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The Journal of Biomedical Research, 2016, 30(5):361-372

JBR

Review Article

Autoantibodies in Alzheimer's disease: potential biomarkers, pathogenic roles, and therapeutic implications

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Abstract

Alzheimer's disease (AD) is a prevalent and debilitating neurodegenerative disorder in the elderly. The etiology of AD has not been fully defined and currently there is no cure for this devastating disease. Compelling evidence suggests that the immune system plays a critical role in the pathophysiology of AD. Autoantibodies against a variety of molecules have been associated with AD. The roles of these autoantibodies in AD, however, are not well understood. This review attempts to summarize recent findings on these autoantibodies and explore their potential as diagnostic/prognostic biomarkers for AD, their roles in the pathogenesis of AD, and their implications in the development of effective immunotherapies for AD.

Keywords: Alzheimer's disease, autoimmune, autoantibody, biomarker, pathogenesis, immunotherapy

Introduction

Alzheimer's disease (AD) is the most prevalent age-related neurodegenerative disorder. It causes severe cognitive impairment, ultimately leading to dementia and death. It deeply affects the lives of millions of patients and their care givers emotionally and financially. Today over 46 million people live with AD worldwide[1], and one in nine people over age 65 has AD[2]. The prevalence of this devastating disease is expected to triple by the year 2050 due to the increasing age of the population and the current lack of an effective therapy for the disease. The neuropathological hallmarks of AD brains include the accumulation of amyloid-β protein (Aβ) in neuritic plaques and cerebral vessels and neurofibrillary tangles consisting of hyper-phosphorylated tau proteins[3]. The pathogenic mechanisms that lead to the development of AD, particularly the sporadic form of AD, are not fully understood. Compelling evidence indicates that the immune system is intrinsically involved in the progression of AD. Autoantibodies against a variety of molecules have been detected in patients with AD. However, the roles of these autoantibodies in AD are not clear. Recent clinical and experimental studies suggest that these autoantibodies may have the potential to serve as diagnostic/prognostic biomarkers for AD; some may contribute to the pathogenesis of AD, and others may play a protective role, thus facilitating the development of effective immunotherapies for AD.

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Received 15 September 2015, Accepted 26 October 2015, Epub 02 January 2016
CLC number: R741.02, Document code: A
The author reported no conflict of interests

doi: 10.7555/JBR.30.20150131

Autoantibody production and autoimmune diseases

Autoantibodies are produced under physiological or pathophysiological conditions (***Fig. 1***). Physiologically, humans produce natural autoantibodies recognizing self-antigens (autoantigens) to facilitate the recognition and clearance of dead and dying cells[4-5]. Natural autoantibodies are frequently IgM isotype and are spontaneously produced during B cell development. Polyreactive natural autoantibodies are normally low affinity for self-antigens and are primarily produced by B-1 cells that account for most of the B cell repertoire in the fetus and neonate[6]. Natural autoantibodies facilitate phagocytosis of apoptotic cells and inhibit inflammatory pathways. Therefore, natural autoantibodies have a pivotal role in dampening inflammation and maintaining immune tolerance[4]. The production of high affinity autoantibodies, predominantly the IgG class, is promoted by inflammations and infections that trigger antibody affinity maturation toward targeting self-antigens. The breakdown of immune tolerance is a major mechanism leading to pathogenic autoantibody production and autoimmune diseases. By binding to self-antigens with high affinity, pathogenic autoantibodies initiate and maintain the inflammatory cascade responsible for tissue injuries. There are more than 80 different types of autoimmune diseases[7]. Some of the well-known autoimmune diseases include systemic lupus erythematosus, rheumatoid arthritis, Sjogren's syndrome, type-1 diabetes, celiac disease, and multiple sclerosis. Several lines of evidence indicate that AD might also be a type of autoimmune disease[8]. Autoantibodies against various molecules have been detected in AD patients in numerous studies (***Table 1***).

