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REVIEW ARTICLE

Neuroinflammation and Alzheimer's Disease: Implications for Microglial Activation

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Abstract: Microglial activation is a hallmark of neuroinflammation, seen in most acute and chronic neuropsychiatric conditions. With growing knowledge about microglia functions in surveying the brain for alterations, microglial activation is increasingly discussed in the context of disease progression and pathogenesis of Alzheimer's disease (AD). Underlying molecular mechanisms, however, remain largely unclear. While proper microglial function is essentially required for its scavenging duties, local activation of the brain's innate immune cells also brings about many less advantageous changes, such as reactive oxygen species (ROS) production, secretion of proinflammatory cytokines or degradation of neuroprotective retinoids, and may thus unnecessarily put surrounding healthy neurons in danger. In view of this dilemma, it is little surprising that both, AD vaccination trials, and also immunosuppressive strategies have consistently failed in AD patients. Nevertheless, epidemiological evidence has suggested a protective effect for anti-inflammatory agents, supporting the hypothesis that key processes involved in the pathogenesis of AD may take place rather early in the time course of the disorder, likely long before memory impairment becomes clinically evident.

Activation of microglia results in a severely altered microenvironment. This is not only caused by the plethora of secreted cytokines, chemokines or ROS, but may also involve increased turnover of neuroprotective endogenous substances such as retinoic acid (RA), as recently shown *in vitro*. We discuss findings linking microglial activation and AD and speculate that microglial malfunction, which brings about changes in local RA concentrations *in vitro*, may underlie AD pathogenesis and precede or facilitate the onset of AD. Thus, chronic, "innate neuroinflammation" may provide a valuable target for preventive and therapeutic strategies.

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INTRODUCTION

Neuroinflammation represents a key process in many neurodegenerative disorders, including Alzheimer disease (AD), the most common neurodegenerative disorder in the elderly. With continuously ageing societies, AD imposes a massive socio-economic burden with still largely unmet needs concerning the elucidation of underlying neuropathological processes, development of early diagnostic strategies and preventive options. Currently available treatment options exhibit small effect sizes and do not significantly halt or alter the course of the disease, where a significant part, if not most of its progress, has likely taken place before the onset of first clinical symptoms [1]. This highlights the need for a better understanding of causally underlying, and of potentially exacerbating neuropathological processes, which will be a prerequisite for the design of more effective treatment strategies.

The pathophysiology underlying AD, especially sporadic, non-familial AD, is complex and involves both genetic and environmental factors. According to the most prominent pathogenic concept, the amyloid cascade hypothesis, there are two hallmarks, which consist of extracellular Amyloid-beta (Aβ) plaques and development of intracellular neurofibrillary tangles, composed of (hyperphosphorylated) Tau protein aggregates. Both features have repeatedly been demonstrated to significantly contribute to neuronal degeneration, both in animal, cell culture models, and in postmortem studies [2-6]. Moreover, known genetic mutations in familial AD and increased Aβ accumulation in Down's syndrome convincingly demonstrate that amyloid homeostasis plays a central role in AD pathophysiology (for reviews see [7-9]). Deposition of plaques and development of tangles follows a specific neuropathological pattern: a progressive deposition within the brain of extracellular senile plaques, the accumu-

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lation of intracellular neurofibrillary tangles and the neuronal loss in hippocampal and other cortical and subcortical areas. Altered processing of Amyloid Precursor Protein (APP) generates various peptides that, depending on their aggregation states exhibit differential toxicity, which is of great importance for diagnostic purposes and for AD pathogenesis in general [10-13].

