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Are inflammatory profiles the key to personalized Alzheimer's treatment?

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Summary

There is currently no disease-modifying treatment for Alzheimer's disease (AD) and the need is great as the number of people diagnosed with AD is predicted to steadily increase. Inflammation is associated with AD, and is predictive of more advanced disease pathology and cognitive impairment. Moreover, preventing inflammation reduces the risk of developing AD. However, clinical trials with anti-inflammatory treatment have not been successful. One reason may be that there is diversity in the immune response and reducing immune activity with anti-inflammatories is not appropriate in all conditions. Recently, we have begun to apply categorizations, used to characterize the peripheral immune response, to the immune processes of the brain. When we do this, we are able to describe an individual's inflammatory profile within this spectrum. We have observed that patients with early AD are distributed across two broad categories of immune activation. If we recognize the diversity within this cohort of individuals with early AD and use information about immune phenotypes to guide the choice of treatment, then we may expect better clinical outcomes.

The role of inflammation in Alzheimer's disease (AD) has been questioned since the early 1900s when Alois Alzheimer identified microglia, resident brain immune cells, surrounding plaques. In the 1990s, researchers established a link between the use of NSAIDs and prevention of AD [1,2], however, later clinical trials of NSAIDs were not successful [3–10]. Numerous studies report links between AD and genes regulating immunity as well as the expression of immune factors in blood, cerebrospinal fluid (CSF) and brain tissue [11–16]. Imaging studies reveal that microglia, the primary immune cells of the brain, are activated in AD and are predictive of symptom severity [17,18]. While these studies provide evidence that inflammation is related to AD onset and progression, it is not clear how we can modulate the immune system in order to reduce AD occurrence and modulate disease outcome. Current research is focused on the dynamic range of states within the rubric of 'immune activation', and work from our laboratory has demonstrated that patients with early

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AD fall into two broad categories of immune phenotype [19]. We believe that these subsets representing heterogeneity within the early AD population reveal a therapeutic opportunity. With this information, we can make better predictions of how to modulate neuroinflammation and it may be possible to distinguish which patient population may benefit from targeted anti-inflammatory treatments.

This review will begin by describing the neuroinflammatory categories used to determine individual neuroinflammatory profiles. We will then discuss neuroinflammation in AD, how to predict an individual's inflammatory profile and, finally, discuss how this information may one day be used in a personalized treatment approach.

Neuroinflammatory categories

Microglia are the primary immune cells of the CNS, analogous to macrophages of the peripheral nervous system. Microglia activation states are often compared with macrophage activation states [20,21], although they can be qualitatively different [22,23]. These states can be described as resting (in which microglia are actively monitoring the microenvironment) [24], classical activation (defense/attack; M1), alternative activation (restoration/repair; M2a), type II macrophage (M2b) and acquired deactivation (M2c) (Figure 1) [25–33]. However, activation states are not distinct conditions, nor are they points on a continuum from resting to activated [25], but are better thought of as particular points in a nonlinear spectrum [21]. In addition, the AD brain is characterized by the presence of microglia across a range of activation states [31]. Since there is considerable overlap in microglia phenotype between activation states, variance in phenotype within a state and microglia of multiple activation states coexist, simple categorization is contrived. However, broad categories remain useful to generalize an immune profile and make predictions.

Classically activated M1 microglia produce and release proinflammatory factors (e.g., TNF- α , IFN- γ , IL-1 β , IL-6 and IL-12) similar to M1 macrophages, in order to attract and induce activation in other microglia and to respond to injury and pathogens, thus creating a self-amplifying cycle of activation [25–33]. Classically activated microglia also produce and release factors used for defense that can induce oxidative stress and kill pathogens, such as reactive oxygen/nitrogen species, the superoxide anion, nitric oxide and proteases. Under normal circumstances, the M1 response is transient and does not cause damage to surrounding tissue, but if the proinflammatory phase is prolonged, the inflammatory process transitions from being primarily protective to predominantly pathological [34]. For example, an M1 immune response is associated with both memory impairment and neuronal death [35–39]. A sustained neuroinflammatory environment is more likely to occur in advanced age and can be exacerbated by AD pathology [32]. Microglia from aged mice respond more robustly to INF- γ /TNF- α -induced activation [35] and are more resistant to IL-4-induced conversion from M1 to M2a than microglia from young mice [40]. Microglia examined *in vitro* respond to the AD-associated protein β -amyloid (A β) by releasing factors characteristic of an M1 response [41], and this response is exaggerated in microglia derived from AD brains [42]. Moreover, in AD, pathological protein species, such as A β , as well as signals from dying and dead neurons, fuel immune activation over decades. Therefore, there is not a distinct period in AD pathogenesis in which a population of microglia is activated and later

