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Literature Review Article

A Human Perspective on the Immunopathology of Microglial Cells in Alzheimer's Disease

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Abstract

Alzheimer's Disease (AD) has, in recent years, become the focus of intensive research efforts aimed at determining the various factors, as well as their degrees of involvement, in its pathogenesis and progression. Of such factors, the immunocompetent microglial cells have repeatedly been implicated as potentially key contributors to the disease process—having namely garnered much attention from genome-wide association studies, as well as studies conducted using murine models. Despite the versatility and convenience of these models, AD remains a distinctly human condition. The present review aims to consolidate evidence regarding the nature and putative role played by microglial activation in the pathogenesis and progression of AD, as it pertains to the aging human brain.

Introduction

Alzheimer's Disease (AD), a debilitating and ultimately fatal neurodegenerative disease, has been identified as the most common cause of dementia in the western world, and constitutes a growing concern in the face of aging populations across the globe [1]. First characterized histologically by Alois Alzheimer in 1907, the disease manifests clinically through a progressive functional decline in both the cognitive and behavioral capacities of sufferers, including perhaps most notably the symptom of memory impairment [2-4]. Though clinical diagnoses may reliably be made upon clinical examination and neuropsychological testing of patients, diagnosis can be confirmed postmortem by the identification of senile plaques and tau pathology in neocortical brain tissue [5]. Senile Plaques (SPs) have long been defined as representing extracellular aggregates of the Amyloid-β peptide (Aβ), while tau pathology involves hyperphosphorylation of the microtubule-associated tau protein. The subsequent intraneuronal deposition of hyperphosphorylated tau results in Neurofibrillary Tangles (NFTs) and neuropil threads formation, as well as the appearance of dystrophic neurites in the brain parenchyma [6]. The abundant presence of these histopathological hallmarks in AD, in addition to widespread neuroinflammation, are generally believed to lead to neurodegeneration and neuronal impairment—resulting in the clinical symptoms of AD.

The amyloid cascade hypothesis posits that the deposition of the Aβ peptide into insoluble aggregates constitutes a primary driver in the pathogenesis of AD, by giving rise to downstream neurotoxic events such as NFT formation, mitochondrial dysfunction, oxidative stress and ultimately, neuronal and synaptic loss [7]. A variation of the amyloid cascade hypothesis links Aβ deposition to the chronic state of inflammation observed in the AD brain, by suggesting that the direct activation of microglial cells by Aβ represents a crucial intermediary step in the induction of neurotoxic downstream pathology (Figure 1) [5,8]. Following aberrant activation, microglial cells begin releasing pro-inflammatory cytokines, reactive oxygen species (ROS), complement, as well as neurotoxic factors [8,9]. In doing so, microglial cells putatively promote neurodegeneration both directly, through the release of neurotoxic mediators, and indirectly, by facilitating Aβ and hyperphosphorylated tau deposition in a self-sustaining process [10,11]. The amyloid cascade hypothesis has long dominated the field of Alzheimer's research, as it offers an explanation for the development of SPs and tau pathology in individuals with mutations of the APP gene or APP-processing genes in familial AD [12]. This hypothesis, or rather, its microglial-centric variation, pervades much of the current literature regarding the involvement of microglial activation in the progression of AD—perhaps due to the convenient fit between documented neuroinflammation and the microglial-activating capabilities of Aβ [13]. However, several other hypotheses, including the mitochondrial dysfunction and cholinergic deficit hypotheses, provide different perspectives on amyloidosis with regards to disease progression [7,14,15]. The prion hypothesis, which has recently resurfaced and gained some traction in the field, proposes that the geographical propagation of both tau and Aβ deposits at various disease stages may occur through a prion-like mechanism—that is, by the corrupting interaction of aberrant protein conformations with native states [16]. Despite the amyloid cascade hypothesis' influence, it has failed to account for findings of high