While the amyloid cascade hypothesis has been the central pathogenic concept for decades, emerging evidence suggests that inflammatory processes in the central nervous system (CNS) may also significantly contribute to the pathophysiology of AD, likely involving a variety of different CNS cell types and homeostatically controlled functional processes, eventually affecting neuronal homeostasis and precipitating increased neuronal cell death in a rather indirect manner. Recent Genome-Wide Association Studies (GWAS) have identified variants in the gene Triggering Receptor Expressed on Myeloid cells 2 (TREM2), a molecule involved in macrophage survival, to be associated with AD, supporting a direct involvement of the "immune system" in the AD pathophysiology [14, 15].

For decades the brain has been considered an immunologically privileged site, but this notion has gradually been weakened, not least by Besedovsky's study in 1983, which suggested that specific neurochemical changes are observable inside the brain upon a peripheral immunological challenge [16]. So in fact, the CNS is an immunologically active site, with complex immune responses mediated by different cell types, connected to the periphery across and despite the blood brain barrier (BBB). Recent developments in neuroimmunology have demonstrated numerous neuro-immunological connections, including proof for innervation of peripheral lymphoid organs, responsiveness of both neuronal and immune cells to canonical neurotransmitter- and cytokine signaling, and finally the responsiveness of microglial cells, the brain's innate immune cells, responding also to peripheral immune challenges [17]. Thus, it is justified to assume that the brain and the immune system both speak a common "biochemical language". Even though AD like other neurodegenerative disorders is not considered a typical immune-pathology, a role of the immune system in their pathogenesis has been repeatedly suggested [18-20]. Various proinflammatory stimuli, including but not limited to local ischemia, acute trauma, peripheral inflammation, or neuronal cell death in general, have been demonstrated to differentially affect surrounding glial and immune cells [21-24]. Although it is widely believed that neuroinflammation is secondary to the pathology caused by the presence of plaques and tangles, it may at least exacerbate the neuronal loss [25-27].

In the following, we will give a brief review of recent concepts and advances linking AD pathogenesis with specific immunological changes. In particular we will focus on a potential role for microglial cells in (early) AD pathogenesis and discuss "microglial activation" as a putatively druggable target for disease-modifying therapeutic approaches.

CYTOKINES, LYMPHOCYTES AND ASTROCYTES IN AD

Cytokines are a large family of low molecular weight proteins that are secreted by numerous cell types and that provide an essential basis for intercellular communication [28]. Depending on the type of the secreting cell, the target cells and most importantly the type of an immune response (pro- or anti-inflammatory), there are specific pro- but also anti-inflammatory cytokine signatures in the CNS [29-31]. Cytokines binding to their respective receptors drive a cascade of intracellular events and play a critical role in the initiation of immune responses. Most cytokines, including their receptors, have been detected in numerous areas of the brain, even if their precise mapping remains incomplete [32, 33]. The known capacity of the cytokines to induce expression of other cytokines, their regulatory role in host defense and inflammatory diseases, and the hallmarks of AD neuropathology highlight the importance of cytokines in AD pathogenesis (Fig. **1**).

Most of the known cytokines can be synthesized and released within the central nervous system by various cell types, including astrocytes, microglia and neurons. Different functions of the cytokines have suggested a central role for cytokine signaling in the CNS, potently affecting neuronal homeostasis and, upon pathologically altered signaling, potentially resulting in impaired cognitive functions that are characteristically present in several neuropsychiatric disorders such as depression or dementias [34-37]. In more detail, some cytokines, such as interleukin (IL)1β, IL-6 and tumor necrosis factor alpha (TNFα) have been associated with cognitive decline and dementia [38-40].

In AD, various reports exist on altered central and peripheral cytokine levels. A meta-analysis of Swardfager *et al.* strengthens the role of higher peripheral concentrations of IL-6, TNF-α, IL-1β , Transforming growth factor -(TGF)-β , IL-12 and IL-18 [41].