deactivated. Instead, neuroinflammation is probably sustained over time by the local activation and deactivation of individual microglia. This further suggests that the microenvironment may be influenced simultaneously by competing interests, both attack and repair, and this is consistent with our data indicating that both M1 and M2a markers are elevated in late AD [19].

The aggressive innate immune response is, under nonchronic and nondisease conditions, punctuated by a transition to an anti-inflammatory, alternative activation state, M2a, which is focused on resolution of the inflammatory response, phagocytosis of pathogens, removal of cellular debris and tissue repair [25–33]. M2a is characterized and induced by anti-inflammatory cytokines (IL-4 and IL-13), as well as chitinase-like lectins and c-type lectin receptors (e.g., the mannose receptor), and release of IL-1Ra and Arg1. The M2a activation state is generally thought to be preferred over the potentially deleterious M1 state [14,43]. Microglia may also present an M2b phenotype, also called the type II macrophage, which is characterized by markers of both M1 and M2. The M2b state is known to be triggered by immune complexes, Toll-like receptor activation and the IL-1 cytokine family. Edwards and colleagues showed that immune complexes activate Fc γ receptors and trigger the macrophage phenotype to switch to this unique state [44], which is characterized by elevations in some M1 markers (particularly IL-1 β , TNF- α and IL-6, but not IL-12) and IL-10 [21,45,46]. There were also some markers that were identified to be more specific for an M2b phenotype, including CD86 [44]. We do not detect evidence of an M2b profile in AD [19], but we hypothesize that it is stimulated by the immune complexes formed by various immunotherapies that are currently in clinical trials for use in AD. Microglia can progress to an M2 state called acquired deactivation, M2c, which is characterized by immunosuppression and clearance of apoptotic cells. M2c is characterized and induced by anti-inflammatory cytokines (IL-10 and TGF- β) as well as Arg1 and absence of nitric oxide production. Finally, the immune response may transition back to a ‘resting’ state, although it probably remains primed for subsequent events.

Microglia activation & inflammatory biomarkers in AD

PET scans and immunohistological analysis in AD patients and age-matched healthy controls demonstrate that activated microglia (identified by expression of the peripheral benzodiazepine receptor or MHC II) increase in number in the brains of patients with AD; are found near primary disease pathology (A β plaques, neurofibrillary tangles, and dead or dying neurons) 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 [18,47–50]. Genome-wide association studies have identified immune factors (e.g., genes associated with IL-1, IL-18, complement receptors, human leucocyte antigen, CD33 and clusterin) with late-onset AD [11,13–15,51–53]. Measurements of cytokines and inflammatory biomarkers in blood and CSF from AD patients demonstrate elevations of proinflammatory factors, such as the proinflammatory cytokines TNF- α , IL-1 β , IL-6 and IL-12 as well as complement [54,55]. Similarly, microglia collected post-mortem show a bias toward the production of proinflammatory factors when exposed to an immune challenge [22,23].

Neuroinflammation is sufficient to drive a type of dementia, known as dementia pugilistica, but it is unlikely to be the primary etiological factor in the development of AD. Neuroinflammation is present early in AD pathogenesis [12,17,18]. It is stimulated by other early features, such as A β fibrils and by later AD pathologies, such as A β plaques, neurofibrillary tangles and neuronal debris, as well as disease risk factors, such as cholesterol and adiposity [56,57]. Neuroinflammation may also be stimulated by infection, injury or comorbidity with other pathologies, such as diabetes or cardiovascular disease [58,59]. Moreover, neuroinflammation contributes to the development of AD, as reducing neuroinflammation decreases AD risk, and neuroinflammation can promote neurodegeneration through activation of the TNF- α receptor death domain, oxidative stress and excitotoxicity. Therefore, neuroinflammation is a possible therapeutic target with the potential to modify disease outcome.