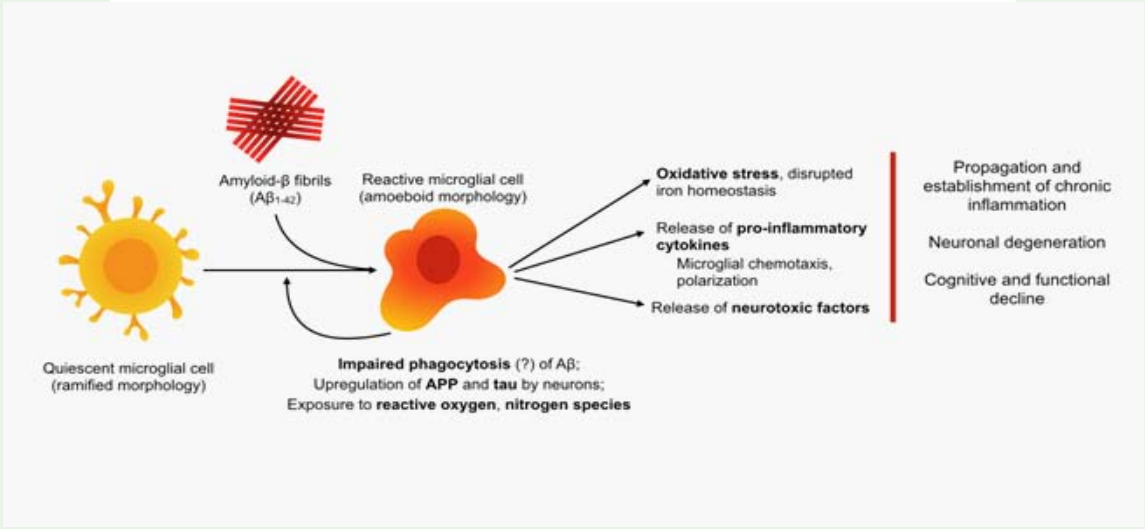

Figure 1: Potential drivers and consequences of microglial activation, and their implications in human AD.

neuritic plaque load and AD lesions in non-demented individuals through its inherent emphasis on Aβ accumulation as the disease-driving step [17,18]. Further, the failure of Aβ-centric treatments in clinical trials, such as tramiprosate and semagacestat, has prompted a certain paradigm shift in recent years, leading many to question the relevance of this explanatory framework [19,20].

Limitations of Mice Models in AD

The advent of transgenic mouse models for AD in the early 2000s has provided myriad ofnew opportunities for the study of disease pathogenesis and hypothesis testing to an area of research previously limited by the inherently cross-sectional nature of postmortem studies [21]. The basic premise for the vast majority of these transgenic models lies in the generation of amyloid deposits, which can be achieved through the constitutive overexpression of the Amyloid Precursor Protein (APP), or through mutations in the presenilin genes, which form a proteolytic complex involved in the processing of APP into Aβ [21,22]. The modification of endogenous genes (known as gene targeting) or introduction of transgenes to the murine genome allows the development of organisms which, upon aging, display several characteristics of the AD brain. Such features include diffuse and dense-core extracellular amyloid deposits, neuroinflammation, dystrophic neurites as well as cerebral amyloid angiopathy [21-23]. Though tau pathology may be induced in murine models through the introduction of a *MAPT* transgene into embryonic stem cells, such lesions must be produced independently of amyloidosis—a feature which may undermine the validity of murine tau models when considering the complex interplay of pathological processes in human AD [22,24]. The use and combination of various mutations to mimic AD in mice have yielded a considerable number of models, each unique with regards to the temporal development, as well as the nature and type of lesions present—the specifics of which have been reviewed elsewhere [21,23]. Despite their numerous applications, murine models often paint an incomplete picture of the disease's neuropathological hallmarks and, by extension, of its processes. An important discrepancy of the murine model lies in the extent and distribution of neuronal loss, which fails to match that found in the AD human brain [23]. In addition, though the study of the microglial response in mice models may prove convenient in assessing involvement, causal and temporal relationships during AD pathogenesis, it is important to consider that inherent differences between the mouse and human immune systems could have an impact on the therapeutic (and potentially clinical) relevance of such findings [10]. The present review aims to consolidate evidence regarding the nature and putative role played by microglial activation in the pathogenesis and progression of AD, as it pertains to the aging human brain.

Neuroinflammation and the Implication of Microglial Cells in AD Pathogenesis

Under homeostatic conditions in the adult brain, microglial cells have been estimated to account for 10-15% of neuroglia in the Central Nervous System (CNS) and are generally acknowledged as resident immunocompetent cells [5,25]. Originally identified in 1932, microglial cells have since been the subject of much speculation and controversy with regards to their functionality within the brain [26]. In healthy tissue, the microglias adopt a 'ramified' morphology, and are thought to play a critical role in the maintenance of an extracellular environment for optimal neuronal functioning and communication [27]. Such functions may include the clearing of cellular debris as required, antigen presentation, as well as the sensing of threats, or tissue insults in the CNS [26,27]. Microglial cells have been found to play an active role in synaptic pruning and remodelling—and have been documented to interact directly with degenerating synapses in the aging brain of mice [28]. Thus, despite their quiescent state, these cells are highly dynamic and carry out proactive functions in the absence of infection, ischemic insults, trauma or neurodegeneration [5,26,27]. Upon encountering potentially harmful stimuli or evidence of neuronal damage, microglial cells undergo extensive phenotypic changes—a process generally referred to as 'activation'. The process of microglial activation is characterized by changes from the ramified to the large, amoeboid morphology, increased motility in response to chemotactic signals, some degree of proliferation, changes in gene expression, as well as increased secretion of a vast range of pro-inflammatory mediators [5,26]. Microglial activation has also been reported to enhance the cells' capacity for localized phagocytosis [9,10,29,30].