Previous studies have shown that TGF-β s may have both beneficial and detrimental effects in AD. TGF-β 1 is an anti-inflammatory cytokine which protects neurons against damage induced by aggregates of Aβ, excitotoxins and hypoxia/ischemia. Its overproduction in astrocytes reduces Aβ accumulation and promote Aβ phagocytosis in rats and in cultured microglial cells. In the AD brain, chronic inflammation and neuronal vulnerability to Aβ may be due to reduced TGF-β 1 signaling, thus favouring the onset of AD [42, 43]. Several studies have shown increased levels of inflammatory cytokines and cytokine receptors expressed and released by peripheral blood mononuclear cell (PMBC) of AD patients [44-47]. Both IL-1 and IL-6 have been shown to increase the synthesis of amyloid precursor proteins by specialized cells [48], and were able to promote Aβ accumulation, playing a role in disease progression [49]. Anti-inflammatory cytokines, such as IL-10 play an important role in neuronal homeostasis and cell survival. An *in vitro* study showed that pre-exposure of glial cells to IL-10 inhibits Aβ-induced production of proinflammatory cytokines [50]. Polymorphisms in genes that encode inflammatory cytokines have been identified as risk factors in AD, but although cytokine dysregulation may be evident during different phases of AD disease, the underlying patho-mechanisms remain subject to discussion [51-56].

More recent evidence suggests that the radical concept of a perfectly controlled "blood brain barrier" may not be true, not least in AD-associated neurodegeneration. At physio-

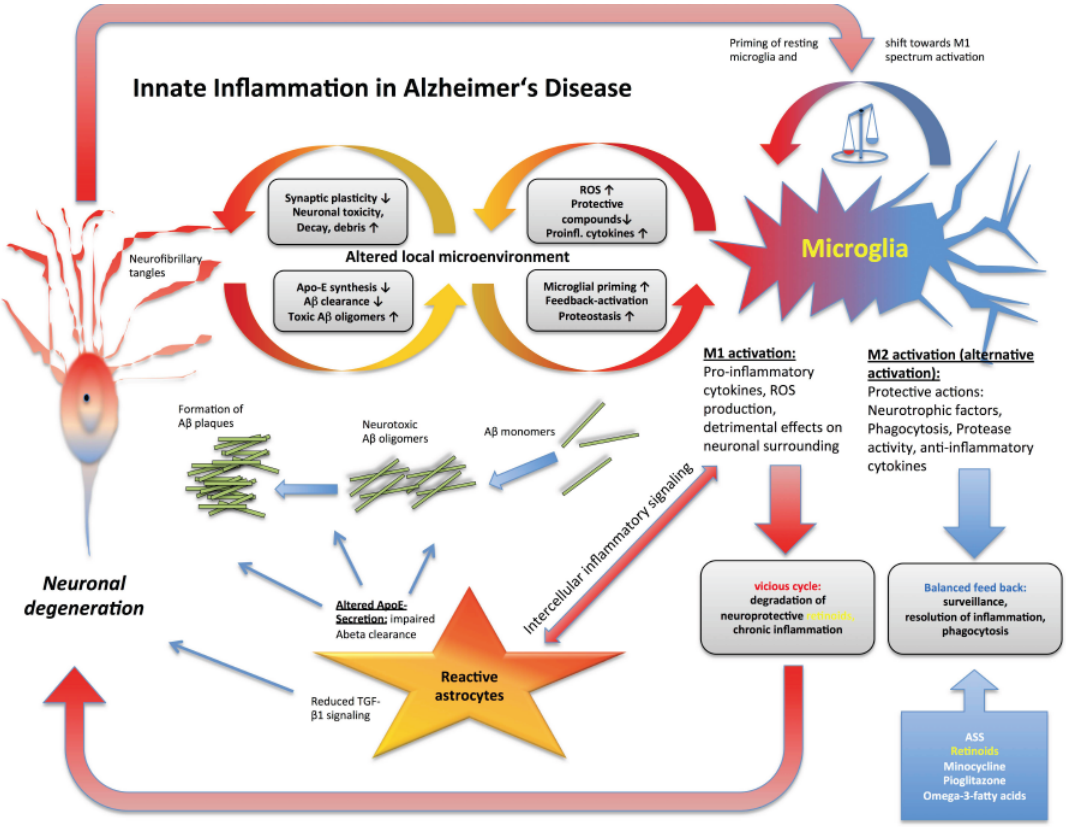

Fig. (1). Microglial M1/M2 polarization**,** Aβ deposition and the cytokines network are determinant for a pro-inflammatory environment that contribute to neurodegeneration. The role of minocycline and other compounds in differentially targeting microglial polarization, as a promising pharmacological strategy in the treatment of AD

