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Neuroinflammation in Alzheimer's disease; a source of heterogeneity and target for personalized therapy

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Abstract

Neuroinflammation has long been known as an accompanying pathology of Alzheimer's disease. Microglia surrounding amyloid plaques in the brain of Auguste D were described in the original publication of Alois Alzheimer. It is only quite recently, however, that we have a more complete appreciation for the diverse roles of neuroinflammation in neurodegenerative disorders such as Alzheimer's. While gaps in our knowledge remain, and conflicting data is abound in the field, our understanding of the complexities and heterogeneous functions of the inflammatory response in Alzheimer's is vastly improved. This review article will discuss some of the roles of neuroinflammation in Alzheimer's disease, in particular, how understanding heterogeneity in the individual inflammatory response can be used in therapeutic development and as a mechanism of personalizing our treatment of the disease.

Keywords

Microglia; amyloid; Alzheimer's; cytokines; phenotypes; inflammation

Microglia

The key mediators of the neuroinflammatory response in the brain are its resident immune cells, microglia. In the early 1920s, Pio Del Rio Hortega made the first clear identification of microglia in the brain. Prior to this, however, glia were recognized by Nissl in 1899, who thought them to be neuroglia and hypothesized that they had abilities for migration and phagocytosis (reviewed by (Barron, 1995). In their resting state, microglia extend ramified processes that survey the local micro-environment for invading pathogens, cellular debris and toxins (Streit et al., 1988). In response to these detrimental stimuli, microglia retract their extended filopodia to form a condensed "ameboid" structure (Lynch, 2009). This "activated" form governs a course of inflammation to follow suit with the objective of

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restoring homeostasis of the parenchyma and the eradication of pathogenic activity (Ousman and Kubes, 2012). In the last two decades, linked by myeloid derivation, the immunological response of microglia has been found to work in parallel in the central nervous system (CNS) to that of macrophages in the periphery (Colton et al., 2006). Therefore, many of the ideologies that define peripheral macrophage activity have been utilized to underpin the basis of neuroinflammation in the central nervous system (CNS). The term “activated” when referring to microglia has been synonymous with a cytotoxic, proinflammatory response in the brain.

Roles of microglia in Alzheimer’s disease

The presence of “activated” microglia were first described in the Alzheimer’s disease (AD) brain by Alois Alzheimer himself in his original report on Auguste D. in 1907. Alzheimer reported the presence of “gliose” associated with the plaques and tangles, which are the pathological hallmarks of AD (Alzheimer et al., 1995). Key studies by Streit and Perry in the late 1980s and early 1990s demonstrated that microglia responded to injury by becoming activated and presenting cell surface antigens commonly associated with monocytes and macrophages (Hume et al., 1983, Perry et al., 1985, Streit and Kreutzberg, 1987, Streit et al., 1989, Bell et al., 1994). These findings, along with the gliosis observed in the AD brain, quickly led to the hypothesis that the microglia were contributors to the disease process. Key observations contributing to this hypothesis included elevated proinflammatory cytokine levels in the AD brain such as IL-1 β , TNF α and IL-6, and *in vitro* studies showing that these proinflammatory cytokines led to neuronal toxicity and death (Akiyama et al., 2000). The autotoxic loop was proposed for neurodegenerative diseases such as AD, which hypothesized that the activation of microglia was initially a result of tissue injury and amyloid plaque deposition and this initial activation led to further tissue damage that would then result in further microglial activation and, thus, the process would continue (McGeer and McGeer, 1998a).

The hypothesis that microglial cells may have a beneficial effect in AD, as well as detrimental effects, emerged from several key *in vivo* studies. The first, in 2001, resulted from an attempt to initiate the autotoxic loop in an amyloid depositing mouse model. Lipopolysaccharide (LPS), a gramnegative bacterial cell-surface proteoglycan, was intracranially injected into the brains of aged APP/PS1 transgenic mice and, surprisingly, significantly lowered amyloid-beta (A β) deposition within 7 days (DiCarlo et al., 2001). Further, microglia took center stage when anti-A β immunotherapy emerged as a therapeutic approach to lower brain amyloid through the generation of anti-A β antibodies. First described in 1999, Schenk and colleagues hypothesized that a key mediator by which A β immunotherapy lowered A β was microglial-mediated phagocytosis through Fc γ receptor activation (Schenk et al., 1999). Later studies showed that microglial activation occurred in relation to amyloid reductions with both active and passive immunotherapy (Wilcock et al., 2001, Wilcock et al., 2004a). Both the immunotherapy studies and the LPS studies demonstrated that microglia could have a beneficial role in the neurodegenerative disease process, as well as a cytotoxic, detrimental role that had previously been hypothesized.