Neuroinflammation, which can broadly be defined as a chronic and self-sustaining inflammatory state in the CNS, has repeatedly been implicated as an accompanying neuropathological feature of AD, and has long been hypothesized to constitute a driver of the disease process [11,31,32]. Though neuroinflammation likely arises as a result of complex interactions between several glial components (i.e. microglia, astrocytes, etc.), researchers have sometimes applied a microglia-centric reductionist perspective to investigate the chronic inflammatory state rampant in the AD brain. This focus on microglial cells may partly be explained by several lines of evidence demonstrating the close association between Aβ deposits and reactive microglial cells in postmortem tissue samples [9,17,33]. This colocalization effect, first documented in 1927 by Bolsi, is still being reproduced in recent works [13]. Yet, and rather paradoxically, the role of the neuroinflammatory response in the context of neurodegeneration in AD remains elusive—potentially representing either a non-specific microglial response to the threat of extracellular aggregates, or by contrast, a unique inflammatory response to the chemotactic and neurotoxic properties of the Aβ peptide [34]. The implication of microglial cells in AD, however, runs deeper than their observed interaction with Aβ.

Over the past decade, several Genome-Wide Association Studies (GWAS) have revealed that a number of single nucleotide polymorphisms in inflammation-linked genes may confer some protection, or conversely be linked to a greater risk of developing AD—genetic loci which include that of the Triggering Receptor Expressed On Myeloid Cells 2 (*TREM2*) and CD33, a sialic acid lectin found on cells of hematopoeitic origin [35-38]. *TREM2* represents a locus of interest in AD, as homozygosity for loss of function mutations of this particular gene has been associated with a form of early-onset dementia in carriers [39]. Additionally, certain allelic variants of the *TREM2* gene have been linked to a higher risk of AD in carriers [39]. The locus of CD33, a transmembrane receptor involved in phagocytosis and depletion of pro-inflammatory cytokines in the periphery, was likewise implicated via an allelic variant (*T* allele) shown to be protective against the development of AD in carriers, relative to the more common *G* allele [36]. Though CD33 had previously not been characterized in the brain, a recent postmortem examination of AD tissue demonstrated that CD33 is indeed expressed on immunoreactive microglial cells, and that the marker is significantly overexpressed in AD tissue [36]. Furthermore, human carriers of the protective *T* allele were shown to exhibit lower levels of $CD33^+$ microglial cells in a dose-dependent fashion—that is, homozygosity for the *T* allele was correlated with the lowest number of CD33-immunoreactive microglia [36]. Last but not least, certain allelic variants of the *APOE* gene, which are expressed by glial cells, have repeatedly been linked to increased risk or protection against the development of AD [1]. Taken together, the implication of microglial-associated genes in AD by GWAS highlight a potentially crucial role for microglial cells in the pathogenesis of the disease.

Oxidative stress has repeatedly been implicated in the pathogenesis of the disease, as both potential initiator and consequence of microglia-driven neuroinflammation. Indeed, increases in lipid peroxidation, protein and nucleic acid oxidation can readily be observed in the brains of AD patients relative to controls [40,41]. While under stress (or perhaps during the instigation of early disease-modifying processes), microglial cells have the ability to produce reactive oxygen and nitrogen species (i.e. superoxide, nitric oxide), which may damage neurons and trigger cell death, both apoptotic and necrotic [42]. Exposure of microglial cells to such reactive species has been shown to result in activation of the transcription factor NF-κB—thus promoting microglial upregulation of pro-inflammatory cytokines and mediators [41]. Dysfunctions in iron homeostasis have been implicated in the promotion of oxidative stress in AD, as ferrous iron may bind Aβ and catalyze the production of free radicals via the Fenton reaction [43]. Altered iron storage, in which microglial cells play a key role through their marked expression of the iron-binding protein ferritin, may thus represent another point of involvement for microglial cells in the pathogenesis of AD [42].

The existence of tissue samples showcasing profuse levels of Aβ aggregates and NFTs from patients having demonstrated no discernible cognitive impairment during their lifetime has long been acknowledged, and represents a perplexing caveat to the amyloid cascade hypothesis [17]. If, indeed, the progressive cognitive impairment observed in AD stemmed from an initial aggregation of the Aβ peptide and its downstream effects, one might call into question the set of neuropathological conditions seemingly protective against neurodegeneration and cognitive decline in such individuals. Interestingly, these so-called "High Pathology Controls" (HPCs)—as identified by Lue and colleagues in 1996—showed reductions in both synaptic loss and neuroinflammation (including microglia reactivity) when compared to postmortem tissue from AD cases [18]. These findings led the authors to posit that neuroinflammation may be necessary for the synaptic loss to occur in the predisposed, 'high-pathology' brain [18]. A few years later, neuroinflammation and microglial activation once more became subjects of interest with the emergence of epidemiological evidence suggesting that regular use of Nonsteroidal Anti-Inflammatory Drugs (NSAIDs), such as ibuprofen or naproxen, was linked with a reduced risk of developing dementia [44]. Subsequent studies performed on human brain samples seemed to yield inconsistent findings. When conducted using a small sample size, postmortem evaluations of cortical samples from AD sufferers taking NSAIDs revealed no improvement with regards to plaque or NFT load relative to non-medicated AD cases. Though a two-fold increase in microglial cell activation was detected in the samples of AD patients *vs.* controls, no significant differences were found between levels of microglial reactivity in the NSAID-medicated AD cases compared to their non-medicated counterparts [45]. By contrast, a significant reduction in microglial activation was documented in non-demented elderly patients with a history of NSAID use compared to non-demented elderly patients with no history of NSAID use [46]. In both groups, approximately 60% of samples were found to have SPs, allowing for an examination of microglial activation and NSAID use in the context of amyloid deposition [46]. Remarkably, the $NSAID^+$/SP^+ patients were found to have a four-fold reduction in the number of activated microglia [44,46]. Ultimately, the inconsistencies discussed above reflect the contentious role of microglial activation in AD—the suppression of which could help to slow neurodegeneration through depletion of anti-inflammatory and neurotoxic mediators, while paradoxically eradicating any beneficial attempts at Aβ phagocytosis [44].