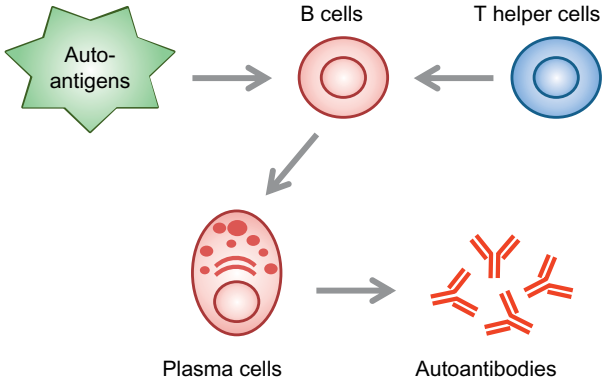

Fig. 1. **Schematic illustration of autoantibody production.** Under certain physiological and pathological conditions, B cells recognize endogenous constituents of the body as antigens (autoantigens). With the stimulation of the T helper cells, B cells differentiate into plasma cells that produce antibodies specific to the autoantigen (autoantibodies).

These autoantibodies may serve as biomarkers for the diagnosis and prognosis of the disease. Some of the autoantibodies may directly participate in the pathogenic process of the disease development; others may mediate the clearance of toxic autoantigens, thereby mitigating the progression of the disease.

Autoantibodies as potential biomarkers for AD

Currently, definite AD diagnosis relies on confirmation of brain pathology by autopsy. As the number of people developing AD is expected to increase sharply in the next decades, there is an urgent need to develop diagnostic tests applicable to living people. The confirmatory diagnosis of AD in early stages could facilitate early therapeutic intervention and treatment of the disease. Sensitive and specific biomarkers are also valuable for prognostic purposes and for monitoring disease progression and response to therapy. Thus, there has been much research effort to identify reliable biomarkers for AD[9]. Compared to biomarkers that require brain imaging and collection of the cerebrospinal fluid (CSF), the blood-based biomarkers are particularly desirable because they are less expensive, relatively non-invasive, and easily accessible[10, 11]. Through the search of such blood-derived biomarkers, some autoantibodies have emerged as potentially effective biomarkers for AD (***Table 1***).

Autoantibodies against Aβ

As the primary component of the amyloid plaque pathology, Aβ has attracted paramount attention in the research field of AD. Aβ is the cleavage product of the transmembrane amyloid-β precursor protein (APP). Major species of Aβ are Aβ40 and Aβ42, containing 40 and 42 amino acids, respectively. Although the pathogenesis of AD is not fully understood, it is widely accepted that accumulation of Aβ in the brain, especially the more amyloidogenic Aβ42, due to overproduction (familial AD) or impaired clearance (sporadic AD) initiates the pathogenic cascade, ultimately leading to neurodegeneration and dementia[3]. The potential of using Aβ *per se* as a blood-based biomarker for AD has been investigated extensively but it faces technical challenges and the results are inconsistent[12-13]. The initial report by Gaskin *et al*. that B cells derived from a patient with AD secreted Aβ-specific antibodies[14] ignited the interest in searching for autoantibodies against Aβ in the circulation with the hope of using these autoantibodies as a potential biomarker for AD.

Indeed, Aβ-autoantibodies have been detected in the serum and CSF of patients with AD as well as healthy

Table 1. **AD-associated autoantibodies and their potential roles**

Autoantibody Targets	Biomarker	Pathogenic or Protective	Immunotherapy	References
AD pathology-related				
Aβ	Yes	Protective	Yes	[15-19, 23, 24, 28, 29]
Tau	Possible	Protective	Yes	[82-85, 91-93] [31, 32, 93, 94]
Neurotransmitters and receptors				
Glutamate	Possible	Unknown	No	[34]
DA	Inconsistent	Unknown	No	[25, 37]
5-HT	Possible	Unknown	No	[25, 37]
NMDAR	Nonspecific	Unknown	No	[35, 36]
Glial markers				
S100b	Nonspecific	Unknown	No	[25, 38, 39]
GFAP	Nonspecific	Unknown	No	[39, 40]
Microglia	Nonspecific	Unknown	No	[41, 42]
Lipids				
OxLDL	Possible	Unknown	No	[47]
Phospholipids	Possible	Unknown	No	[48-51]
Ganglioside GM1	Inconsistent	Unknown	No	[52-55]
Ceramide	Unknown	Pathogenic	No	[56]
Vascular related				
Rabaptin 5	Nonspecific	Unknown	No	[60]
RAGE	Inconsistent	Unknown	No	[24, 63, 64]
AT1R	Possible	Unknown	No	[65]
Cellular enzymes				
Aldolase	Nonspecific	Unknown	No	[66]
ATP synthase	Possible	Pathogenic	No	[67, 81]
Others				
Profiled by array-based "autoantibomic" techniques	Possible	Unknown	No	[68, 70-72]