In contrast to the amyloid data, LPS injection into tau transgenic mice showed opposite effects. Intraparenchymal injection of LPS into the rTg4510 tau transgenic mice resulted in exacerbation of tau pathology seven days later (Lee et al., 2010). This was determined by examining several phospho-epitopes of tau as well as Gallyas silver staining-positive neurofibrillary tangles. In addition to the standard microglial cell surface markers including CD45, this study identified additional markers of microglial activation stimulated by LPS; these were arginase 1 and YM1. The importance of these markers will be discussed later in this review. Additionally, LPS injection into the 3XTg mouse model of amyloid and tau pathology exacerbated the tau hyperphosphorylation (Kitazawa et al., 2005). These data suggest that tau and amyloid pathologies have opposite responses to the same inflammatory stimuli, in this case LPS. Whether this is the case for all inflammatory stimuli remains to be determined, however, these data should provide significant caution to the extrapolation of findings in amyloid depositing mice to the overall condition of AD.

Genetic overexpression of individual inflammatory cytokines has yielded data similar to those observed with LPS and anti-A β immunotherapy. Increased expression of TGF β by astrocytes results in reduced amyloid deposition and increased microglial activation in APP amyloid depositing transgenic mice (Wyss-Coray et al., 2001). In addition, an interesting finding in this study showed that while parenchymal amyloid deposition decreased, vascular amyloid deposition (cerebral amyloid angiopathy; CAA) increased in a correlative manner. We observed a similar phenomenon with the anti-A β immunotherapy passive immunization studies, where we found increased CAA despite significantly decreased parenchymal amyloid deposition (Wilcock et al., 2004b). Additional studies with other monoclonal antibodies as immunotherapy have shown persistence of CAA, and many have demonstrated enhanced CAA-associated microhemorrhages (Wilcock and Colton, 2009). The data from Wyss-Coray et al would suggest that inflammatory mechanisms may at least in part, be responsible for the shifted distribution of amyloid from the brain parenchyma to the cerebrovasculature.

TNF α and IL-1 β are considered the major pro-inflammatory cytokines and are studied as classical markers of neuroinflammation. Individually, both have been implicated in an autotoxic loop, as both are capable of inducing cell death *in vitro* and *in vivo* (Good et al., 1996, Akassoglou et al., 1997, Thornton et al., 2006). Yet, when these pathways are targeted in amyloid depositing transgenic mice, the data show that these cytokine pathways may have some beneficial action by ameliorating amyloid deposition. One study that genetically deleted TNF receptors I and II in the 3XTg mouse model of amyloid deposition and tau pathology showed that blocking TNF α signaling actually increases amyloid deposition and tau pathology (Montgomery et al., 2011). Increased expression of IL-1 β in the hippocampus of APP/PS1 amyloid depositing transgenic mice by genetic means resulted in reduced amyloid deposition and enhanced microglial activation (Shafteel et al., 2007). The author suggest that IL-1 β mediated activation of microglia is the mechanism for the reductions in amyloid deposition. However, in contrast to these studies, other studies have shown a clear relationship between IL-1 β and neurodegeneration. In a similar way to the LPS studies, IL-1 β has been shown to be responsible for tau hyperphosphorylation in an *in vitro* co-culture system of microglia and neurons (Li et al., 2003). Also, a positive correlation was

observed when examining IL-1 β levels compared to neurodegeneration in the APPV717F transgenic mice (Sheng et al., 2001). Therefore, while IL-1 β may ameliorate amyloid pathology, it seems that the same pathways may also enhance tau pathology and neurodegeneration.

The contrasting data in different mouse models, cell culture models and stimulating agents clearly paints the picture of a complex process, one that cannot simply be defined as neuroinflammation.