Despite the persuasive evidence linking aberrant microglial responses to the pathoprogression of AD, it is important to consider that microglial involvement is neither strictly limited nor unique to

the disease at hand. In fact, some form of microglial cell activation has been documented in the vast majority of neurodegenerative diseases, such as in amyotrophic lateral sclerosis and in Parkinson's disease, in addition to having been found at sites of ischemic or traumatic injuries [47-49]. In keeping with these findings, the application of a critical gaze when evaluating the relevance of microglial involvement in AD may help to identify potential differentiators with regards to the nature and temporal course of the microglial response. An understanding of the differential involvement of microglial cells throughout the course of this disease may provide novel therapeutic avenues seeking to halt, or prevent altogether, disease progression.

The Microglial response to Amyloid-β

In attempting to differentiate the nature of the microglial response in AD and that of other neurodegenerative diseases, many academics have turned to the Aβ peptide as a potential differentiator. The aforementioned relationship between microglial activation and Aβ deposition has long been acknowledged, and is routinely confirmed by recent studies [17]. Indeed, activated microglial cells—as identified by immunoreactivity to myriad immunohistochemical markers including Iba1 and HLA-DR—display a characteristic tendency to cluster in and around Aβ dense-core deposits [13,34]. From this colocalization predictably arose two important conjectures. First, it was predicted that the accumulation of the Aβ peptide in its fibrillar form is an inherently immunogenic event, and secondly, that this clustering of reactive microglia may result from the chemotactic effect of Aβ in its oligomeric form.

Microglial profile and receptor interactions

The immunogenicity of human Aβ oligomers was confirmed in an elegant 1996 study, which found that *in vitro* exposure of human microglial cells[1] to synthetic Aβ oligomeric variants, such as $Aβ_{1-40}$ and $Aβ_{1-42}$, triggered a neurotoxic response in these cells [13]. Perhaps of greater insight, however, was the finding that an oligomeric species with a stronger tendency for aggregation (i.e. $Aβ_{17-42}$) was unable to elicit microglial neurotoxicity [13]. The implications of these finding are two-fold. First, these are suggestive that neurotoxicity in AD could stem from the inherent immunostimulatory capacities of $Aβ_{1-40}$ and $Aβ_{1-42}$, oligomeric species prominently found in neuritic plaque, rather than from direct Aβ aggregation [13,50]. Second, these findings imply that the N-terminus of the Aβ oligomers ($Aβ_{1-16}$) may play an important role in the activation process of microglial cells in response to Aβ. Though the use of cultured human microglia, such as those utilized by Giulian et al. (1996) in the above study, can be limiting due to low accessibility, these cells have provided critical insight in the characterization of microglial activation in AD. Studies conducted from these cultures have revealed that human microglial cells can be stimulated by exposure to Aβ to express a vast range of immune markers and modulators, including: the costimulatory CD40/CD40L, phagocytic receptors (CD32, CD64, CD68) as well as pro-inflammatory cytokines (namely, IL-1β, IL-6 and TNF-α) [10,51]. When considered along with findings suggesting constitutive HLA-DR expression by microglial cells, this profile is consistent with that of mature Antigen-Presenting Cells (APCs) in the periphery upon encountering danger- or pathogen-associated signals [51]. Interestingly, differences in secretion and expression levels of such immune mediators may vary based on the disease status of the individual (i.e. AD *vs.* nondemented) from which these microglial cells were isolated [52]. When incubated at low Aβ concentrations, elderly human microglia isolated from AD patients were found to secrete significantly higher levels of the Macrophage Colony-Stimulating Growth Factor (M-CSF) and the complement receptor C1q when compared to microglial cells isolated from Nondemented (ND) controls [51]. Such a bias could be reflective of a constitutive difference, which could predispose an individual to develop the disease, or indeed a change in microglial phenotype brought about by pathological processes in AD—a chasm in which the latter seems more probable, given the rampant inflammation documented in AD tissue [11,31,32].