control subjects. A number of studies have been carried out to determine whether the level of Aβ-autoantibodies could be used as a diagnostic and treatment outcome biomarker for AD. Earlier reports indicated that AD patients had significantly lower levels of unbound serum Aβ-autoantibodies than healthy age-matched individuals[15-19], which suggests that reduced levels of Aβ-autoantibodies may affect the removal of Aβ from the brain and contribute to the development of AD. Other studies showed that both AD and control subjects had low and variable concentrations of Aβ-autoantibodies and that neither the presence nor the levels of Aβ-autoantibodies were correlated with the status of AD[20-22]. Notably, however, studies described above only examined the free (unbound) Aβ autoantibodies. In circulation, Aβ-autoantibodies may exist either as unbound form or as antigen-antibody complexes, which could affect the capture efficiency for Aβ-autoantibody and the accuracy of ELISA assays and may explain the wide-range of discrepancy in different studies[23]. Interestingly, a positive association between Aβ-autoantibody titers and cognitive status was demonstrated using affinity-purified IgGs from a cohort of subjects[24], suggesting that sample preparations could also affect the assay results. Using an improved approach, Mruthinti *et al*. observed that the levels of Aβ-autoantibodies were significantly higher in AD patients than in controls[24]. In addition, Gruden *et al*. reported that the levels of autoantibodies reacting with oligomers of a short but neurotoxic fragment of Aβ, Aβ(25-35), were significantly higher in AD patients than in the control group who had undetectable autoantibodies to the Aβ fragment. Further analysis showed that there was a biphasic relationship between autoantibodies to aggregated Aβ(25-35) and the stage of dementia, with the level of the autoantibodies rising during the mild to moderate phase and then descending within the moderate to severe stage[25]. Using acidic dissociation approach to measure both the bound and unbound antibodies, Gustaw-Rothenberg *et al*. also observed that the levels of total serum Aβ autoantibodies were significantly higher in AD patients than the aged-matched control subjects[23,26]. However, there are concerns about this acidic dissociation approach as it

has been shown that exposure of sera to low pH resulted in partial denaturation of antibodies and caused an artifactual increase in apparent anti-Aβ antibody titers[27].

To further clarify the biomarker value of the bound Aβ-autoantibodies, Maftei *et al*. developed a new strategy to specifically determine the antigen-bound Aβ-autoantibodies (intact Aβ-IgG immune complexes) in the serum and CSF from AD patients and control subjects[28]. They found that both serum and CSF levels of Aβ-IgG immune complexes were significantly higher in AD patients compared to control subjects. Moreover, the levels of Aβ-autoantibody immune complexes were negatively correlated with the cognitive status across the groups, declining cognitive test performance accompanied by the increasing levels of Aβ-autoantibody complexes[28]. These findings most likely indicate that there is a decrease in clearance of Aβ-IgG immune complexes in AD rather than an increase in the level of free autoantibodies to Aβ. Indeed, consistent with many previous studies, a recent study showed that the levels of unbound autoantibodies to Aβ were significantly reduced in the serum of patients with AD compared to those of healthy controls, especially in individuals over 65 years of age[29].

Taken together, the aforementioned studies demonstrate that Aβ-autoantibodies show promise as an effective blood biomarker for AD. However, due to different methodologies, varied sample sizes and disease stages, and the existence of bound and unbound forms, the measurements of Aβ-autoantibodies were highly variable and the conclusions were sometimes inconsistent. A uniform procedure needs to be applied so that results can be compared across studies with subjects from different populations. The additional value of using the level of Aβ-autoantibodies for diagnosing AD, predicting/tracking disease progression, and monitoring treatment efficacy in a panel of blood-derived biomarkers warrants further investigation.

