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Elusive Alzheimer's Disease: Can Immune Signatures Help Our Understanding of This Challenging Disease? Part 1: Clinical and Historical Background of Alzheimer's Disease

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Abstract: Alzheimer's disease (AD) is the most common form of dementia. Its most important pathological hallmarks are profound neuronal loss, presence of intracellular neurofibrillary tangles, and extracellular deposition of beta-amyloid protein (Aβ) as beta-amyloid plaques. These latter aggregations result in neuronal degeneration in brain regions important not only for memory, but also for other cognitive functions. One of the most important risk factors for AD is age and with the increase of life-expectancy AD has thus become the most common form of dementia. It is now formally recognized by several new diagnostic criteria that AD is not a homogeneous disease. The current "Holy Grail" is to be able to diagnose variants of AD before they manifest clinically and before irreparable brain damage is done. To achieve this goal, robust and reliable biomarkers that reflect the pathogenesis of AD have to be implemented. This is of paramount importance because such biomarkers may provide clues to pathways that can be targeted for interventions aimed at disease prevention or improvement. Although much attention has focused on Aβ as a major component of AD, Aβ may be a lesser attractive target since an increasing amount of data has raised concerns about its causative role in AD. This review will be in two parts, this first part will deal with the current clinical knowledge and the questions raised by the Aβ cascade hypothesis in the pathogenesis of AD and the second part will aim to synthesize our current knowledge and to discuss new data that suggest how immune alterations may contribute to the development of AD and may therefore provide beneficial targets in novel approaches for the treatment of AD. [*Discovery Medicine* 15(80):n-n, January 2013]

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Introduction

Alzheimer's disease (AD) is presently the most common form of dementia (Grossberg and Desai, 2003). The recent report *Rising Tide: the Impact of Dementia on Canadian Society* raised the gloomy prospect of 1,125,200 cases of AD and other dementias in Canada by 2038 at an estimated cost of $158 billion. The pathological hallmarks of AD include profound neuronal loss, presence of intracellular neurofibrillary tangles and extracellular deposition of beta-amyloid protein (Aβ) as beta-amyloid plaques. These latter aggregations lead to the neuronal degeneration in brain regions important not only for memory, but also for other cog-

nitive functions. The most important risk factor for AD is age (McNeal *et al*., 2001) and with the increase of life-expectancy AD has become the most common form of dementia. However, vascular risk factors, such as hypertension, hypercholesterolemia, and disturbed glucose metabolism are now also recognized as additional factors contributing to AD (Kivipelto *et al*., 2005; Miklossy, 2003; Hölscher, 2011; Maksimovich, 2012; Orehek, 2012; de La Monte, 2012). There are two forms of AD (Figure 1): the early onset familial AD that develops before the age of 65, due to genetic mutations and the late onset or sporadic AD that occurs after the age of 65, both involving the amyloid-beta cascade. Deregulation of amyloid precursor protein (APP) metabolism either because of genetic mutations or other unknown factors resulting in an overproduction and deposition of Aβ is presently considered as one of the critical factors for the development of both types of AD (Robinson and Bishop, 2002; Castellani *et al*., 2010). Furthermore, alterations in amyloid precursor protein metabolism have been described not only in the brain, but also in the periphery including in T lymphocytes (Magaki *et al*., 2008). Therefore, AD may be considered not only a disease of the brain, but also a systemic disease affecting the whole organism (Griffin, 2011; Sardi *et al*., 2011).