How do we determine an individual's immune profile? The definition of microglia activation assumed by PET scans and immunohistological staining uses microglia surface receptor expression, most often the peripheral benzodiazepine receptor (translocator protein of 18 kDa) and MHC II; however, this, unfortunately, does not reflect the dynamic range of activation states [31,60]. It can be more clinically informative to approximate the immune profile by identifying immune factors in the CSF, such as complement [55]. Neither PET nor CSF, however, are practical as widely used forms of screening as 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 [23]. 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.* that include many inflammatory markers (i.e., GCSF, MCSF, ICAM, TNF- α , TNF receptor and RANTES), which, when evaluated together, are both diagnostic and predictive of AD [61]. However, two follow-up studies found that most markers did not vary between age-matched controls and AD patients, and that they did not distinguish between mild cognitive impairment and AD [62,63]. In a similar study, 11 proteins, of which many were inflammatory markers, were found to correlate with AD severity [64]. Our recent work identified six serum proteins that are reflective of the brain inflammatory state (M1: MIP1 α and VCAM1; M2a: IL-1Ra, ICAM1, haptoglobin and fibrinogen) (Figure 1B) [19].

Clinical intervention may be complicated by immune phenotype

Interventional trials with NSAIDs in AD have not been promising overall, although some have indicated modest improvement. An early clinical trial of the NSAID indomethacin in mild-to-moderate AD demonstrated significantly less decline over a 6-month period; however, 50% of the nonresponders dropped out of the study [65]. Later trials of indomethacin showed small protective effects over a 12–13-month period that did not reach clinical significance owing to a small sample size [66]. A recent clinical trial of the NSAID ibuprofen with the gastroprotectant esomeprazole given to patients with mild-to-moderate AD for 1 year showed decreased cognitive decline only in those individuals who carried the

APOE4 allele [67], which is in agreement with some epidemiological reports showing an interaction between NSAID use and the *APOE4* genotype [68,69].

Most large-scale interventional clinical trials of anti-inflammatories, however, have shown no improvement and some serious side effects, including trials of aspirin [3], the antimalarial and anti-inflammatory hydroxychloroquine [4], the corticosteroid prednisone [5], and the NSAIDs rofecoxib, naproxen and diclofenac [6–9]. In these trials drugs were tested for 4 years or less and in patients diagnosed with mild-to-moderate AD. ADAPT compared the efficacy of the NSAID naproxen and the selective 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 significantly increased risk (~60%) of these side effects in patients treated with naproxen [10,70,71].

Why was there such diversity in the outcomes of clinical trials of anti-inflammatories? It is possible that the large ADAPT study and other interventional trials showed poor outcome owing to drug choice and because the cohort, advanced in age and high risk, probably had a well-established inflammatory response years prior to the intervention with NSAIDs in these clinical trials [10,70,71]. Results from epidemiological and interventional studies are consistent with the idea that early changes occurring during a preclinical phase lead to the development of AD, and that interruption of certain processes during this period may prevent disease development, while targeting these same systems later in the disease state may be ineffective [2,67,70,72].

Although the ADAPT trials were terminated prematurely, further investigation into this cohort found that NSAIDs are protective if initiated before symptom onset, but are harmful after the development of cognitive impairment [73], and that the efficacy of NSAIDs may depend upon the rate of decline [74]. Recent work in our laboratory 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 [19]. 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 [58,59]. While comorbidities are often reasons 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 may be successful.

Clinical intervention guided by the immune profile

Once we know a patient's immune profile, what can we do with this information? 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. For example, the ADAPT trials were terminated prematurely owing to concern over vascular events and risks [10], and an M2a immune profile is associated with the same category of risk factors [19]. Therefore, performing a simple evaluation of plasma proteins that are indicative of an M2a immune profile (IL-1Ra, ICAM1, haptoglobin and fibrinogen) may allow us to make informed selections of participants for trials and immune therapy that minimizes these risks. An alternate view is that the M2a phenotype reflects the presence of cerebrovascular comorbidities with AD. Individuals with an M2a-biased phenotype also have a higher density of A β plaques [19]. 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 [101]) of drugs targeting A β directly or indirectly by targeting enzymes that cleave APP. Similar to NSAIDs, clinical trials of drugs targeting A β have not been overwhelmingly successful [75], but may be improved by selecting participants who 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 α 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 preclinical stages of AD is becoming more realistic as we develop improved screening techniques [76]. 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 Pittsburgh compound B. Other scanning methods can highlight early regional changes in metabolism or hypo-function, 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 the early inflammatory profile [19], two studies of large cohorts, the Cache County Study and the Cardiovascular and Health Study found that carriers of *APOE4* benefitted more from NSAID treatment [68]. Similarly, the Cardiovascular Health Study showed that NSAIDs significantly reduced the risk of AD in carriers of *APOE4* [77].