Autoantibodies against tau

Neurofibrillary tangles in AD brains primarily consist of the hyper-phosphorylated tau, a microtubule associated protein. Unlike autoantibodies against Aβ, autoantibodies against tau are not prevalent. An earlier study showed that tau autoantibodies were rarely detected in patients with neurodegenerative diseases, suggesting that tau is an extremely poor autoantigen[30]. A later study reported the detection of autoantibodies against tau in both unphosphorylated and phosphorylated forms in the serum of a small number of AD and healthy subjects and provided some preliminary evidence for a higher level of anti-phosphorylated-tau autoantibodies of IgM class in AD patients than in controls[31]. Interestingly, a recent study measured autoantibodies against tau and neurofilaments in the serum and CSF of patients with AD, with other dementia, with neuro-inflammatory diseases, and healthy controls and found that AD patients had significantly higher levels of autoantibodies to tau and heavy neurofilament than the other groups[32], suggesting a specific change in anti-neurocytoskeletal immunity in AD. However, another recent study showed that the levels and the avidities of anti-tau autoantibodies were increased in patients with multiple sclerosis[33]. Therefore, the biomarker value of tau autoantibodies requires further evaluation.

Autoantibodies against neurotransmitters and related receptors

Alterations of neurotransmitters such as glutamate, dopamine (DA), and hydroxytryptamine (5-HT) are associated with the progression of AD dementia. Autoantibodies to glutamate were detected in the plasma of AD patients more frequently than in the plasma of healthy subjects, and among the patients who had glutamate autoantibodies, the level of the autoantibodies in patients with moderate and severe dementia was 2-fold higher than that in patients with mild dementia[34]. Autoantibodies against the glutamate receptor, N-methyl-D-aspartate receptor (NMDAR), have also been found to be more prevalent in dementia patients than cognitively healthy controls[35]. However, a recent study suggested that the prevalence of NMDAR autoantibodies was related to age rather than to the status of AD or vascular dementia[36]. Plasma concentrations of immune complexes and antibodies to serotonin and DA were significantly higher in AD patients compared to age-matched healthy controls[37]. However, significant increases of autoantibodies against DA could only be found in subgroups of moderate dementia[25], limiting its biomarker value for AD diagnosis. On the other hand, the overall level of 5-HT autoantibodies was significantly higher in AD patients than in the controls[25,37]. 5-HT autoantibodies increased during mild dementia and plateaued subsequently[25]. Clearly, the utility of these autoantibodies as AD biomarkers requires confirmation from further studies.

Autoantibodies against glial markers

Astrocytes and microglia are activated in AD brains. Autoantibodies to S100b, glial fibrillary acidic protein (GFAP), and microglia have been found to be increased in patients with AD. S100b is an acidic calcium-binding protein produced by astrocytes, which plays a role in neuronal development and survival but high levels of S100b leads to neuronal apoptosis[38]. An early study

reported the presence of autoantibodies to S100b in the serum of patients with AD but the autoantibody levels in AD patients overlapped with those in vascular dementia and aged healthy controls[39]. A later report showed that the levels of S100b autoantibodies exhibited a biphasic relationship with the stage of the dementia, similar to the levels of autoantibodies to oligomeric Aβ(25-35), rising during the mild to moderate phase and then falling within the moderate to severe stage[25].

Autoantibodies to another astrocyte-specific protein, GFAP, have also been identified in patients with dementia and in aged healthy controls, with higher titers found in patients with AD[39-40]. In addition, autoantibodies specific to microglia were also detected at a high frequency in the CSF of patients with AD[41]. A later study confirmed the presence of CSF anti-microglial antibodies in the majority of patients with definite AD and also in subjects with moderate AD type neuropathology but not in healthy controls[42]. Taken together, the presence of autoantibodies to astrocyte markers and microglia indicates an increased immune response to glial activation. However, the overlap across dementia groups and aged healthy controls limits the use of these autoantibodies as specific biomarkers for AD. Some evidence suggests that the presence of glia-related autoantibodies may be a consequence of the breakdown of the blood-brain barrier (BBB) in aging and in brain disorders rather than a specific change in AD[39].

Autoantibodies against lipid molecules:

Various lipids have been implicated in the development of AD[43-44]. Oxidative stress leads to the production of oxidized lipids and associated molecules, which are immunogenic. For example, autoantibodies to oxidized low-density lipoproteins (oxLDL) are present in the circulation and have been studied extensively in cardiovascular disease[45-46]. Interestingly, autoantibodies to oxLDL were found in the CSF of patients with AD and other neurodegenerative dementia and in healthy controls[47]. The CSF antibody titers to oxLDL, independent of plasma antibodies to oxLDL, were significantly increased in patients with AD compared to controls and to patients with frontotemporal lobar degeneration. However, the implication of these CSF antibodies in AD is not clear.

