the bone marrow from embryonic hematopoietic precursor cells, whereas more recently, studies have shown that these cells may in fact arise from progenitors in the embryonic yolk sac early during development [21]. Under normal conditions, microglia exist in a quiescent (or resting) state, and are morphologically characterized by small-shaped soma and highly ramified processes [22]. One of the main functions of resting state microglia is to vigilantly monitor the CNS for the detection of pathogens and host-derived ligands, including pathogen-associated molecular patterns (PAMPs) and danger-associated molecular patterns (DAMPs) [20, 23]. The expression of pattern recognition receptors (PRRs) on their molecular surface makes them well equipped for this purpose [24]. In response to invading pathogens, microglia get activated and undergo morphological changes including enlargement of their soma and shortening of their cellular processes [25]. Activated microglia play an important role in the phagocytosis of pathogens and in the clearance of cellular debris and degenerating cells at the lesion site [26]. In addition to their phagocytic activity, activated microglia participate in the presentation of antigens to T cells, thereby coordinating the dialogue between the innate and adaptive immune systems during an inflammatory response [27, 28].

Mounting evidence points to the fact that microglia-mediated inflammatory response is a "double-edged sword", executing both detrimental and beneficial functions [29, 30]. When activated, microglia produce inflammatory mediators including cytokines, chemokines, inducible nitric oxide synthase (NOS), cyclooxygenase-2 (COX-2) and free radicals like reactive oxygen species (ROS), which may disturb neuronal functions and produce cellular damage [20, 31]. Activated microglia also produce a wide array of neuroprotective factors that help prevent neuronal injury, including brain-derived neurotrophic factor (BDNF), glial cell-derived neurotrophic factor (GDNF) and nerve growth factor (NGF) [31-33]. This duality in the effect of microglia on immune-mediated inflammation suggests that these immune cells adopt different functional phenotypes based on their surrounding environment. Depending on their activation state, microglial cells have been broadly classified into a proinflammatory M1 phenotype or an anti-inflammatory M2 phenotype [34]. However, it should be noted that this classification is not universally accepted by research findings, and there are still a lot to learn about the mechanisms underlying microglia functions during these different activation states [35].

The M1 phenotype is "classically activated" by Toll-like receptors or interferon-gamma (IFNγ), and plays a vital role in destroying invading pathogens by producing proinflammatory cytokines, ultimately causing neuronal damage in local tissues [14, 20]. In contrast, the M2 phenotype is "alternatively activated" by interleukin 4 (IL-4) or IL-13, and is involved in the release of high levels of anti-inflammatory cytokines, thus playing fundamental roles in tissue repair and angiogenesis [14]. Interestingly, microglia that have been polarized into an M1 or M2 state can rapidly switch their phenotype in order to adapt to their surrounding microenvironment, thus providing researchers with the possibility of targeting imbalances of macrophage polarization for various therapeutic applications [36]. For instance, M1 macrophages can be polarized to M2-like macrophages following experimental manipulations that inhibit the PI3K/AKT signalling pathway [37] or the NF-κB, MAPK and AKT pathways [38], whereas M2 macrophages can be reprogrammed into an M1 phenotype in response to lipopolysaccharide (LPS) and IFNγ [39, 40].

3. MICROGLIA IN ALZHEIMER'S DISEASE

There is an extensive number of studies indicating that inflammatory pathways are altered in AD owing to exacerbated immune response [41, 42]. The observation that inflammatory processes may promote neuronal loss and cognitive decline [43, 44], together with evidence associating polymorphic variations of inflammatory cytokines with AD [45-47], argue for a potential role of microglia in AD pathogenesis. Microglia are one of the first immune cells that get activated and recruited to the site of injury during an inflammatory response. Understanding how they are involved in AD could not only help decipher the cellular and molecular mechanisms underlying neurodegeneration, but could also open up new avenues for therapeutic interventions. One of the first ground-breaking findings implicating microglia in AD date from studies in the early 1990s showing that these immune cells are highly engaged in the formation of Aβ plaques in the brains of AD patients [41, 42]. More recently, data from studies utilizing animal models of AD have also demonstrated the presence of activated microglia at sites of Aβ deposition, suggesting that these glial cells might physically interact with Aβ and regulate their levels in the brain [43, 44].