If we want to manipulate the immune system, how do we do it? NSAIDs failed clinical trials, but may be more effective if an individual's inflammatory profile is known. Leoutsakos *et al.* 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 those demonstrating no decline [74]. We expect differential effects, such as those between M1- and M2a- biased immune profiles, and believe that drug treatments that do not suppress immune function overall, but instead modulate these profiles, will have the most benefit (Figure 1A). 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 [14]. Another similar drug, VP025, reduces age- and

lipopolysaccharide-induced elevations of proinflammatory cytokines, increases expression of anti-inflammatory CD200 and restores long-term potentiation in rats [78]. Another possible course of treatment may be to promote 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 [32,79,80]. 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 [81]. We predict that directed targeting of specific immune functions will benefit individuals with preclinical or early AD.

Conclusion

The field of neuroinflammation in AD has burgeoned since the 1990s. In general, the perspective has been that neuroinflammation should be suppressed, but the interventional trials with NSAIDs in AD patients did not succeed. The field is currently applying the spectrum of inflammatory phenotypes characterized in the body periphery to the diversity of the inflammatory responses seen in the brain. It is becoming apparent that making distinctions between the different types of inflammatory states may be predictive of disease progression and may offer an opportunity to individualize the approach to treatment. Biomarkers from blood plasma and serum offer the most reasonable method for individual access to this information. There are a handful of biomarkers that correlate with disease progression and severity, and some biomarkers from blood predict the neuroinflammatory profile. The treatment approach will probably be different for patients with early AD who are M1 versus M2a biased, but the treatment approach for these situations remains to be determined.

Future perspective

We are currently beginning to understand the various immune phenotypes present in the brain of cognitively normal individuals and those with AD. As we work to determine a battery of biomarkers that reliably reflects the brain inflammatory phenotype, researchers are developing drugs that selectively target and modulate specific immune phenotypes instead of pan suppressors. It is possible that in the next 5 years both of these endeavors will have some success, allowing us to determine an individual's immune profile and adjust our therapeutic approach accordingly.

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Website

101. ClinicalTrials.gov. www.clinicaltrials.gov

Practice Points

- Inflammatory phenotypes occur within a spectrum between resting, proinflammatory, deactivated and repair.
- The immune response can be deleterious or supportive, depending upon the inflammatory state and the duration of that state.
- Inflammatory profiles in early Alzheimer's disease (AD) differ from cognitively healthy individuals and those with advanced AD.
- Early AD is characterized by a dichotomous distribution between M1- and M2-biased inflammatory profiles.
- Inflammatory profiles may be predictive of disease progression and responsiveness to treatment.
- Identifying an individual's inflammatory profile, in combination with other disease risk factors and cognitive state, will help to guide the approach to treatment.
- In order to use this information to personalize treatment, it is first imperative that we better understand whether it is best to amplify or suppress immune activation under various circumstances in AD.
- We also need to identify or exercise additional immune-modifying treatments that can push the immune system toward a specific profile.