The documented neurotoxic capabilities of Aβ, and the apparent necessity of microglial cells to generate such neurotoxicity *in vitro*, strongly suggests a pathogenic relationship in which the Aβ peptide acts as a ligand to a putative microglial receptor [17,32]. Indeed, Aβ fibrils and/or oligomers alone have been found to be poor inducers of neuronal damage, even at micromolar concentrations[2] *in vitro* [32]. Such ligand-receptor interactions in AD could have profound therapeutic implications, and the identification of associated receptors has accordingly been the subject of much discourse. Though numerous Aβ-binding proteins have been identified, the Receptor for Advanced Glycation End Products (RAGE) was rapidly singled out as an important player in the Aβ-microglia interactions upon its characterization. In cultured human adult microglial cells, co-incubation of aggregated Aβ with anti-RAGE $F(ab')_2$ fragments significantly reduced the dose-dependent release of M-CSF by the microglia [53]. In addition to blockage of M-CSF release, treatment of Aβ-exposed microglial cells with anti-RAGE $F(ab')_2$ seemed to decrease microglial migration towards discrete Aβ deposits [10,53]. Together with findings of increased RAGE immunoreactivity upon exposure of microglial cells to Aβ postmortem, these findings suggest that ligation of Aβ could mediate microglial activation, proliferation and chemotaxis in a pathogenic positive feedback mechanism driven by Aβ accumulation [10].

In addition to RAGE, scavenger receptors have been implicated in the microglial response to the Aβ peptide in AD. Scavenger receptors are commonly expressed on macrophages in the periphery, as they effectively bind and allow for the internalization of negatively-charged molecules (i.e. oxidized low-density lipoproteins, etc.) [54,55]. The function of such receptors befits their title of scavengers, as they assist in the clearance of a number of waste products through endocytosis [54,55]. The class B Scavenger Receptor (SR) CD36, also known as SARB-2, has been identified as a receptor for fibrillar Aβ, and as such a mediator of microglia-driven inflammation [54-56]. Interestingly, a study by Ricciarelli, et al., which examined brain specimens from sporadic AD cases and elderly, high-pathology controls[3], found that CD36 expression in the frontal cortex was correlated with Aβ load, regardless of disease status [54]. These findings were taken to suggest that increased expression of CD36 in these high-pathology controls could represent an early, transitionary period for non-cognitively impaired, high-pathology individuals into clinical AD [54]. Though it may be speculated that early involvement of microglia via the interaction of CD36 and Aβ could explain (at least in part) the correlation detailed above, it is difficult to draw temporal links based on the limited data available. In addition, such speculations should be made cautiously, as they rely heavily on the assumption that high-pathology controls represent a transitionary population at subclinical

disease stages—an assumption which could well prove unfounded [54]. Due to scarcity of available elderly human microglia, a study performed using N9 mouse microglia and human macrophages cell lines detected a significant decrease in ROS (particularly in H_2O_2) secretion from cells incubated with fibrillar Aβ and treated with anti-CD36 Monoclonal Antibodies (mAbs) [56]. Though this experimental framework remains to be applied to human microglial cells, due to potential differences in NO and ROS metabolism between human and rodent microglia, the findings detailed above highlight a complementary pathway through which Aβ-driven neuronal damage may occur in AD [17]. Though incompletely understood, the complex neuroinflammatory response observed in the human AD brain evidently stems from a variety of receptors and corresponding downstream signalling pathways. RAGE may preferentially stimulate M-CSF release, while SRs may contribute to ROS-driven neurotoxic damage [54,56]. An effective treatment approach seeking to reduce neuroinflammation in AD may accordingly require the targeting of a combination of inflammatory pathways.

Inefficient phagocytosis of Aβ

The capacity of microglial cells for phagocytosis, though well documented, remains a contentious topic within the context of AD, due its controversial contribution to pathogenesis and progression [57,58]. Though mice models have shown that microglial activation may prevent amyloidosis, the contribution of 'protective' phagocytosis by microglia in humans is disputed, perhaps in part driven by the scarcity of studies characterizing the phagocytic response in human AD [59]. Phagocytosis of Aβ, either in its oligomeric or fibrillar forms, has been shown to occur *in vitro*, and is currently regarded as a potential route of Aβ removal *in vivo* [12,58]. Phagocytosis, or rather, internalization of Aβ was initially demonstrated by a series of experiments by Wisniewski and colleagues, which documented the presence of fibrillar Aβ in distended vesicles within the microglia *in vitro* [60,61]. It is interesting to note that the Wisniewski studies were, at the time of publication, interpreted to mean that the microglia played a role in the pathogenesis of AD by acting not as phagocytic cells, but rather as active contributors to Aβ deposition [60]. The expression of APP by microglial cells suggests that some contribution to Aβ plaque deposition by the microglia may in fact occur in AD—but the hypothesis that the observed aggregation of microglial cells near Aβ deposits indicates that such cells drive amyloidosis, rather than simply stand as a reflection of Aβ-induced chemotaxis and activation of the microglia, appears to have fallen out of favour [30,58].