It is now formally recognized by the new diagnostic criteria of the International Working Group (IWG) and National Institute on Aging - Alzheimer's Association (NIA-AA) (Visser *et al*., 2012; Budson and Solomon, 2012; Grandy, 2012) that AD is not a homogeneous disease. The current "Holy Grail" is to be able to diagnose AD forms before they manifest clinically and, importantly, before irreparable damages are done. To be able to do so, we need robust and reliable biomarkers which reflect the pathogenesis of AD (Visser *et al*., 2009; Sperling *et al*., 2011; Heister *et al*., 2011; McKhann *et al*., 2011). This is important because identifying such pathways might offer new targets for interventions aiming at the prevention or amelioration of cognitive manifestations (Petersen *et al*., 2001). Although much attention has been focused on Aβ itself in this respect, it may not actually be as attractive a target as thought if

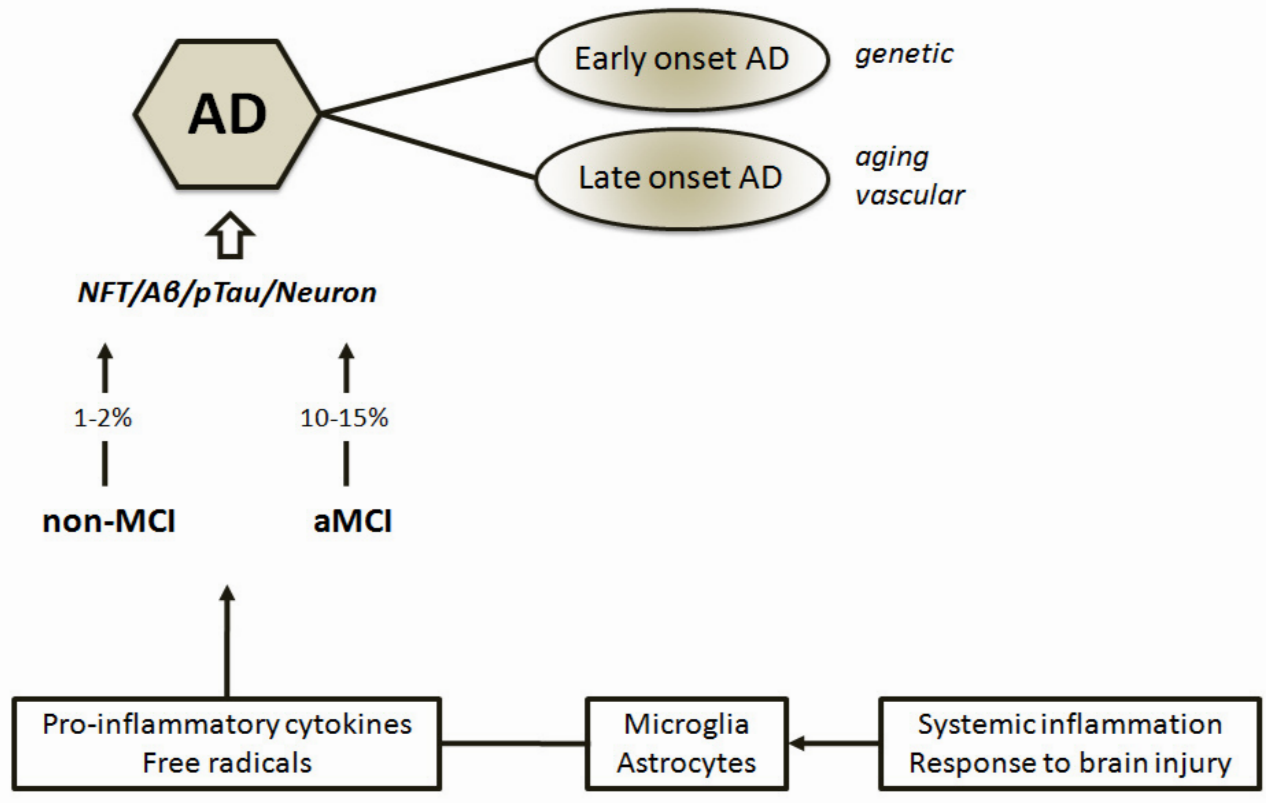

Figure 1. The onset of Alzheimer's disease. Insults in the periphery and in the brain activate microglia and astrocytes. The resulting pro-inflammatory environment is a key factor for accumulation of beta amyloid plaques and neurofibrillary tangles (NFT). Individuals with latent amnestic mild cognitive impairment (aMCI) are more likely to become AD patients. While early onset of AD has a strong genetic component, the late onset form is more related to aging *per se* and to vascular events.