Further evidence providing a link between microglia dysfunction and AD pathogenesis comes from genetic studies showing that a null mutation in TREM2 (Triggering Receptor Expressed on Myeloid cells 2) gene, which is specifically expressed by microglia in the CNS, is associated with severe neuritic tau hyperphosphorylation and reduced ability of microglia to envelop amyloid deposit [48]. In addition, genetic deletion of the complement factors C1q and C3, or the microglial complement receptor CR3, reduces the number of

phagocytic microglia and the degree of early synapse loss, suggesting that complement activation can act as an early mediator of plaque associated synapse loss in AD by triggering the activation of phagocytic microglia [49]. Microglia and CR3 also play a crucial role in Aβ homeostasis inasmuch as ablation of CR3 in APP-transgenic mice leads to decreased Aβ accumulation, most likely as a result of increased secretion of Aβ-degrading enzymes and increased ability of microglia to degrade extracellular Aβ [50]. However, despite significant progress in the understanding of the interaction between microglia and Aβ in AD, whether the accumulation of Aβ in the brain precedes microglia activation still remains a subject of debate [51-54].

Microglia interact with Aβ, but also with APP, through specific PRRs, including CD14, CD36 and Toll-like receptors, which are highly expressed on their surface [55-58]. This interaction is required for phenotypic activation of microglia and induction of phagocytosis, and results in the clearance of Aβ from the brain [20, 59]. Inductors of inflammation, such as LPS, also activate microglia to promote the degradation of Aβ [60]. Consistent with the view that microglia are involved in Aβ clearance, impairment of microglia function in transgenic mice facilitates the progression of AD and results in increased Aβ accumulation in the brain [61, 62]. Besides providing beneficial effects to the host, activation of microglia by Aβ or APP also results in an upregulation of inflammatory mediators including inducible nitric oxide synthase (iNOS), tumor necrosis factor-alpha (TNF-α), interleukin-1beta (IL-1β) and IL-6, ultimately leading to exacerbated inflammatory response and severe neuronal loss [63-65] (Fig. **1**).

Taken together, the aforementioned studies suggest that microglia exert dual functions in AD in a context-dependent manner. While moderate activation of microglia provides protective effects by facilitating the clearance of Aβ in the brain, overactivation of these cells by Aβ or APP could trigger an exaggerated inflammatory response that may worsen the neurodegenerative processes in AD. However, despite significant progress in research, very few reports have investigated the relationship between microglia and the formation of NFTs in AD. Although studies thus far seem to point for a role of microglia in the internalization and degradation of tau, the major component of NFTs [66, 67], further investigations are warranted for a better understanding of the molecular mechanisms underlying the role of microglia in AD pathogenesis.

4. ASTROCYTES DURING HEALTHY AND INFLAMMATORY CONDITIONS

Astrocytes are the most abundant glial subtype in the CNS, and similar to microglia, play a crucial role in the regulation of neuroinflammation [68]. Also referred to as astroglia, astrocytes exhibit a star-shaped morphology with cellular processes extending from the soma [69]. In the healthy CNS, astrocytes perform several physiological functions involved in ion homeostasis, neurotransmitter transmission, growth factor secretion, synaptic remodeling, and oxidative stress regulation [42, 70]. In addition, astrocytes play a fundamental role in the protection and differentiation of dopaminergic neurons [71, 72], and have been associated with CNS pathologies like schizophrenia [73, 74] and Parkinson's disease [75, 76], where dopamine neurotransmission is incriminated.

Because of their close proximity to blood vessels and their interaction with endothelial cells, astrocytes also participate in the maintenance and permeability of the blood-brain barrier (BBB), a multi-cellular unit involved in the exchange of molecules in and out of the brain [77, 78]. Ana-