logical conditions, T-lymphocytes trafficking in and out of the brain are discussed to impact on neuronal integrity and function. Altered T-cell homeostasis may thus influence cognitive behavior, and modulate proinflammatory conditions associated with reduced levels of neurogenesis. Several studies have demonstrated that T-cells are needed for normal brain function, regulating the activation of myeloid cells, and that specific populations of T-cells are present in distinct compartments of the CNS [57, 58]. Since T-lymphocytes are present in inflamed areas of AD brains and increased expression of HLA-DR has been observed to co-localize with neuritic plaques, an involvement of an adaptive immune reaction in AD cannot be excluded [59]. Although after Aβ immunization in AD mouse models, the production of anti-Aβ antibodies, stimulation of microglial phagocytosis and removal of senile plaques was observed, clinical efficacy of Aβ immunization remains to be demonstrated [60, 61]. *In vitro* studies have not been able to identify an Aβ-induced lymphocyte proliferation and the presence of anti-Aβ antibodies in the serum of AD patients, indicating that an existence of a T-cell tolerance to Aβ could be hypothesized [62, 63].

Like microglial cells, astrocytes also play a major role in neuroinflammation. Proinflammatory activation of astrocytes includes induction of early response genes, expression of various adhesion proteins, cytokines, eicosanoids, and proteases. Astrocyte activation is furthermore accompanied by upregulation of glial fibrillary acidic protein (GFAP). At the morphological level, astrocytic swelling, hyperplasia, and proliferation are observed, eventually resulting in the development of glial scars, also known as reactive "gliosis". Such activated astrocytes are termed "reactive astrocytes", a neuropathological hallmark coming along with many, if not all neurodegenerative diseases. Astrocytes may also act as immune effector cells, and may mediate immunological processes *via* a local production of chemokines and cytokines [64, 65], to which even neurons may respond directly. Neurons are known to express molecules that were originally considered specific for immune functions, such as class I major histocompatibility complex (MHC-1), complement, cyclooxygenases and immunomodulatory cytokines including tumor necrosis factor alpha (TNFα) or interleukine-6 (IL6) [66, 67].

In AD there is an increase in astrocyte numbers around ghost tangles, which are believed to be the left-overs of former tangle-filled neurons, and around Aβ plaques. They exhibit distinct morphological characteristics in each of these pathological interactions, possibly indicating a distinct role in each. The reaction to extracellular Aβ accumulation consists in astrocyte accumulation in plaques in the cerebral cortex and subcortical gray matter [68]. Animal models of AD suggest that astrocytic activation may occur early during the progress of AD. At the same time, astrocytes are often found to co-localize with activated microglia, a finding that suggests intercellular inflammatory signaling between these two cell types to take place and points to a joint contribution in the process of AD-related neuroinflammation.

MICROGLIAL CELLS

The myeloid cell lineage plays a crucial role in the development of innate and adaptive immune responses in the CNS, which is represented by astrocytes, oligodendrocytes, and ependymal cells on the one hand, a cell population also termed "macroglia", and by microglial cells on the other hand. Microglia are specialized CNS macrophages originally termed "Hortega cells", since they were first extensively described by Piu del Rio-Hortega in the 1920s [69].