Assessing the spectrum of neuroinflammation

Macrophages are circulating immune effector cells that are prodigious phagocytes, essential for the clearance of cellular debris and invading pathogens. The macrophages monitor the tissue environment and respond rapidly to any perturbations that may occur. It is thought that both macrophages and microglia originate from the same lineage of bone marrow hematopoietic stem cells that undergo differentiation into monocytes, but this has been questioned in recent studies that suggest microglial progenitors originating from the yolk sac (Mizutani et al., 2012). Progenitor cells either from the bone marrow stem cells or the yolk sac differentiate into macrophages, of which there are several types based on their tissue occupancy, or microglia if they enter the brain (reviewed in (Mosser and Edwards, 2008a) and summarized in figure 1). Macrophages are well understood to generate a variety of responses dependent upon the stimuli they are presented with. For instance, the presence of interferon- γ (IFN γ) or TNF α from T-cells, antigen presenting cells or natural killer cells will stimulate the macrophage to express secrete proinflammatory cytokines and produce oxygen and nitrogen radicals. This state is termed ‘classically activated’ or M1 activated macrophages. The M1 state has high microbicidal activity and is important as a defense mechanism, yet can also cause damage to the host if not tightly regulated (Dale et al., 2008). Indeed, classically activated macrophages are implicated in the development of autoimmune pathologies (Szekanecz and Koch, 2007).

Stimulation of macrophages by IL-4 and / or IL-13 results in an M2a state, sometimes called ‘wound-healing’ (Edwards et al., 2006). The M2a macrophage state is characterized by high IL-1 receptor antagonist (IL-1Ra) and high arginase as well as expression of chitinases and other mediators that are known to contribute to the accumulation and re-organization of extracellular matrix (Zhu et al., 2004). The M2a responses are primarily observed in allergic responses, extracellular matrix deposition and remodeling. The M2b macrophage state is stimulated by immune complexes (IgG antibody – antigen complexes), toll-like receptor activation or IL-1 receptor ligands. This state is a combined M1 and M2a state, where arginase is high and IL-12 is low, but IL-1 β , IL-6 and TNF α are also high. CD86 also appears to be a relatively specific marker for the M2b state (Mosser, 2003). Finally, the M2c macrophage state is stimulated by IL-10 and is sometimes referred to as a ‘regulatory’ with anti-inflammatory activity (Mosser, 2003, Sternberg, 2006). M2c macrophages express TGF β and high IL-10 as well as matrix proteins such as pentraxin and versican. The M2c state can also be generated through the hypothalamic-pituitary axis derived glucocorticoids that inhibit the expression of pro-inflammatory cytokine genes and decrease the stability of

their mRNA (Sternberg, 2006). The M2c macrophages contribute to an environment that results in defective pathogen killing and enhanced survival of organisms.

In 2006, Colton and colleagues showed that the AD brain and transgenic mouse models of amyloid deposition express not only classical inflammatory mediators characterized as M1, but also express high levels of “alternative” inflammatory markers associated with M2 states (Colton et al., 2006). These studies were followed up by many groups including ourselves, and the concept of M1 and M2 expanded into the neuroscience field (Wilcock et al., 2011, Lee et al., 2013a, Lee et al., 2013b, Selenica et al., 2013, Sudduth et al., 2013a, Sudduth et al., 2013b). Further, more recent investigations of peripheral macrophages have redirected this inflammatory model towards a dynamic range of heterogeneous states forming the contemporary model of microglial activation (reviewed in (Mandrekar-Colucci and Landreth, 2010, Olah et al., 2011)). It is important to emphasize that these divisions reflect a continuous spectrum rather than discrete antagonistic groups; the nomenclature has been applied for classifying amplified functional abilities of the cells as a point of reference at a given time. Importantly, transcriptome-based network studies have recently shown that there is a spectrum of macrophage responses to stimuli as opposed to the polarized M1-M2 responses (Xue et al., 2014).