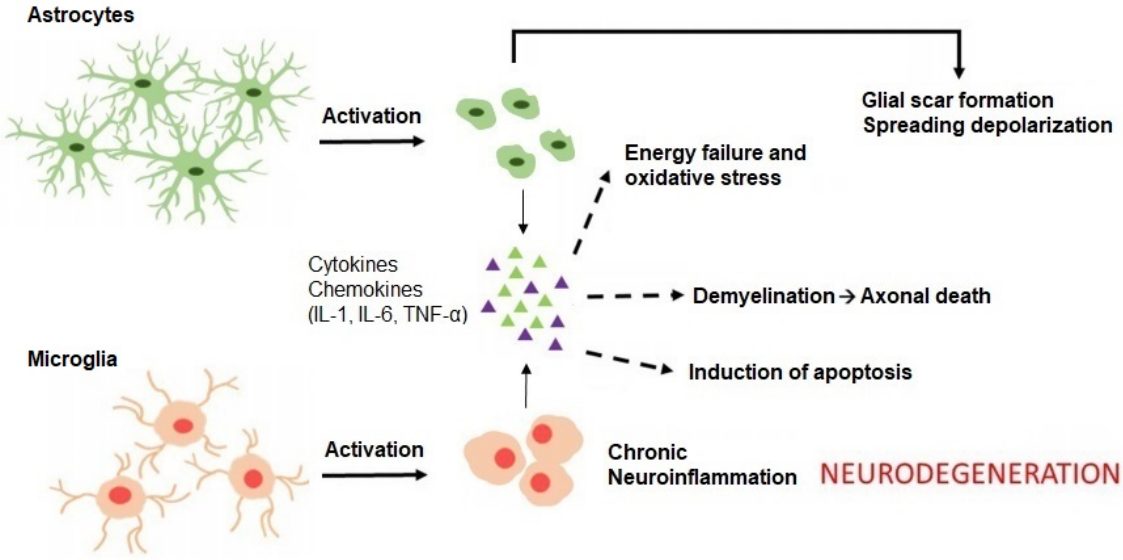

Fig. (1). Detrimental effects of glial-mediated inflammation. Activation of microglia and astrocytes by Aβ or following a signal of damage leads to the secretion and release of inflammatory chemokines and cytokines, including IL-1, IL-6, and TNF-α. These pro-inflammatory elements trigger a cascade of events, such as oxidative stress, demyelination and apoptosis, which eventually lead to neurodegeneration and cognitive decline. Reactive astrocytes also contribute to scar formation around injured tissue by accumulating around amyloid plaques. Adapted with permission from [65]. (*The color version of the figure is available in the electronic copy of the article*).

tomically, astrocytic terminal processes, known as endfeet, almost completely cover the outer surface of the endothelium, forming a lacework of fine lamellae [77]. Through the release of soluble factors such as GDNF, transforming growth factor-beta (TGFβ), basic fibroblast growth factor (bFGF) and angiopoetin-1 (ANG-1), astrocytic endfeet participate in the regulation of angiogenesis and in the formation of endothelial cell-to-cell junctions, thus preserving the function and structural integrity of the BBB [79, 80]. Astrocytic expression of growth factors and cytokines also tightly regulates the permeability of the BBB during inflammatory conditions, and in doing so help control the passage of immune cells into the CNS [81, 82].

Upon activation by pathogens, astrocytes produce a wide array of inflammatory cytokines that can have beneficial or detrimental consequences. In addition, astrocytes express major histocompatibility complex (MHC) class II molecules on their surface, thus acting as antigen-presenting cells for T cells [83, 84]. Depending on their surrounding environment and activation state, astrocytes either suppress [85, 86] or enhance [87, 88] T-cell functions. Although astrocytes are mainly neuroprotective [89], they participate in perpetuating the self-destructive environment by secreting various chemokines and proinflammatory cytokines, including IL-1β and TNF-α [90, 91]. In addition, astrocytes have the capacity to physically interact with microglia, thereby exerting a significant control over their activation [92], phagocytic capacity [93], and ability to secrete inflammatory mediators such as TNF-α [94], IL-12 [95] and iNOS [96].

5. ASTROCYTES IN ALZHEIMER'S DISEASE

Early evidence implicating astrocytes in the pathological processes of AD comes from the observation that these glial cells are associated with senile plaques in the brains of AD patients [97]. More recently, studies have reported profound astrogliosis in the brain of animal models of AD [98] and AD patients [99], where reactive astrocytes accumulate around amyloid plaques *via* phagocytosis of local degenerated dendrites and synapses, encircling Aβ deposits in a manner reminiscent of glial scarring [42, 65] (Fig. **1**). Upon activation by Aβ or following a signal of damage or injury, astrocytes also participate in the secretion of inflammatory cytokines including IL-1, IL-6, and TNF-α, thereby promoting the neurodegenerative processes in AD [65] (Fig. **1**). Although the mechanisms by which astrocytes react with Aβ remain largely elusive, astrocytes express a wide array of receptors, including the receptor for advanced glycation end-products (RAGE), lipoprotein receptor-related proteins (LRPs), membrane-associated proteoglycans and scavenger receptor-like receptors, which recognize and bind to Aβ [42, 100]. On the other hand, Aβ aggregates can stimulate the production of chemotactic molecules including monocyte chemoattractant protein-1 (MCP-1), which help mediate the recruitment of astrocytes to the site of lesion [101, 102]. In addition to promoting the accumulation of immune cells in and around senile plaques, Aβ also contributes substantially to the inflammatory processes mediated by astrocytes. For instance, isolated senile plaques or Aβ aggregates from human AD brains lead to reactive astrogliosis when co-cultured with glial cells [93]. Aβ also activates astroglial nuclear factor-kappa B (NFκB) and complement signalling to impair synaptic density and dendritic morphology [103], and potentiates the production of inflammatory mediators by astrocytes in response to scavenger receptors ligands [104] and LPS [105], thereby contributing to the neurodegenerative changes observed in AD.