current doubts concerning its causative role are substantiated (Selkoe, 2012; Naylor *et al*., 2012; Richard *et al*., 2012; Skaper, 2012). This first part, of a two-part review series, will deal with the current clinical knowledge and the questions raised by the Aβ cascade hypothesis in the pathogenesis of AD and the second part will aim to synthesize our current knowledge and to discuss new data that suggest how immune alterations may contribute to the development of AD and may therefore provide beneficial targets in novel approaches for the treatment of AD.

What Is Alzheimer's Disease?

AD was originally described by Alois Alzheimer in 1907 in a 51-year old patient (Alzheimer, 1907). He described the case of a middle-aged woman with progressive loss of memory accompanied by disorientation associated with behavioral problems such as hallucinations and agitation. Clinically, all the hallmarks of what we know as AD were present. Moreover, Alzheimer described two distinct lesions in the cortex of this patient that show histopathologically as extracellular plaques, now known as amyloid beta plaques (AP), and intracellular neurofibrillary tangles (NFT) (Alzheimer, 1907; 1911). However, he also described that the disease may also be present without any NFTs. Even over a century ago, the relationship of this new entity to senile dementia was being debated. Psychiatrists and neurologists at that time considered that the disease described by Alzheimer corresponded to an early form of senile dementia (pre-senile dementia). However, it was nonetheless clearly distinct from the form properly called senile dementia according to the clinical and anatomical criteria, even if the histopathological lesions were similar. It is of note that it is only as relatively recently as the 1970s that this thinking was reversed, and based on neuropathological and genetic data, AD came to be considered as a specific entity for the first time. Senile degenerative dementia is the most frequent representative of this entity (Tomlinson *et al*., 1970). This way of thinking has far-reaching consequences by influencing the actual clinical practice. More specifically this thinking has led to the difficulty to recognize the clinical differences between the two original entities, to accept that other causes as well as Aβ may be at the origin of AD, and to develop new pharmaceutical means except those targeting the modulation of Aβ.

Alzheimer's disease and aging

The most important risk factor for AD is age, and some forms were already linked to aging by Alzheimer under the appellation of senile degenerative dementia. This early notion stemmed from the findings that the histopathological features observed in the first Alzheimer patient (AP and NFT), were also present in increasing amounts in overtly-healthy non-demented elderly subjects (Buée *et al*., 2000; Sojkova *et al*., 2011; Maarouf *et al*., 2011). Later, these changes were established as highly specific for AD in forms related to mutations in genes involved in various parts of the Aβ processing machinery or in the presenilin 1 and 2 genes (Goate *et al*., 1991; Sherrington *et al*., 1995; Levy-Lahad *et al*., 1995). However, these cases represent only 1-5% of all Alzheimer dementia. The remaining 95-99% represent late-onset AD and thus suggest that there is a close relationship between the appearance of these lesions and the aging process (Castellani *et al*., 2010). Some authors consider that the presence of NFT could be a marker of aging, whereas Aβ deposition only accelerates this process. These observations lead to the conclusion that there are several forms of AD associated with various histopathological features (Warren *et al*., 2012). Furthermore, this interpretation is underlined by the dichotomy between the presence of the lesions and the clinical symptoms and signs (Prohovnik *et al*., 2006). Do we need a threshold of these histopathological changes for the disease to be clinically manifested? Taking into account the new diagnostic criteria of the IWG and the NIA-AA the answer is unequivocally yes (Visser *et al*., 2012). This means that the diagnostic and the prognostic evaluations of the current biomarkers in the brain (easily revealed by PIB or florbetapir PETscan) and cerebrospinal fluid (CSF) are based on the probability that the quantity of Aβ and hyperphosphorylated Tau protein bear a direct relationship with the development, progression, and severity of AD. The observations imply a causal relationship, although it is not yet firmly established that these markers are the cause of AD (Selkoe, 2012). Furthermore, there are at the present no other biomarkers for AD available, although many studies have proposed to consider a number of candidate markers even by serological analysis (Doescke *et al*., 2012; Rocha de Paula *et al*., 2011; Angata *et al*., 2012). A recent paper using genome-wide gene expression profiling searched for biomarkers distinguishing AD from "normal" aging in the brain (Podtelezhnikov *et al*., 2011). The results confirmed that AD is similar to as well as distinct from the process of normal aging, confirming earlier thoughts by investigators in the field. Four categories were assessed which were BioAge (biological age), Alz (Alzheimer), Inflame (inflammation), and NdStress (Neurodegenerative stress). BioAge (genes statistically associated with neuronal loss, glial activation, and lipid metabolism) and Inflame (inflammatory cytokines and microglial genes) are markers of early stages while the other two are markers of late-stage disease. Thus, aging is associ-