Reservations remain with regards to whether a direct translation of this peripheral model can be applied to the differing cellular environment in the CNS yet, this far, they have proven to be highly applicable. An M1 state is stimulated as an initial response in inflammation and detected by a scope of immune receptors. The cytokines $\text{INF}\gamma$, $\text{TNF}\alpha$, $\text{IL}1\beta$ and IL-6 show marked M1 polarizing functions in both macrophages and microglia (Mosser and Edwards, 2008b). With the intention of eradicating injurious pathogens and aberrant cellular deposits such as $\text{A}\beta$, microglia release bi-products of oxygen and nitrogen radicals. Left unmodulated, the accumulation of these oxidative species has an injurious effect on the surrounding tissue, most critically initiating neuronal death that accounts for the atrophic brain seen in AD (McGeer and McGeer, 1998a). Moreover, phenotypic diversity in the brain is tightly controlled by a vast network of cytokines, similar to peripheral immune responses. For example, an M1 phenotype is classified by high IL-12 and low IL-10 ; the inverse can be seen in an M2 phenotype.

The immune response has a self-modulatory ability to dampen down the M1 state by accelerating the M2 immune profile. In particular, M2 activation has the overall function of enhancing repair, protection and deactivation of the immune response (Cherry et al., 2014). Alternative activation was first identified by (Stein et al., 1992) through the application of IL-4 on peritoneal macrophages revealing the additional phagocytic role by an enhanced expression of mannose receptors (MRC1) which perform the essential functions of adhesion and internalization of invading pathogens. Exposure to IL-4 or IL-13 results in the M2a phenotype expression of a dichotomy of phenotypic markers including chitin-like proteins (CHL3 in humans and YM1) in mice and arginase 1 (ARG1) specifically enhancing proline and polyamine production for collagen formation in cell growth (Albina et al., 1990, Welch et al., 2002, Gordon and Martinez, 2010, Wilcock, 2012). M2a phenotypic genes are strongly associated with the ability to orchestrate wound healing by remodeling of the extracellular matrix. Acquired “deactivation” of the immune response and additional tissue

remodeling is achieved by an M2c phenotype that is initiated by IL-10 exposure. The role of an M2b phenotype is relatively unknown. Nonetheless, it has been defined by an elevated expression of the CD86 and major histocompatibility complex II (MHCII) receptors in comparison to the lower constitutive expression of these receptors across all immune phenotypes (Mosser, 2003). It has been shown that the M2b phenotype is enhanced with exposure to immunoglobulin (IgG) stimulation on the surface of pathogens. The Fc receptors, FC[uni1D67]R1 and FC[uni1D67]R3, have a high affinity to IgGs permitting recognition of pathogenic activity and instigating a downstream cellular response and, therefore, are considered useful indicators of microglia in the M2b phenotype. Specifically, FC[uni1D67]R1 and FC[uni1D67]R3 presentation are directly influenced by immunoglobulin (IgG) stimulation (Miles et al., 2005). Evidently, the M2 phenotypic markers and enhanced M1 phenotypic markers, yet a low IL-12 and a high IL-10 secretion, are specific to the M2b state (Filardy et al., 2010, Wilcock, 2012). Further investigations are required to underpin the specific functions of an M2b state. It can be hypothesized that the apparent blend of functional states of this novel phenotype could encompass the beneficial aspects of the polarized spectrum and, therefore, offers a potential means of combatting AD pathologies.

With regards to the role of neuroinflammation in AD, our lab has recently shown an increase in an M1 and M2a phenotype in early AD patients (Sudduth et al. (2013c). An M2a phenotype is more applicable to the “more pathologically advanced patients” with an enhanced senile plaque load. As mentioned, the fibrotic properties of an M2a phenotype extra-cellular matrix remodeling have been suggested to yield greater A β deposits (Sudduth et al., 2012). This is juxtaposed when taking into account the potential phagocytic properties of this phenotype which permit microglia to uptake A β depositions (Frautschy et al., 1992, Kopec and Carroll, 1998). Nevertheless, *in vivo* evidence has shown that the regular phagocytic activity of these cells is distorted with the progression of the disease (Koenigsknecht-Talboo and Landreth, 2005). The phenotypic changes during the normal course of aging have been grossly understudied. Sierra et al. (2007) (Sierra et al., 2007) have shown endogenous levels of IL1, IL-6 and TNF are increased in aging mice. Furthermore, this study proposes a skewed M1 phenotype that could be injurious when left unregulated. Therefore, it is imperative to consider the role of neuroinflammation in aging as potentially amplifying the toxic environment of the brain milieu toward the pathology of AD.