The effect of astrocytes on Aβ in AD remains a subject of controversy. Numerous studies have indicated that reactive astrocytes participate in the clearance of Aβ *in vitro*, suggesting a direct role for these glial cells in the attenuation of the neurodegenerative processes in AD [102, 106, 107]. In transgenic mice with AD-like pathology, the astrocyte-mediated clearance of Aβ is mediated by the increased expression of neprilysin [108] and insulin-degrading enzyme [109]. Extracellular brain clearance of Aβ is also promoted by the secretion of matrix metalloproteinase (MMP)-2 and MMP-9 by astrocytes [110]. However, despite being effective in mediating the degradation of amyloid plaques, astrocytes could also produce Aβ under certain inflammatory conditions. For instance, TGF-β1 alone [111] or IFN-γ in combination with TNF-α [112, 113] or IL-1β [113] drives the production of Aβ by astrocytes. Astrocytes could also engulf large amounts of Aβ that are partly digested, eventually leading to astrocytic defects and neuronal apoptosis [114]. Moreover, astrocytes can release many trophic factors that may exert either beneficial or detrimental functions in AD. For instance, GDNF secreted from astrocytes improves neuronal function and cognitive performance in aged rats [115], whereas overexpression of NGF by astrocytes leads to neurotoxicity and the degenerative loss of hippocampal neurons *in-vitro* [116].

Last but not least are studies implicating astrocytes and other glial cells in the evolution of NFTs in AD. In the parahippocampal cortex of AD patients, the number of activated astrocytes correlates with the number of tangles and the stage of NFTs formation, suggesting a role for astrocyte activation in the progression of NFTs in AD [117]. In addition, thrombin, a serine protease expressed by astrocytes and microglia, accumulates in NFTs [118] and participates in the cleavage of tau [119]. Although these studies propose a potential mechanistic pathway by which activated astrocytes may dampen the neurodegenerative processes in AD, more work is required to better understand the cellular mechanisms underlying the formation and progression of NFTs.

6. CLINICAL AND THERAPEUTIC IMPLICATIONS

Based on the compelling evidence implicating glial-mediated inflammation in AD, numerous studies have explored the possibility of using anti-inflammatory drugs to prevent or halt neurodegeneration. In particular, non-steroidal anti-inflammatory drugs (NSAIDs) have shown beneficial effects in reducing glial cell activation and slowing the progression of AD in animal models of the disease [120, 121]. Although the mechanisms of actions of NSAIDs in AD remain to be fully determined, these drugs bind to and activate the peroxisome proliferator-activated receptor-gamma (PPAR-γ) [122, 123] leading to reduced glial cells activation [124, 125] and cytokine-mediated inflammation