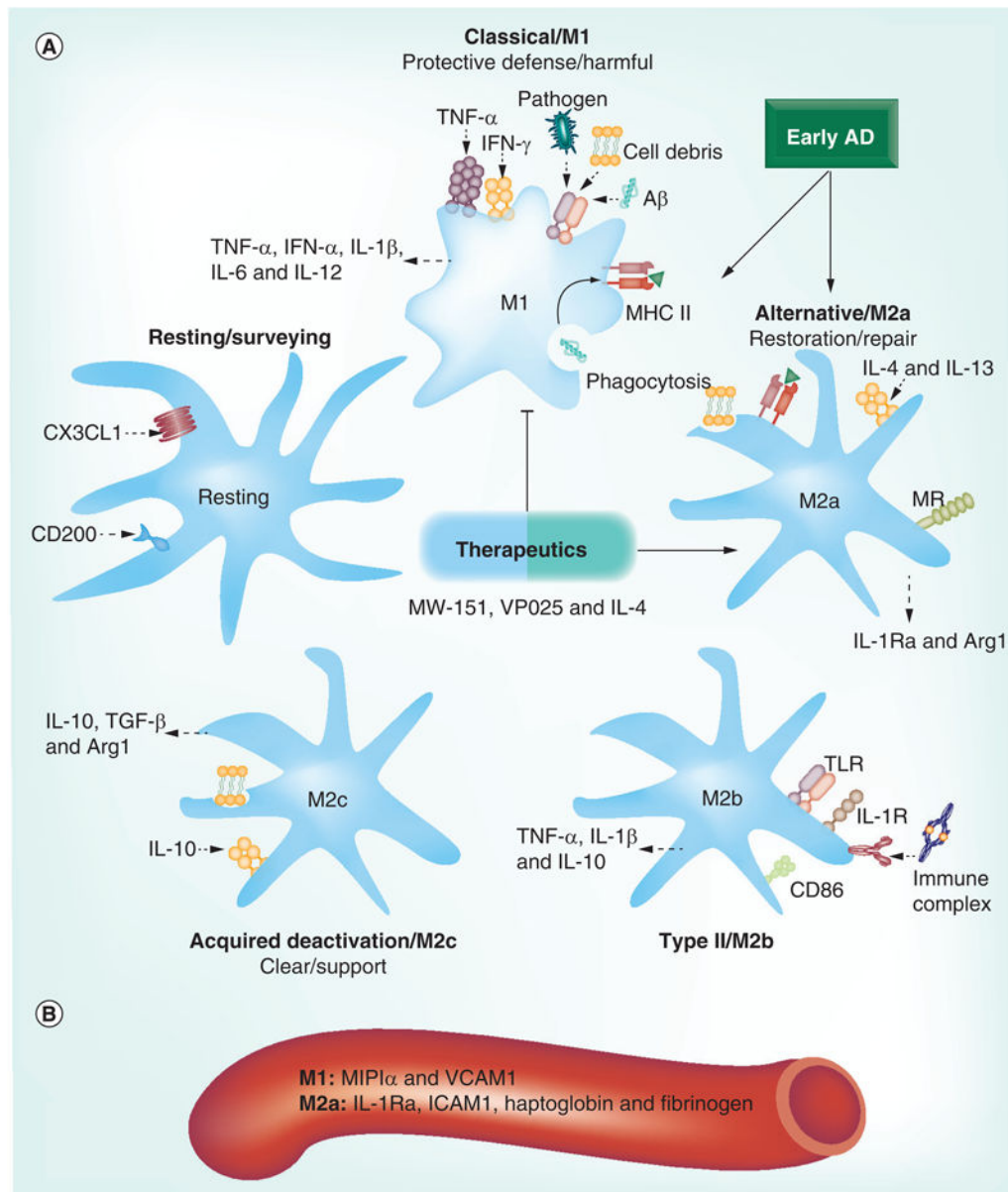


Figure 1. Inflammatory profiles in Alzheimer's disease

(A) Microglia activation states fall within a dynamic range that includes resting, M1, M2a, M2b and M2c. Resting microglia are kept quiescent by CD200 and CX3CL1 (fractalkine). Samples from patients with early AD indicate that their immune profile is polarized toward either an M1 or an M2a phenotype. Microglia become reactive to pathogens, neuronal debris and A β by activation of pattern-recognition receptors, including TLRs, which phagocytose these materials and present antigens with MHC II. Induction by and release of various pro- and anti-inflammatory cytokines differs across activation states and, taken together, can be used to identify these states. Therapeutics aimed at polarizing toward specific activation states, rather than robustly suppressing microglia activity, show promise for AD treatment.

(B) Proteins from human blood (MIP1 α and VCAM1 for M1; and IL-1Ra, ICAM1, haptoglobin and fibrinogen for M2a) may be useful peripheral markers to predict the central

immune profile. A β : β -amyloid; AD: Alzheimer's disease; MR: Mannose receptor; TLR: Toll-like receptor.