Although most neuropsychiatric disorders are discussed to involve neuroinflammation to some extent at varying points in time during the course of the disease, a clear-cut distinction must be drawn between classical neuroinflammatory processes underlying *e.g.* autoimmune disorders of the CNS such as multiple sclerosis (MS), and the neuroinflammation that appears to occur in AD and other neuropsychiatric disorders. While MS-related pathophysiology has been shown to predominantly involve lymphocyte-driven demyelination [70, 71], in most other neurodegenerative disorders such a direct, contributing involvement of the adaptive immune system has not been observed. Instead the brain's innate immune system, represented by microglia, appears to be essentially involved, which seems especially relevant for AD-related pathology [72]. In fact, even processes such as synaptic turnover and cellular plasticity are today considered to crucially involve microglial cells, which help to eliminate not only ceased cells' detritus, but even participate in synaptic plasticity by "stripping" redundant synaptic boutons [73].

Microglial cells are the tissue-specific macrophages of the brain and represent one of the most important non-neuronal cell types in the CNS, forming an integral part of the CNS network [73-75]. These cells are normally found at a ramified phenotype, distributed in a regular pattern throughout the healthy CNS and each microglial cell is thought to be in charge of "actively sensing" its local microenvironment. During normal, physiological surveillance of the microenvironment, they fulfil a plethora of essential duties in maintaining complex homeostatic processes of the developing and adult CNS. Since microglia can also act as professional antigen presenting cells (APC), the precise contribution of adaptive and innate immune responses of microglia to AD pathology is not yet fully understood [76]. A number of receptor- and non-receptor-mediated interactions between microglia, cytokines and components of the AD senile plaques have been reported, suggesting that a vicious circle might be generated. For example, IL-1 can regulate Amyloid Precursor Protein (APP) processing and Aβ production *in vitro* and fibrillar Aβ increase proinflammatory cytokines and reactive oxygen species production [77]. Moreover, various receptor-dependent interactions of microglia with Aβ plaques and soluble oligomers have been reported [27, 78-80]. Apart from scavenging functions in physiological or pathologically altered Aβ metabolism, microglial cells also contribute to various other physiological functions of the brain. They are for example also essentially involved in modulating synaptic plasticity by "stripping" inactive, obsolete synaptic connections and are known to specifically interact with neuronal and glial cells *via* many more pathways [73, 75]. As macrophages, which may either arise from surveilling, ramified microglia or from invading monocytes, they are also capable of receiving chemotactic signals from adjacent and remote areas, can rapidly change in morphology towards an activated, ameboid-like phenotype and eventually becoming capable of phagocytosis to remove malfunctional tissue structures, bacteria and infected, apoptotic or otherwise abnormal cells and structures. It is therefore not surprising that an accumulation of activated microglial cells is frequently observed at various lesion sites in the CNS. However, being integral part of a physiological immune response in the CNS, it is still unclear, whether these observations represent a physiological consequence in response to another preceding pathological process in AD patients' brains, or whether an altered microglial function might be underlying, or at least contributory to, AD pathogenesis. In this context, a histopathological study by Streit, Braak and colleagues demonstrated that in AD patients' brains at sites of neurofibrillary degeneration there were numerous dystrophic microglial cells present [72]. Looking at brains from 19 human subjects at different Braak stages, the authors demonstrate data suggesting that microglial dystrophy may occur early, potentially even before the onset of classical Aβ and Tau pathology. The authors conclude that it may not be "microglial activation" that results in AD pathology, but rather a premature loss of proper microglial function, especially when taking into account that microglial cells were originally meant to protect rather than destroy neuronal structures [72]. A direct causal connection or underlying cell-biological mechanism directly connecting microglial malfunction with the initiation of the disease, however, has not been demonstrated so far. Against the background of lipopolysaccharide (LPS) -activated microglia to negatively impact neurons, removing protective factors from the local microenvironment, it might also be a question of maintaining a physiological balance between M2- and M1-polarized microglial cells in the healthy brain in order to avoid neuronal degeneration and, possibly, onset of AD-related pathology [81].