In line with the involvement of oxidative stress in AD, a series of studies reported that the levels of redox reactive autoantibodies (R-RAAs) to phospholipids (aPLs) were significantly decreased in the CSF and serum of AD patients compared to healthy controls[48-50]. A recent study with samples from Alzheimer's Disease Neuroimaging Initiative (ADNI) further confirmed a decreased level of R-RAA aPLs in sera from the AD diagnostic group compared to the healthy controls. However, the sera from the mild cognitive impairment (MCI) subjects contained a significantly higher R-RAA aPL activity than the sera from AD patients or healthy controls[51]. Although replications are needed in studies with larger sample sizes, these findings suggest the potential of R-RAA aPLs as a blood biomarker for detection of AD in the early stage.

Other studies evaluated the autoantibodies against glycosphingolipid-related molecules, such as ganglioside GM1, in patients with dementia, and showed that GM1 autoantibodies in the serum are associated with the age of the patients and the severity of dementia[52-53]. However, an earlier study indicated that the GM1 autoantibody levels lacked sufficient specificity and sensitivity for use as a diagnostic marker[54]. A recent study also showed that there were no differences in the serum levels of GM1 autoantibodies among AD, vascular dementia, and normal controls[55]. Interestingly, a recent study in a transgenic mouse model of AD found an age-dependent increase in autoantibodies to ceramide, a sphingolipid[56]. Although the level of ceramide has been associated with AD[57-59], the connection between ceramide autoantibodies and AD has not been established in human patients.

Autoantibodies against vasculature-related molecules

Vascular risk factors are associated with an increased risk of AD. The blood-brain barrier (BBB) plays a pivotal role in maintaining normal brain function. Screening a human microvascular endothelial cell cDNA library with sera from patients with AD revealed that rabaptin 5, a protein involved in cellular vesicle trafficking, is an autoantigen in AD patients[60]. Autoantibodies to rabaptin 5 were found in the majority of serum samples from AD patients but not in the sera from healthy controls; however, some samples from systemic lupus erythematosus patients also contained rabaptin 5 autoantibodies, indicating that these autoantibodies are not a disease specific marker.

The receptor for advanced glycosylation end products (RAGE) has been identified as the major receptor at the BBB to mediate the flux of Aβ from the blood to the brain[61]. It has been shown that affinity-purified IgGs specific for the peptide of RAGE were increased significantly in AD individuals compared to the age-matched controls. RAGE autoantibody titers were also negatively correlated with cognitive status as the more cognitively impaired individuals tended to exhibit higher RAGE-autoantibody titers[24]. Intriguingly, RAGE autoantibody titers were found to be highest in the AD-diabetic group, followed in the decreasing order

by the non-diabetic AD group, and the elderly diabetic group. The control non-diabetic elderly group had the lowest level of RAGE antibody. Consistent with the human data, chemically-induced diabetes in rats was associated with high levels of anti-RAGE IgGs, suggesting a common pathogenic process in diabetes and AD[62]. These findings also suggest that the levels of RAGE-autoantibodies might have the predictive value, particularly for AD with diabetes. A further study provided additional evidence for the association of high levels of RAGE autoantibodies with cognitive decline in AD[63]. However, a more recent study failed to establish a consistent relationship between RAGE autoantibodies and cognitive function[64]. Thus, the possibility of RAGE autoantibodies as blood biomarkers for AD remains ambiguous.

Interestingly, autoantibodies to the angiotensin 2 type 1 receptor (AT1R), an important player in controlling blood pressure and volume, were recently identified in patients with AD[65]. It was shown that AD patients had significantly higher levels of AT1R autoantibodies compared with healthy controls, particularly in patients without hypertension and diabetes. Furthermore, the levels of AT1R autoantibodies positively correlated with CSF total tau and phosphorylated tau levels but inversely with blood pressure in AD. Whether AT1R autoantibodies could be used as a biomarker for AD awaits further investigation.