ated with similar histopathological changes as AD. The outcome of this study clearly showed an absence of correlation between the severity, composition of the senile plaques, and the clinical manifestations of AD. It is of note, however, that many age-associated alterations including oxidative stress, mitochondrial dysfunction, and inflamm-aging, may predispose to the development of AD, at least under certain conditions. These data warrant the reconsideration of the etiopathogenesis of AD in its sporadic forms in elderly subjects.

Alzheimer's disease and vascular dementia

There is an ongoing debate on the co-existence or the contribution of vascular factors to AD as originally proposed by Alzheimer (Alzheimer, 1907; Derouesné, 2008). In many cases both large and small alterations are detected in the arteries of AD patients' brain. The frequency of mixed dementia makes it difficult to distinguish between AD and vascular dementia (VaD) (Thomlinson *et al*., 1970), despite Hatchinski's attempts to do so by creating a specific clinical score (Hachinski, 1974; Moronay *et al*., 1997). The recent recognition that vascular risk factors such as hypertension or hypercholesterolemia are also risk factors for AD makes the debate even more topical (Kivipelto *et al*., 2005; Miklossy, 2003; Hölscher, 2011; Maksimovich, 2012). Recent studies that suggest that we may be beginning to see a decreasing occurrence of AD due to better management of the vascular risk factors make it even more confusing but even more important to distinguish AD from vascular dementia (Qiu, 2012; Solomon *et al*., 2013). However, the Nun Study showed that only individuals with AD pathology associated with subcortical infarcts presented clinical symptoms and signs of dementia (Snowdon *et al*., 1997). These findings raise the pertaining question concerning the relationship between typical AD pathological alterations and vascular changes in the brain (Gorelick *et al*., 2011; 2012). It is to be emphasized that there are no data that link vascular alterations to the neurodegenerative lesions found in AD brains (Figure 1). Whether this link is via systemic inflammation or immune changes remains to be elucidated.

New criteria for diagnosis

Over the last few years, great progress has been made in refining the early clinical diagnosis of AD. This is of importance because the clinical emergence of the symptoms is recognized mostly at a very late stage, when excessive damage has already been done. One approach already taken many years ago was to introduce the clinical entity of "mild cognitive impairment" (MCI) in an attempt to identify people who would progress to AD (Figure 2). It is now well-accepted that MCI generally represents a transitional state between the cognitive changes of normal aging and early AD (Baars *et al*., 2009). Among the different MCI subtypes, amnestic MCI (aMCI) is the most common. aMCI typically presents itself with prominent memory impairment and is likely to progress to AD (Petersen *et al*., 1999). People with MCI have an annual AD diagnosis rate of 10-15% as opposed to a rate of 1-2% for the general elderly population, with most progression to AD occurring within 3 years of detection (Devanand *et al*., 2008; Okonkwo *et al*., 2008; Karas *et al*., 2008). Occasionally, MCI remains mild and may not progress