Microglial cells rapidly respond to a variety of pathogenic stimuli, including those associated with ischemia, local or systemic infections, and most importantly AD-related pathology [82, 83]. Under physiological conditions, microglia can phagocytose and degrade toxic Aβ oligomers, thus microglial activation and migration towards a lesion site always represents an integral part of the physiological reaction in response to a primary cytotoxic, inflammatory or infectious insult [84, 85]. An increasing body of evidence suggests that some byproducts of this physiological reaction may not be beneficial for adjacent neuronal cells. In a recent *in vitro* study using murine primary microglial cells, proinflammatory microglial activation with lipopolysaccharides was demonstrated to strongly induce catabolic enzymes capable of efficiently degrading retinoic acid, which represents a locally synthesized, homeostastically regulated neuroprotective small molecule [81]. Another *in vitro* study was able to demonstrate that conditioned media from microglial cell cultures exerted differential effects on developing neuronal cells depending on the activation state of the microglial cells [86-90]. Thus, proinflammatory activation of microglial cells is associated with significant changes in the microenvironment, which may certainly be required for an effective im-

mune response, but which may not necessarily be beneficial for adjacent neuronal cells. Inflammatory markers such as cyclo-oxygenase-2 (COX-2), IL-1β, TNF-α, and fractalkine (CX3CL1) were highly expressed in Aβ-burdened neurons, and activated astrocytes and microglia were associated with these neurons [91]. In other words, these observations suggest that microglial cells, upon activation, may always directly or indirectly cause some "collateral damage" to neighboring neuronal cells while fulfilling their scavenging duties. Against this background it becomes clear that microglial dynamics are likely homeostatically regulated, and that microglial activation may not be considered only black or white and simply be completely blocked in a therapeutic approach to avoid potential negative consequences [92-94]. Instead, distinct microglial functions, not least in healthy tissue, as well as factors determining the homeostatic process of microglial activation and deactivation must be explored to a further extent. Particularly a direct or indirect contribution of microglia to brain metabolic pathways involving classical AD-related targets such as amyloid or TAU, but also small molecules such as retinoic acid, may be of interest [95-97]. Interestingly enough, microglial cells are highly responsive to the endogenous neuroprotectant retinoic acid, which dampens proinflammatory activation [98-100]. Moreover, microglia carry a variety of classical "neuronal receptors", including the well-studied N-methyl-D-aspartate (NMDA)-receptor, which represents a ligand-gated, ionotropic ion channel that upon exposure to high concentrations of glutamate may also result in microglial activation [87]. Most studies addressing microglial activation use bacterial lipopolysaccharides, often isolated from specific E. *coli* strains, to model activation *in vitro*. Moreover, primary microglial cultures as well as animal models of AD are most frequently performed in mice, a well-studied mammalian species for which most biotechnological strategies and transgene techniques have been well established and optimized. Despite these advantages, there is ample evidence for significant phylogenetic differences between the primate and the murine immune system, especially when it comes to age-related, ontogenetic changes of the human brain and the brain's innate immune system [101-103]. While activation of murine microglia and macrophages is frequently assessed by simply measuring nitric oxide (NO) release or induction of inducible NO-synthetase [104], this defense mechanism likely plays a different role in the human [105, 106]. Although various human cells are able to synthesize NO, at least in adult human macrophages, this pathway seems to be either absent or completely different from murine species [107, 108]. Finally, recent preclinical research has shed more light on the differential process of microglial activation, which may not only be considered as active and inactive. Instead, microglial activation can have different facets and dimensions of polarization, including pro- but also alternative, anti-inflammatory features [109].