Assessing neuroinflammation in the AD patient

Positron Emission tomography (PET) scans in AD and age-matched healthy controls demonstrate that activated microglia (identified by expression of the peripheral benzodiazepine receptor) increase in number in the brains of patients with AD, are found near primary disease pathology in brain regions that later degenerate, precede and are predictive of pathology and clinical symptoms, and correlate better with memory impairment than primary disease pathology such as A β plaques (McGeer and McGeer, 1998b, Sheffield et al., 2000, Cagnin et al., 2001, Xiang et al., 2006, Edison et al., 2008). Measurements of cytokines and inflammatory biomarkers in blood and CSF from AD patients demonstrate elevations of pro-inflammatory factors, such as the pro-inflammatory cytokines TNF, IL-1 β , IL-6 and IL-12 as well as complement (Swardfager et al., 2010,

Fagan and Perrin, 2012). Similarly, microglia collected post-mortem show a bias toward the production of pro-inflammatory factors when exposed to an immune challenge (Durafour et al., 2012, Melief et al., 2012).

The definition of microglia ‘activation’ assumed by PET scans uses microglia surface receptor expression, most often the peripheral benzodiazepine receptor (translocator protein of 18 kDa); this, unfortunately, does not reflect the dynamic range of activation states (Venneti et al., 2006, Colton and Wilcock, 2010). It can be more clinically informative to approximate the immune profile by identifying immune factors in the CSF, such as complement (Fagan and Perrin, 2012). Neither PET nor CSF, however, are practical as a widely used forms of screening because PET scanning is expensive and CSF collection is intrusive and risky. Furthermore, immune factors from the periphery also enter and play a role in brain inflammation (Melief et al., 2012). Therefore, it is reasonable to use more easily obtained blood serum and plasma to identify biomarkers of an individual’s neuroinflammatory phenotype.

The field is currently investigating blood proteins that will serve this function. A set of 18 markers (out of 46 markers investigated) were identified by Ray et al. (Ray et al., 2007) that include many inflammatory markers (ie. granulocyte colony-stimulating factor (GCSF), macrophage colony-stimulating factor (MCSF), intracellular adhesion molecule 1 (ICAM), TNF, TNF receptor, chemokine ligand 5 (RANTES), and, when evaluated together, are both diagnostic and predictive of AD. However, two follow-up studies these biomarkers found that most did not vary between age-matched controls and AD, and that they did not distinguish between mild cognitive impairment (MCI) and AD (Marksteiner et al., 2011, Bjorkqvist et al., 2012). In a similar study, 11 proteins, of which many were inflammatory markers, were found to correlate with AD severity (O’Bryant et al., 2011). Our recent work identified six serum proteins that are reflective of the brain inflammatory state (M1: macrophage inflammatory protein 1 (MIP1) and vascular cell adhesion protein 1 (VCAM1); M2a: IL-1 receptor antagonist (IL1Ra), ICAM1, haptoglobin and fibrinogen) (Sudduth et al., 2013b).

Clinical implications of immune phenotype differences

Interventional trials with non-steroidal anti-inflammatories (NSAIDs) in AD have not been promising overall, although some have indicated modest improvement. An early clinical trial of the NSAID indomethacin in mild-moderate AD demonstrated significantly less decline over a 6 month period, however, 50% of the non-responders dropped out of the study (Rogers et al., 1993). Later trials of indomethacin showed small protective effects over a 12-13 month period that did not reach clinical significance due to small sample size (de Jong et al., 2008). A recent clinical trial of the NSAID ibuprofen with the gastroprotectant esomeprazole given to patients with mild to moderate AD for one year showed decreased cognitive decline only in those individuals who carried the ApoE4 allele (Pasqualetti et al., 2009), which is in agreement with some epidemiological reports showing an interaction between NSAID use and the ApoE4 genotype (Fotuhi et al., 2008, Szekely et al., 2008).