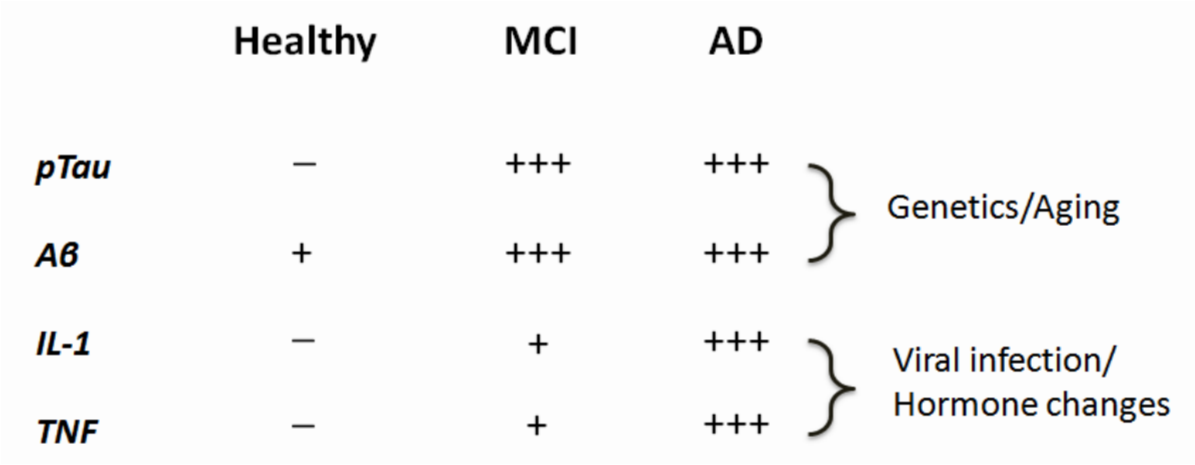

Figure 2. Physiological and inflammatory steps: from health to AD. An intermediate stage prior to AD is mild cognitive impairment. While the accumulation of beta amyloid plaques and pTau does not increase much during conversion from MCI (mild cognitive impairment) to AD there is a significant enhancement of the inflammatory state.

to dementia (Ritchie *et al*., 1996). Thus, an important issue is to distinguish aMCI patients who are predicted to progress to AD from those who are not. A reliable predictive assessment would help to better understand the process of AD disease. Moreover, distinguishing "converters" from "non-converters" could make it possible to implement strategies to reduce the risk of or to delay AD, bearing in mind that early therapeutic interventions are more likely to be effective.

These observations prompted refinement of the AD diagnostic criteria with the introduction of preclinical AD (asymptomatic at risk for AD or pre-dementia without AD or presymptomatic AD) which is detectable even before the aMCI diagnosis by clinical evaluation and with the use of biomarkers of CSF (Visser *et al*., 2012; Dubois *et al*., 2010). This suggests that AD may be diagnosed decades before its clinical appearance and could be more amenable to treatment for preventing the progression to overt AD. The new criteria of AD, which were principally developed as clinical research tools, are based on clinical evaluation and biomarkers from the CSF (Dubois *et al*., 2007). This presupposes, as mentioned above, that these biomarkers truly represent the clinical stage and they reflect AD causation. These criteria are not formally accepted for everyday clinical use, but many clinicians try to use the MCI diagnosis to offer a better prognosis to their patients (Reiman *et al*., 2011; Budson and Solomon, 2012).

Together, the available diagnostic criteria suggest that we cannot yet assess all aspects and diversity of AD. It is therefore difficult to make sub-groups according to symptomatology, progression, and biomarkers. This is a serious drawback for the design of clinical trials and the development of new criteria, except perhaps those that rely solely on the presence of Aβ (Naylor *et al*., 2012).

What Causes Alzheimer's Disease?