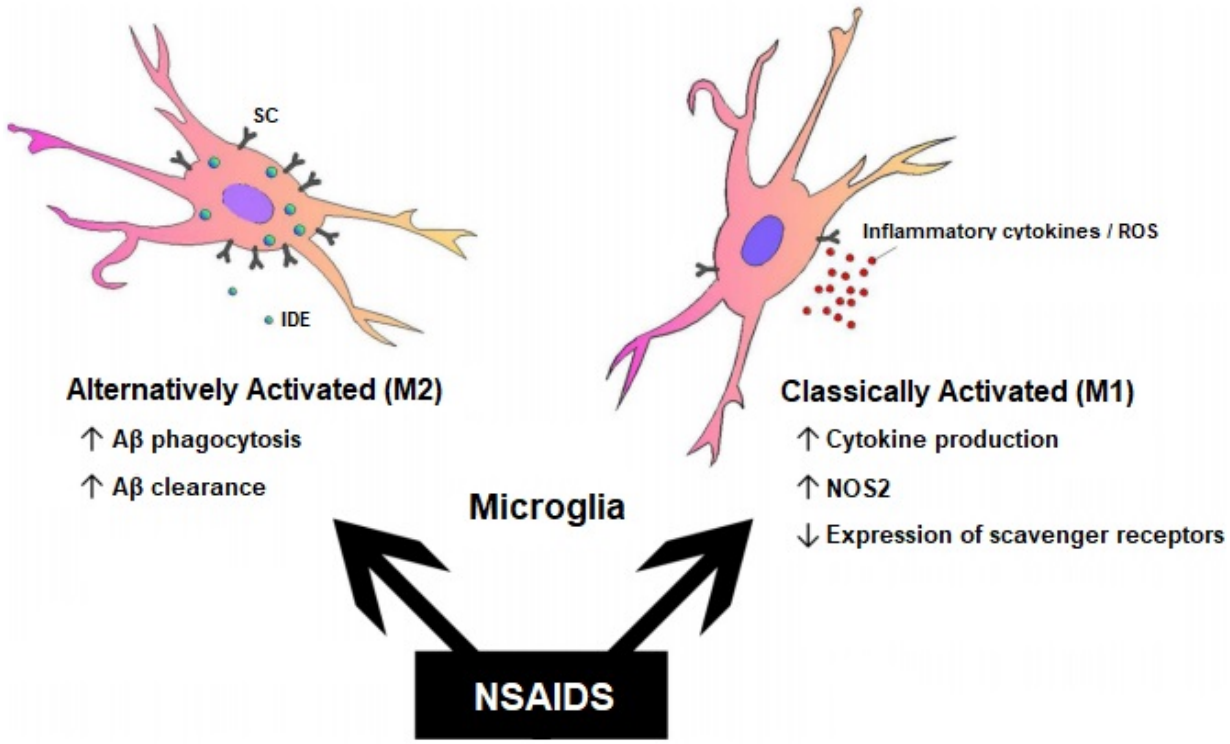

Fig. (2). Differential effects of NSAIDs on microglia and AD pathogenesis. The therapeutic effects of NSAIDs may differ depending on the stage of AD. Alternatively activated (M2) microglia are present during the early stage of the disease, whereas classically activated (M1) microglia are present during the late stage of the disease. Furthermore, different subsets of NSAIDs have different affinity for immune and inflammatory targets in the brain, thus resulting in a range of effects including reduced inflammatory mediators and altered Aβ production. Abbreviations: insulin degrading enzyme (IDE); scavenger receptors (SC). Adapted with permission from [120].

[126, 127]. In mice overexpressing APP, a transgenic model of AD, treatment with the NSAID ibuprofen results in reduced microglial activation and amyloid plaque load [128, 129]. Consistently, a number of other NSAIDs were shown to selectively lower $A\beta_{42}$ levels in the brain of transgenic mice as a result of decreased activity of γ-secretase, the enzyme responsible for the generation of Aβ from APP [130]. The view that NSAIDs delay some forms of AD pathology is also supported by *in-vitro* studies showing that these anti-inflammatory drugs selectively prevent the accumulation of Aβ peptides in culture cells, likely through a decrease in APP production or metabolism [131, 132]. Similar to NSAIDs, PPAR-γ agonists such as pioglitazone or GFT1803 show beneficial effects in attenuating the neurodegenerative processes of AD, namely by reducing Aβ plaque deposition and glial cells activation [133, 134]. However, despite robust preclinical evidence highlighting the protective effects of NSAIDs in AD, clinical trials of these drugs for the treatment of AD have mostly been disappointing so far [135-138], most likely due to the fact that NSAIDs' effect may differ depending on whether they are used in early or late stages of disease [120] (Fig. **2**). Glucocorticoids, a class of corticosteroids, have also been investigated for the treatment of AD due to their anti-inflammatory and immunosuppressive properties. *In-vitro* studies show that glucocorticoids inhibit cortical astrocyte proliferation [139] and exert neuroprotective functions against inflammation by down-regulating the production of nitric oxide (NO) from microglia [140]; effects that are reversed upon the addition of RU-486, a glucocorticoid receptor blocker [139, 140]. Glucocorticoids were also shown to inhibit both Aβ and LPS-induced pro-inflammatory cytokine and chemokine production in mice [141]. However, notwithstanding the beneficial effects of glucocorticoids *in-vitro* and *in-vivo*, clinical trials have failed to observed notable differences in cognitive decline between glucocorticoid-treated and placebo-treated patients [142], thus urging the need for more efficient therapeutic approaches.