Thought the internalization of Aβ by human microglia has since been demonstrated by several studies, questions surrounding the ability of such cells to degrade internalized Aβ remain, at present, largely unanswered [12,13,30]. *In vitro* studies, such as that by Rogers and Lue, suggest that co-incubation of human microglial cells and Aβ deposits leads to the progressive removal of plaque over a 2-4 week period [30]. Yet, such findings do not necessarily indicate the ability of microglial cells to degrade large Aβ aggregates, nor that Aβ phagocytosis occurs with any degree of efficiency *in vivo*, during the development of AD. Exogenous application of activated human microglial cells to unfixed, postmortem sections of the AD brain results in limited phagocytosis and at least partial degradation of Aβ, as indicated by the presence of small intracytoplasmic granules [12]. These findings are supplemented by that of studies suggesting that microglial phagocytosis may become impaired during the development of AD. A compelling argument can be made based on the increased risk of AD conferred by rare missense mutations in the *TREM2* gene, which encodes a type I transmembrane glycoprotein preferentially expressed on microglial cells in the CNS [39,62]. A recent report by Kleinberger, et al. suggests that mutations in the gene coding for the TREM-2 receptor impair murine microglial phagocytosis of $A\beta_{1\text{-}42}$ aggregates [62]. Though this finding remains to be validated using human microglial cells, its relevance is made evident at the epidemiological level by GWAS which have identified a significant risk increase of AD in carriers of certain *TREM2* alleles [35,63]. Impaired phagocytosis in AD, however, may result from more than the reduced activity of faulty receptors. Lucin and colleagues have demonstrated that levels of beclin 1, an intracellular mediator of receptor-mediated phagocytosis, and associated protein Vsp35 were significantly reduced in microglia isolated from the superior and middle frontal gyri of AD cases, relative to nondemented controls [64]. Beclin-1 was further shown to play an important role in the recycling of TREM-2—a role which accounted for reduced Aβ phagocytic abilities in microglia with disrupted beclin-1 expression[4] [64].

In addition to characterizing the phagocytic response of microglial cells during AD, some researchers have turned their gaze to perivascular macrophages as a source of phagocytic potential in the CNS. Pey and al. recently investigated the distribution of CD163—a scavenger receptor with phagocytic potential, whose expression is restricted to perivascular macrophages [65]. The association of $CD163^+/Iba1^-$ microglial cells with Aβ in the parenchyma suggests recruitment of peripheral macrophages in an attempt to control amyloidosis. CD163 immunoreactivity was reduced in Parkinson's Disease (PD) cases relative to AD—a finding which may be attributable to the intracellular *vs.* extracellular nature of lesions in PD and AD, respectively [65]. Phagocytosis of Aβ (or lack thereof) during the pathoprogression of AD seems to represent, despite the present scarcity of human studies on the matter, a crucial piece in our understanding of the aberrant microglial response in AD. Whether this response be viewed primarily as a loss of 'protective' capacities of microglia due to senescence, or conversely as a consequence of frustrated attempts at phagocytosis of Aβ, is currently unknown—but may be elucidated in part by deepening our understanding of phagocytosis and its contribution to the pathogenesis of AD in humans [9].

Phenotypic alterations of microglial response in AD

The study of immunocompetent cells often involves the classification and delineation of various phenotypes, as an attempt to codify the astounding complexity of behaviours exhibited *in vivo* by such cells. Microglial cells, being no exception to this trend, were initially categorized, based on HLA-DR immunoreactivity, as either polarized towards the M1 or M2 phenotypes [66]. As part of this dichotomy, borrowed from the nomenclature of macrophage polarization, the M1 phenotype represents 'classical activation', and is associated with the release of pro-inflammatory markers such as IL-1β, IL-6 and TNF-α [65]. Its antipode, the M2 'alternative activation' phenotype, was once associated with the microglial secretion of IL-10 and TGF-β, as well as an increase in phagocytic activity—thus potentially lending itself to a protective role in the context of AD

[65,66]. The polarization scheme of microglial behaviour, has since been expanded to comprise four distinct phenotypes—M1, M2a, M2b and M2c—the details of which are reviewed elsewhere [66-68]. According to this classification, the M2a phenotype promotes tissue repair and wound healing, while the M2b polarization involves Fc-mediated activation of microglial cells by immune complexes, such as opsonized Aβ [66,68]. Lastly, the M2c phenotype corresponds to a relatively quiescent state, known as 'acquired deactivation', yet may involve a certain degree of phagocytosis [68].

Though an overwhelming majority of the work surrounding microglial polarization in AD has been performed using animal models, certain studies have contributed to our understanding of this phenomenon in humans. In a recent comparison of polarized microglia from early and late-stage AD cases[5], Sudduth and colleagues demonstrated the phenotypic heterogeneity of microglial cells, which were identified as belonging to the M1, M2a and M2c subsets [69]. Interestingly, examination of early-stage AD cases yielded distinct polarization of microglia towards either the M1 or M2a phenotypes. Yet, the microglial cells from the late-stage AD cases displayed a global elevation of inflammatory marker expression—a finding which stands in sharp contrast to the dichotomy exhibited by early-stage cases [69]. Based on these observations, the authors posited that the polarized microglial responses may help to explain conflicting findings with regards to the role of microglial cells in AD, such as the disputed protective effect conferred by regular NSAID use described above [44,69]. The apparent lack of a microglial response biased towards the M2b phenotype is corroborated by Wilcock, et al., in a study which aimed to characterize the inflammatory phenotype in both sporadic AD cases and in Down Syndrome (DS) cases exhibiting AD-type pathology [3]. M2b polarization, which was demonstrated in DS samples but not in AD cases, may represent a key differentiator in the AD microglial response. Though such studies raise important questions surrounding the nature of the microglial response, they fail to provide clinical data to supplement their phenotypic findings, thus limiting their application with regards to AD progression and pathogenesis [3]. Another differentiator of the microglial response in AD may lie in the expression and distribution of CD163, identified as a marker of the M2c phenotype [65,68]. $CD163^{+}$ microglia appear more prominently in stained AD brain sections, relative to stained samples from PD cases—though the clinical relevance of this finding remains unclear [65]. The characterization of the inflammatory response in AD, as well as the factors that modulate the polarization of microglial cells in humans, though arduous, may yield findings which transcend the study of AD to that of other neurological conditions.