The most popular theory concerning the cause of AD remains the amyloid beta cascade hypothesis (Selkoe, 2012). Aβ is a degradation product of APP found in neurons and other cells. Normally, APP is cleaved by α-secretase into soluble non-amyloidogenic products. For some reason not yet fully understood, a shift in secretase activity towards β-secretase (BACE) activity may occur, and BACE cleaves APP into Aβ peptides of different lengths which can become amyloidogenic by forming fibrils. Thus, the overproduction or decreased clearance of Aβ is the starting point of the reaction cascade leading to neurodegeneration and the characteristic histopathological hallmarks of AD, i.e., the extracellular beta-amyloid plaques composed of aggregated Aβ fibrils and of neurofibrillary tangles composed of hyperphosphorylated Tau (a component of the microtubules). It is debated whether the oligomeric Aβ or the extracellular Aβ is the most toxic, but it is clear that either form is neurotoxic (Hardy and Selkoe, 2002),

With respect to AD, the crucial question is: what is the mechanism responsible for the shift from α- to β-secretase activity? This shift can happen in the sporadic form of AD, and may be due to the accumulation of cholesterol in discrete nanoscale structures of the cell membrane known as lipid rafts (Harris and Milton, 2010). There is an increase in plasma membrane cholesterol with age, as observed in lymphocytes (Larbi *et al*., 2006; Eckert *et al*., 2003; 2010). Moreover, the contribution of the ApoE4 genetic background (ApoE4 is a constituent of low-density lipoproteins), one of the most important susceptibility genes for late-onset AD, can also contribute to the increase in plasma membrane cholesterol. The increase in plasma membrane cholesterol may contribute to the shift in secretase activity toward the β-isoform. Certainly, brain glucose hypometabolism (Cunnane *et al*., 2011) and other as yet unknown factors may also contribute.

What can initiate Aβ production?

Currently, we do not know why Aβ is formed and whether it actually has a physiological as well as a pathological role. Aβ may even have neuroprotective roles and also may enhance neurogenesis (Porayette *et al*., 2009). It may be suggested that Aβ is produced in reaction to an insult in the brain. In this connection some investigators proposed that Aβ acts as an anti-infectious agent (Holmes and Cotterelle, 2009; Wozniak *et al*., 2007; Lukiw *et al*., 2010; Soscia *et al*., 2010) or as a reaction to declining sex hormone homeostasis with age (Clark and Atwood, 2011). Whether this can be protective against further infections of neighboring cells or to maintain neurogenesis is not known (Figure 2). Overall, it appears that the role of Aβ goes beyond being the pathological causative agent of AD.

Accumulation of Aβ, for example after an infection, should trigger a mechanism of removal once the infection has been controlled. This situation is particularly relevant to the currently most widely-accepted causative hypothesis of AD, which is Aβ-initiated neuroinflammation (Eikelenboom *et al*., 2011; Fung *et al*., 2012; Broussard *et al*., 2012). However, there is still debate as to whether Aβ is the causative agent of AD (independently of what induced its overproduction or decreased clearance) and triggers neuroinflammation

(Haga *et al*., 1989; Itagaki *et al*., 1989; Akiyama *et al*., 1996), or alternatively whether its production is reactive, induced by the action of systemic and local brain inflammation caused by other agents (Brugg *et al*., 1995; Buxbaum *et al*., 1998; Goldgaber *et al*., 1989; Marx *et al*., 1999, Liao *et al*., 2004; Giunta *et al*., 2008).

Is Aβ the cause of Alzheimer's disease?

The most popular hypothesis concerning the pathogenesis of AD states that Aβ is the cause of the disease, mostly because Aβ is the major component of the beta amyloid plaques. In early onset AD, there is firm evidence that a genetic basis exists for the production of Aβ on cleavage of APP by BACE. In the late form of AD, there is also an increase of Aβ probably because of its decreased clearance — but it is not known what initiates its production or is responsible for the decreased clearance. This is a challenging situation to investigators in the field as well as clinicians since at present there is no unequivocal data to account for either mechanism. However, it is shown that Aβ triggers an inflammatory response by activating microglial cells and astrocytes (Solito and Sastre, 2012). It can be suggested that initially these cells most probably eliminate Aβ but they eventually become overwhelmed due to overproduction of Aβ as AD progresses. As a result, microglial cells and astrocytes produce increasing quantities of pro-inflammatory molecules and free radicals that eventually kill neurons by "friendly fire" and cause the clinical symptoms and signs of the disease. In addition, hyperphosphorylation of the Tau protein within the axons is facilitated by Aβ and that leads to neurofibrillary tangle formation. In this scenario, Aβ can indeed be considered the causative agent of AD and this sequence of detrimental events has justified the huge therapeutic investments that have been made in trying to find ways to prevent Aβ accumulation. However, does this line of thinking correspond to a valid answer to the cause of AD?