As discussed earlier, many inflammatory responses mediated by microglia and astrocytes exert protective functions in AD. Therefore, directing or instructing the machinery responsible for the activation of these glial cells may prove more beneficial than supressing it. Notably, studies employing mouse models of AD have shown that injection of LPS [143] or delivery of gamma oscillations [144] in the hippocampus increases the activation of resident microglial cells and significantly reduces the cerebral Aβ load within the brain parenchyma. The view that microglial activation may be beneficial in AD is also bolstered by studies showing that stimulation of microglia with macrophage colony-stimulating factor (M-CSF) increases the phagocytosis of opsonized aggregated Aβ in culture medium [145], and improves cognitive functions in mice with AD-like pathology [146]. However, under other circumstances, glial cells activation can have deleterious roles in AD, and experimental manipulations that inhibit their activation or signalling may prove more effective in ameliorating cognitive functions. In APP/PS1 mice, a

well-established model of AD, inhibition of astrocytes signalling with adeno-associated virus vectors [147] and selective suppression of astrocytic gamma-Aminobutyric acid (GABA) synthesis resulted in improved cognitive functions including learning and memory [148]. In another study, Heneka and colleagues showed that NLRP3 inflammasome inhibition in the APP/PS1 model of AD skews microglial cells to an M2 phenotype and results in enhanced spatial memory and decreased deposition of Aβ [149]. In addition, inhibition of Aβ-induced microglial activation resulted in increased protection against cell injury and toxicity [150], decreased proinflammatory genes expression [151], and enhanced level of neurotrophic factors [63] *in-vitro*. Together, these findings concur with the view that glial cells exert both protective and detrimental functions in AD, and suggest that the regulation of their activity and function might be an appealing way to promote neuroprotection and prevent cognitive decline.

Although the strategy to modulate glial cells activation has shown great potential in promoting neuroprotection in AD, its proper use has been limited by the fact that the microenvironment surrounding microglia and astrocytes during chronic neuroinflammation may impair their function. Another avenue of therapeutic intervention that might be more appealing in AD is the transplantation of bone marrow (BM)-derived precursor cells from healthy donors. The rationale behind this approach is based from the observation that microglia derived from BM progenitor cells are more competent in eliminating amyloid plaques compared to their resident counterparts [152, 153]. In a mouse model of AD, intracerebral transplantation of BM-derived mesenchymal stem cells (MSCs) restored defective microglial function and resulted in reduced Aβ deposition, decreased tau hyperphosphorylation, and improved cognitive functions [154]. Consistent with these findings, intracerebral transplantation of BM-MSCs in APP/PS1 mice promoted the differentiation of resident microglia into an M2 phenotype, which resulted in marked reductions of Aβ deposition and memory impairments [155]. MSCs derived from other sources, including adipose tissues [156] and human umbilical cord blood [157], have also been shown to provide beneficial effects in experimental AD in terms of promoting learning and memory recovery. The finding that transplanted stem cells or neural precursor cells survive and exert beneficial properties *in-vivo* constitutes a major step towards the development of novel and more efficient approaches for the treatment of AD. However, notwithstanding the beneficial effects of cell therapy in animal models of AD, further studies are needed to investigate its safety profile and long-term efficiency, notably in clinical settings.

CONCLUSION

The studies showcased in the present review support the notion that glial-mediated inflammation is a double-edged sword, performing both detrimental and beneficial functions. The response of microglia and astrocytes to CNS insults is regulated in a context-dependent manner by specific inflammatory mediators that dictate their functional phenotype. While some studies have indicated that glial activation prevents the progression of AD by facilitating the clearance of Aβ in the brain, others have shown that impaired or exacerbated glial activation increases the production of proinflammatory cytokines and Aβ in the brain. This duality in the effects of glial-mediated inflammation on the progression of AD-related pathologies have prompted investigators to explore different—and sometimes opposite—strategies for the treatment of AD. However, despite significant progress towards the development of new therapeutic approaches in animal models of AD, there is still no cure for this disease in humans, and patients are left with the same choices and disappointing prognosis they faced decades ago. It is therefore essential for future studies to continue characterizing the mechanisms of glial-mediated inflammation in AD, including potential cross-talk between different cellular signalling. A better interpretation of data from animal studies and their relevance in the context of human health is also needed, as this could open the way to numerous opportunities in terms of potential implications in the clinic.

CONSENT FOR PUBLICATION

Not applicable.

CONFLICT OF INTEREST

The author declares no conflict of interest, financial or otherwise.

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