Microglial Activation and Tau

Though the microglial response has repeatedly been implicated in end-stage assessments of AD brains, and its association with Aβ deposits heavily researched both in humans and animal models, the relationship existing between aberrant activation of microglia and tau pathology remains poorly understood. The lack of extensive characterization of this relationship in humans seems to generate an interesting paradox, in light of evidence suggesting that NFT load may constitute a more potent correlate of cognitive decline and thus disease progression than amyloid load [17,70]. Indeed, tau immunoreactivity was demonstrated by Vehmas, et al. as a strong indicator of dementia, in a postmortem histopathological examination of both definite and 'probable' (MCI) AD cases [17]. In a relatively large cohort of confirmed AD cases, Hayes and colleagues surprisingly reported no correlation between activated microglial cell load, as identified by ferritin immunoreactivity, and Aβ load in stained brain sections [11]. However, levels of hyperphosphorylated tau were found to correlate significantly with microglial load [11]. One might speculate that this finding suggests a role for microglial activation as an intermediary between amyloid deposition and tauopathy. Furthermore, a recent study by Lee et al. found that exposure of neuroblastoma cells to the Conditioned Medium (CM) of activated human microglia resulted in a 7-fold increase of APP expression, and a corresponding 4-fold increase in tau expression *in vitro* from the neuroblastoma cells [32]. Further treatment of the neuroblastoma cells exposed to activated microglia CM with both NSAIDs and/or IL-10 resulted in a substantial decrease in tau mRNA levels [32]. From these findings, it may be hypothesized that rampant and aberrant microglial activation may result in a microenvironment that promotes the overexpression of both APP and tau from human neurons *in vivo*. Such a phenomenon could, on the basis of tau self-propagation, provide a trigger and allow for the seemingly independent spread of pathological tau in a caudal-rostral fashion [1,16,32]. Though much remains to be done in order to understand how tau overexpression may contribute to NFT formation, the above findings may nevertheless bear important pathogenetic and treatment implications.

Quantifying Microglial Activation in Real-Time

The study of AD in humans, though a fascinating and necessary pursuit, is inherently limited, in many cases, to *in vitro* or postmortem experimental protocols. In the last several years, however, the use of Positron Electron Tomography (PET) technology has allowed for an exploration of the previously unseen—the living, working AD brain, along with aspects of its metabolism. Neuroimaging techniques such as PET take advantage of the binding capabilities of radioligands *in vivo*, such as that of [^{11}C]-Pittsburgh Compound B ([^{11}C]PiB) to Aβ, and can thus be utilized in clinical trials as a means to quantify Aβ-targeting treatment outcomes [71,72]. Coupled to the use of other radiotracers, such as [^{11}C]PK11195 and [^{11}C]DAA1106, which bind to the Peripheral Benzodiazepine Receptor (PBR)[6] expressed at high levels on activated microglial cells, [^{11}C]PiB allows for an examination of disease progression and quantification of the neuroinflammatory response in living AD patients [69,71]. By enabling researchers to explore the temporal relationships between pathogenic components, and to analyze clinical implications of such pathological findings, PET imaging provides a new insightful perspective to the study of AD [69,71,72].

The first attempt at quantifying the degree of microglial activation relative to amyloid load *in vivo* was carried out by Edison and colleagues, who measured [^{11}C](R)PK11195 retention in both AD cases and ND controls [8]. Though the degree of Aβ deposition, as measured by [^{11}C]PiB uptake, was not correlated with cognitive impairment, significant increases in both microglial activation, as well as Aβ load were observed in AD cases, relative to controls—thus corroborating previously discussed postmortem findings [8,13,34]. More recently, PET imaging of

microglial activation in AD has lent itself to the investigation of so-called 'Prodromal' AD (pAD) cases—that is, putative AD cases at early disease stages, characterized by mild cognitive impairment [72,73]. Schuitemaker, et al. found no differences in the binding