Is Aβ a consequence and not the cause of Alzheimer's disease?

More than two decades ago, some groups suggested that inflammation precedes the onset of AD and indeed may cause beta amyloid plaque formation (Griffin *et al*., 1989). Numerous studies demonstrated increased pro-inflammatory cytokines such as interleukin-1 (IL-1) and tumor necrosis factor α (TNF-α) in patient CSF and serum and, moreover, suggested that their levels correlated with the transformation of MCI to AD despite a lack of changes in Aβ or pTAU (Tarkowski, 2002; 2003; Laurin *et al*., 2009; Schultemaker *et al*., 2009; Buchave *et al*., 2009). These data are not consistent with the notion that Aβ triggers AD onset, but they do not exclude a secondary pathological role for Aβ once the disease is already advanced (Selkoe, 2012; Richard *et al*., 2012). The question is of course what initiates these inflammatory changes well before the appearance of Aβ. There are several views on this, which are not mutually exclusive. It was observed that systemic inflammation, as well as trauma, may exacerbate pathogenic brain TNF levels in AD independently of Aβ but possibly acting as a trigger for its accumulation (Figure 2) (Clark *et al*., 2010). Some researchers support the idea that the increase of TNF in the brain is the result of viral infections (Carter, 2008). Age-associated alterations of sex hormone levels have also been suggested to induce an increase of pro-inflammatory cytokines such as TNF in some brain regions (Clark and Atwood, 2011). From these data, it would appear that once TNF production is initiated in the brain, it remains there for an extended period of time (Qin *et al*., 2007). In addition, although without specifically stating that cerebrovascular alterations seen in AD may cause AD via brain inflammation, some researchers question these vascular alterations as being a significant contribution to AD (Tarkowski, 2002; Meguro *et al*., 2012).

Conclusion

A conservative interpretation of these disparate data would be that diverse pathways can initiate and drive AD, whereby some reactions can be protective at the beginning but become pathogenic over time. At present, it is difficult to ascertain which of the several competing hypotheses is most likely to be applicable. It seems quite clear, that one should move away from considering solely the Aβ cascade hypothesis with the exclusion of all other possibilities, especially when we recognize the poor correlation between Aβ and sporadic AD as well as the failure of clinical trials attempting to lower Aβ load therapeutically. Unfortunately, these therapeutic approaches have not produced any tangible benefit, nor have they diminished the prevalence or the progression of AD (Castellani *et al*., 2009; Castellani and Smith, 2011). Certainly, several aging-related processes can be considered as potential etiological factors, including oxidative stress, mitochondrial alterations, presence of ApoE4, repetitive brain injury, and infections (Corder *et al*., 1993; Neve and Robakis, 1998; van den Heuvel *et al*., 2007; Reis *et al*., 2010; Swerdlow *et al*., 2010; Lunnon *et al*., 2012; Giunta *et al*., 2012; Sohal and Orr; 2012; Ball *et al*., 2012). One major contributory mechanism to the etiology of AD may be immunosenescence and the associated inflammaging (Franceschi *et al*., 2000; Fulop *et al*., 2007; Lang *et al*., 2010; Pawelec, 2012), which could be the path-

way integrating many of these individually-evoked age-related changes. In the second part of this review we will consider whether the immune signature can help to better understand AD and the eventual role of Aβ.

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Disclosure

Authors report n conflicts of interest.

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