Most large-scale interventional clinical trials of anti-inflammatories, however, have shown no improvement and some poor side effects, including trials of aspirin (Group et al., 2008), the anti-malarial and anti-inflammatory hydroxychloroquine (Van Gool et al., 2001), the corticosteroid prednisone (Aisen et al., 2000) and the NSAIDs rofecoxib, naproxen, and diclofenac (Scharf et al., 1999, Aisen et al., 2003, Reines et al., 2004, Thal et al., 2005). In these trials drugs were tested for 4 years or less and in patients diagnosed with mild to moderate AD. The Alzheimer's Disease Anti-inflammatory Prevention Trial (ADAPT) compared the efficacy of the NSAID naproxen and the selective cyclooxygenase-2 (COX-2) inhibitor celecoxib to prevent onset of AD in a high risk group and showed that treated groups tended to have worse mental scores. The trial was terminated early because of concerns about cardiovascular and cerebrovascular risk due to celecoxib and showed significantly increased risk (~60%) of incident in patients treated with naproxen (Martin et al., 2008, Meinert et al., 2009).

It is possible that the large ADAPT study and other interventional trials showed poor outcome due to drug choice and because the cohort, advanced in age and high risk, likely had a well-established inflammatory response years prior to the intervention with NSAIDs in these clinical trials. Results from the epidemiological and interventional studies are consistent with the idea that early changes occur during a pre-clinical phase that lead to the development of AD, and that interruption of certain processes during this period may prevent disease development, whereas targeting these same systems later in the disease state may be ineffective (Stewart et al., 1997, Zandi et al., 2002, Martin et al., 2008, Pasqualetti et al., 2009).

Although the ADAPT trials were terminated prematurely, further investigation into this cohort found that NSAIDs are protective if initiated before symptom onset, but harmful after the development of cognitive impairment (Breitner et al., 2011), and that the efficacy of NSAIDs may depend upon the rate of decline (Leoutsakos et al., 2011). Recent work in our lab has found that both M1 and M2a markers are elevated in tissue from advanced AD brains. Interestingly, however, this work also identified a dichotomous distribution between M1- and M2a-biased inflammatory profiles in early AD brain tissue samples that was related to AD pathology and appeared only in diseased brain regions (Sudduth et al., 2013b). Heterogeneity in the immune profile may be derived from individual propensities toward certain inflammatory states, features and magnitude of AD pathology, a lasting result of previous immune challenges or injury, and current general medical health as well as common comorbidities such as cardiovascular disorders, epilepsy, atherosclerosis and depression (Backman et al., 2003, Leoutsakos et al., 2012). While comorbidities are often reason for exclusion from medical trials, they must be addressed in clinical practice. We believe that heterogeneity in the immune profile may partially explain the failure of interventional anti-inflammatory trials, and addressing this heterogeneity may enable us to predict for whom a directed anti-inflammatory treatment is successful.

Using immune phenotype to personalize the treatment of Alzheimer's

Data gathered from blood serum, blood plasma, CSF and PET imaging can be used to direct treatment, particularly in early stage AD when the population falls into two broad categories

of M1- or M2a-biased. For example, the ADAPT trials were terminated prematurely due to concern over vascular events and risks [69], and an M2a immune profile is associated with the same category of risk factors (Sudduth et al., 2013b) [11]. In fact, the M2a-phenotype may reflect the presence of cerebrovascular co-morbidities with AD. Therefore, performing a simple evaluation of plasma proteins that are indicative of an M2a immune profile (IL1Ra, ICAM1, haptoglobin and fibrinogen) may allow us to make informed selections of participants for trials and immune therapy for patients that minimizes these risks. Individuals with an M2a-biased phenotype also have a higher density of A β plaques (Sudduth et al., 2013b). This relationship suggests that the presence of serum proteins indicative of an M2a profile may predict a better response to therapies targeted at A β . There are at least 19 current clinical trials (ongoing or initiating; clinicaltrials.gov) of drugs targeting β -amyloid directly or indirectly by targeting enzymes that cleave amyloid precursor protein. Like NSAIDs, clinical trials of drugs targeting amyloid have not been overwhelmingly successful (Mangialasche et al., 2010), but may be improved by selecting participants that are more likely to benefit. In addition, individuals with an M1-biased profile may benefit from a therapy that selectively targets M1 immune functions, while allowing or promoting the processes of restoration and repair associated with an M2a phenotype. A blood screen for elevations in the proteins MIP1 and VCAM1, or other markers indicative of an M1 profile, will allow us to make better predictions about treatment for this population.