MICROGLIAL ACTIVATION IN AD

Pathological activation of microglia, or "microglial malfunction", seems to be an early event in AD, preceding cognitive impairment that is observed later in the course [72, 110-112] and is accompanied by release of several pro-inflammatory factors, such as complement, cytokines, chemokines and acute phase proteins, responsible for perpetuating the inflammatory reaction [113-117]. On the other hand, like other macrophages, microglia can also be activated/ polarized towards a rather protective, anti-inflammatory phenotype. While classical activation of macrophages can be achieved through TH(1)-type cytokines such as interferon-g or lipopolysaccharides, a TH(2)-type cytokine driven polarization is termed "alternative macrophage activation" and involves cytokines such as IL-4 and IL-13 [118, 119]. Various substances and conditions have been demonstrated to polarize macrophages and microglial cells towards the classical, also termed M1, or the alternative pathway which is termed M2 activation. A recent report by Medeiros *et al.* demonstrated that the nonsteroidal anti-inflammatory agent acetylsalycilic acid can induce M2 activation and be of beneficial effects in a murine AD model [120]. Another recent study on the effects of the pleiotropic anti-inflammatory antibiotic and prototype inhibitor of microglial activation minocycline has revealed that the drug selectively inhibits M1 polarization of microglia [121]. With respect to AD pathology, a remarkable study using the peroxisome proliferator-activated receptor (PPAR)-γ agonist pioglitazone revealed dramatic changes in plaque load of drug-treated APPswe/PS1Deltae9 mice, which correlated with appearance of plaque-loaded M2 instead of M1 microglia/macrophages, suggesting selective M2-polarizing effects of pioglitazone to underlie this histopathological observation and the reversal in memory deficits, which was also observed by the authors [122]. *In vitro* studies using human microglial cells also revealed increased expression of CD206, a marker for M2 polarization, upon exposure to omega-3-fatty acids, which are agonists at retinoid-x-receptors and PPARs [123].

Recently,the role of glial metabolic shift in neuroinflammation has exhaustively reviewed [124] and the modulation of microglial activation has proposed as new therapeutic strategy for Alzheimer's disease [125]

Interestingly, microglial cells express receptors classically described for brain-specific communication such as neurotransmitter receptors and those first discovered as immune cell-specific such as for cytokines and chemokines, by which microglial cells can communicate with macroglial cells, neurons and with cells of the immune system [75, 126, 127]. In this context, it is also noteworthy that microglial cells have been identified to express functional NMDA-receptors that, upon exposure to ligands, trigger microglial activation [87, 128].

TARGETING MICROGLIAL ACTIVATION: A STRATEGY FOR TREATMENT AND PREVENTION OF AD?

In summary, current evidence supports the notion that a mere inhibition or even ablation of microglial cells in the CNS will not positively impact, but possibly even exert negative effects on the pathogenesis of neurodegenerative diseases. Instead, differentially modifying the activation state of microglia, likely from a predominantly M1 towards an M2 phenotype, seem to represent promising therapeutic strategies. Microglial polarization will therefore remain a putatively early druggable target with disease-modifying poten-

tial in AD. With respect to drugs selectively inhibiting M1 polarization, the study by Kobayashi and colleagues has shed new light on minocycline, a second generation tetracycline with pleiotropic neuroprotective and anti-neuroinflammatory effects [121, 129]. While minocycline has convincingly been demonstrated to inhibit M1 activation of macrophages in various neurodegenerative settings that involve a pro-inflammatory component, there are also important hallmark studies in animal models of AD that report beneficial effects of the well-tolerated drug on AD histopathology as well as cognitive and behavioral outcomes [130-133].

CONCLUSION

It is becoming increasingly clear that differentially targeting microglial polarization, by minocycline or other yet to be identified compounds, may represent a promising pharmacological strategy in the treatment of AD. In comparison to other, currently available therapeutic options that target amyloid metabolism or tau pathology, pharmacologically modulating microglial polarization may provide an approach with truly disease-modifying potential.

CONFLICT OF INTEREST

The authors confirm that this article content has no conflict of interest.

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