potential of [^{11}C]PK11195 amongst AD cases, pAD cases and healthy controls [73]. The follow up of pAD cases allowed for an analysis of binding potential based on clinical progression to disease—an analysis which identified no detectable difference in microglial activation between individuals who remained disease-free, and those who eventually developed dementia [73]. In line with these findings, Wiley and colleagues also reported no statistically significant difference in [^{11}C]PK11195 retention across AD, pAD and control groups [73]. Such negative findings seem to argue against the involvement of microglial activation and resulting neuroinflammation in driving the disease process, or perhaps for the end-stage involvement of such inflammatory processes [73,74]. Conversely, the inability of such studies to reach significance may in part be explained by insufficient affinity or specificity of ligand binding to microglial PBR [72]. The latter seems, however, unlikely in light of a study by Okello, et al., in which individuals exhibiting Mild Cognitive Impairment (MCI) and Aβ loads[7] within range of that observed in AD cases were found to display higher [^{11}C]PK11195 binding potential than their MCI counterparts with low levels of Aβ deposition [75]. Further, 3 of the 5 individuals identified as belonging to the MCI/high Aβ pathology group progressed to clinical AD [75]. While the conflicting findings detailed above are hard to reconcile, the emergence of new radioligands with higher affinity and specificity, such as [^{11}C]DAA1106, may yield more consistent results across cohorts and modes of analysis [69]. Using this new ligand, Yasuno and colleagues demonstrated increased microglial activation in brain regions of a small number of patients with mild to moderate AD, relative to controls [76]. No correlation was found between cognitive scores and binding potential of [^{11}C]DAA1106 in any of the groups [76]. Though such results should be considered preliminary on the basis of the small sample size used, the differentiated microglial responses observed amongst mild AD sufferers and ND controls through PET could represent a novel method for identifying patients at earlier stages of disease.

In addition to allowing for the quantification of microglial activation during the time course of the disease, PET grants the abilities to investigate other aspects of AD in relation to the microglial response. Glucose hypometabolism, a long acknowledged and thoroughly documented feature in AD patients, was hypothesized by Yokokura, et al. to result from activation and local neurotoxic action of microglial cells [77]. Both glucose hypometabolism as well as higher levels of microglial activation were correlated with lower cognitive scores—an interesting relationship which warrants further investigation [77]. Though speculating on the potential involvement of microglial cells in the context of glucose hypometabolism may be tempting, it is poorly justified given the small sample size of the study at hand. In addition to investigating microglial activation and simultaneous pathological processes in AD, neuroimaging offers new avenues to study pathogenic aspects of microglial metabolism throughout the course of disease. Such was the goal of a recent study by Zeineh and colleagues, which set out to observe the localization of iron-containing microglial cells. Hypo intense foci viewed by high-resolution MRI were shown to correlate strongly with microglia as well as iron, in subsequent staining of matching brain sections [70]. Based on these findings, further postmortem studies will be required to characterize the involvement and potential role of iron physiology in the AD microglial response [65]. Advances in imaging techniques such as PET and MRI may one day prove instrumental in identifying individuals at risk of AD. As the technology now stands, PET studies performed on larger samples may help to better capture the dynamic nature of microglial response in AD pathogenesis and progression.

Concluding Remarks

The above review aimed to summarize the available evidence surrounding the microglial response in human AD—primarily consisting of *in vitro* experimental protocols utilizing human microglial cells, postmortem investigations of the human brain, along with PET studies. Though animal models show great merit in hypothesis generation and testing, they may, in certain cases, yield conflicting results [33]. In such instances, it may be of value to look to human studies, in an attempt to gain insight on the potential sources of incongruity in the data. The evidence reviewed above seems to point to an active role taken on by microglial cells in promoting immunopathological, neurodegenerative changes in the AD brain. Indeed, the inflammatory microglial response observed in AD is herein deemed inconsistent with the notion that microglial activation represents an innocuous byproduct of early neurodegenerative changes. A more comprehensive characterization of microglial polarization in human AD seems a promising avenue, both in terms of understanding the effector subset involved in inducing neurotoxicity, as well as in identifying novel immunotherapeutic targets specific to the AD response. With regards to postmortem evidence, every effort should be made to promote the obtainment of clinical data for study samples prior to death, as the current lack of clinical data in postmortem investigations of microglial activation in relation to Aβ or NFTs represents an important lacuna in the literature. The refinement of PET radioligands to exhibit higher affinity or higher specificity towards activated microglial cells may further advance our current understanding of the neuroinflammatory response *in vivo*. As the aforementioned PET studies focus narrowly on the relationship between Aβ load and microglial activation, future studies should attempt to characterize the potential link between hyperphosphorylated tau and the microglial response—rendered possible through the use of ligands such as [F18]-T808 [78]. Ultimately, though the PET studies highlighted above should be replicated on a larger scale with more participants, and potentially include longer follow-up periods, the use of non-invasive imaging technology may eventually constitute an important means of identifying at-risk individuals, in the hopes of stalling disease progression years prior to clinical manifestation [1].

Footnotes

1. Isolated from the postmortem brains of patients with no history of dementia [13].
2. Aβ concentrations far exceeding that which might be observed in vivo, throughout the course of disease [32].
3. Cognitively unimpaired individuals with a considerable degree of Aβ pathology and low tau pathology [50].
4. Performed using murine samples.
5. As established by MMSE scores of patients, 6 months prior to death [65].
6. The PBR receptor is preferentially expressed on microglial cells (relative to astrocytes) [67].
7. As quantified by the magnitude of [11C]PiB retention [70].

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