An individual's inflammatory profile will be most biologically informative and actionable early in the disease process. Fortunately, identifying pre-clinical stages of AD is becoming more realistic as we develop improved screening techniques (Perrin et al., 2009). For example, brain tau pathology can be approximated from measurements in blood and CSF. Likewise, brain plaque burden can be estimated from A β in the blood and CSF as well as PET scanning using the Pittsburgh compound B. Other scanning methods can highlight early regional changes in metabolism or hypofunction, as well as brain atrophy. Early genetic testing can identify those who are at greater risk of developing AD, for example, carriers of the ApoE4 allele. These results may be more useful when used in combination with an individual's inflammatory profile. For example, although our recent work did not identify a relationship between ApoE status and early inflammatory profile (Sudduth et al., 2013b), two studies of large cohorts, the Cache County Study and the Cardiovascular and Health Study found that carriers of ApoE4 benefitted more from non-steroidal anti-inflammatory treatment [60]. Similarly, the Cardiovascular Health Study showed that NSAIDs significantly reduced the risk of AD only in carriers of ApoE4 (Sweet et al., 2012).

While NSAIDs failed clinical trials, they may be more effective if an individual's inflammatory profile is known. Leoutsakos et al. (Leoutsakos et al., 2011) found differential potential benefits from NSAIDs in the preclinical AD population of the ADAPT trials when patients were separated as slow decliners (naproxen), fast decliners (celecoxib), and no decline. We predict differential effects such as these between M1- and M2a-biased immune profiles, and believe that drug treatment that does not suppress immune function overall, but instead modulates these profiles will have the most benefit. One such drug, MW-151, has been recently developed in order to specifically attenuate M1-type immune activity. Early treatment with MW-151 in a transgenic mouse model of AD reduced impairment in long-

term potentiation, the synaptic correlate of memory (Bachstetter et al., 2012). Another similar drug, VP025, reduces age- and LPS-induced elevations of pro-inflammatory cytokines, increases expression of anti-inflammatory CD200 and restores LTP in rats (Martin et al., 2009). Another treatment course may be to drive an M2a immune profile. This could potentially be accomplished by delivery of the anti-inflammatory cytokine IL-4. In mouse models of AD, IL-4 treatment induces an M2 immune profile and enhances microglial clearance of A β (Lyons et al., 2007, Shimizu et al., 2008, Varnum and Ikezu, 2012). In fact, increased production of IL-4 may be partially responsible for the therapeutic effect of currently used acetylcholinesterase inhibitors, although these drugs are not disease-modifying (Lugaresi et al., 2004). We hypothesize that directed targeting of specific immune functions will benefit individuals with pre-clinical or early AD.

Summary and conclusions

It is evident that phenotypic changes within AD individuals is a delicate and complex affair much determined by the state of disease progression and an abundance of individual patient specific factors that are yet to be determined. Therefore, research should be driven in favor of compiling a detailed account of phenotypic changes across the progression of the disease. Our lab has identified with both *in vivo* and *in vitro* studies the ability to instigate robust polarizations of phenotypic profiles. Understanding the methods of modulating and manipulating the immune response has the potential to be a highly successful therapeutic treatment in AD patients. By acknowledging the interplay of the cytokine network and the heterogeneous phenotypic states of patients, the field can offer a far more effective means to refine immune modulation to a personal level.

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Highlights

- Microglial heterogeneity is discussed in relation to Alzheimer's disease and potential functions in the disease.
- The potential beneficial and detrimental roles of inflammation in Alzheimer's disease are discussed.
- Introduction of the concept of an inflammatory spectrum to better characterize neuroinflammatory states in disease.
- A discussion of the role of neuroinflammatory heterogeneity in the treatment and prevention of Alzheimer's disease.

Figure 1.

Neuroinflammatory spectrum of states based on macrophage classifications. Shown in the figure are the activation states of microglia and the general immune function of each state.