Autoantibodies to cellular enzymes

In the search of potential autoantigens in the brain of AD patients, aldolase, an enzyme in the glycolysis pathway, was identified as an autoantigen[66]. Autoantibodies against aldolase were produced in half of AD patients examined. However, some patients with multiple sclerosis and heathy controls also produced autoantibodies against aldolase, thus limiting the value of aldolase autoantibodies as a specific biomarker for AD. Using the proteomic approach, the adenosine triphosphate (ATP) synthase was also identified as a new autoantigen in AD[67]. Autoantibodies to ATP synthase were frequently found in the sera from AD patients but not in age-matched healthy subjects and the patients with Parkinson's disease or atherosclerosis[67], suggesting anti-ATP synthase autoantibodies could be a specific biomarker for AD.

Profiling of autoantibodies associated with AD

Recently, microarray analysis has been applied for autoantibody profiling in attempt to develop immunosignature-based diagnostics for AD. This approach may be termed "autoantibomics" in parallel to other "-omics" technologies. Using protein microarrays containing thousands of unique human antigens probed with sera from AD patients and healthy controls, Nagele *et al*. found that a panel of 10 autoantibody biomarkers could distinguish AD patients from healthy controls with high sensitivity and specificity[68]. Furthermore, this panel of autoantibody biomarkers could also differentiate AD patients from patients with breast cancer and Parkinson's disease with a high accuracy. Interestingly, the autoantigens corresponding to those autoantibodies are proteins that have not been well characterized and their roles in AD are not clear. Using this human protein microarray technique, a recent study further showed that natural autoantibodies are abundant and ubiquitous in human sera and their levels are influenced by age, gender, and disease status[69]. These findings suggest that these autoantibodies may play other roles besides their potential as biomarkers for diseases. Instead of using protein arrays with known identities, Restrepo *et al*. employed peptide arrays containing random sequences of 20-residue peptides to profile autoantibodies in a transgenic mouse model of AD and in elderly human subjects with or without AD[70] The results showed that both AD mice and patients exhibited a distinct immunoprofile compared to controls, suggesting the potential of this technology as a diagnostic tool in AD. A recent study further reported the use of this technique to assess the changes in the immunosignature at different time points of the disease in mice and humans[71]. The results demonstrated that the immune profiles varied at different stages of the disease, questioning the diagnostic value of biomarkers identified at late stages of the disease for detection of the disease in early stages. These observations emphasize the importance of longitudinal studies in establishing effective biomarkers.

In the meantime, Reddy *et al*. reported a related approach involving the use of a peptoid library to discover antibody biomarkers for AD[72]. They used arrays of synthetic molecules called peptoids (oligomers of N-substituted glycines) as antigen surrogates to capture antibodies from serum samples. The levels of the antibodies captured were measured by using a fluorescently labeled anti-IgG antibody. Three peptoids were identified to be able to distinguish patients with AD from healthy controls in an initial discovery cohort. Subsequent analysis with additional samples showed that these peptoids could individually differentiate sera from AD patients and controls with high sensitivity and specificity, suggesting the potential of using a single biomarker for the diagnosis of AD. Similar to the peptide array approach[70], this peptoid technique allows the identification of potential autoantibody biomarkers without prior knowledge of autoantigens and disease pathogenesis.

Although the array-based "autoantibiomic" technologies provide unbiased discovery of biomarkers and show great promise as a diagnostic tool in AD, the results so far are preliminary. For all potential biomarkers described above and others that are not discussed here, further evaluation in independent patient cohorts and in a larger number of samples are required to establish their utility for the diagnosis and/or prognosis of AD.

Potential roles in the pathogenesis of AD

Autoantibodies are known to play pathogenic roles in various diseases in the central nervous system[73]. Some of the autoantibodies described above are not merely markers but also contributors to the pathogenesis of AD. Early studies showed that AD brains had significantly more Ig-positive neurons, which showed neurodegenerative apoptotic features absent in Ig-negative neurons[74-76]. Ig-positive neurons were frequently found in AD brains while they were rarely observed in the brains of healthy controls, suggesting a pathogenic role for autoantibodies in neuron death. Later studies reported that brain-reactive autoantibodies were nearly ubiquitous in human sera, which could contribute to neuropathology under the condition of BBB breakdown as in AD[77-78]. These studies confirmed the abundance of Ig-positive neurons in AD brains, and showed that treatment of cultured neurons with brain-reactive autoantibodies prevalent in human sera increased intraneuronal Aβ42 accumulation, demonstrating a potential role of brain-reactive autoantibodies in the initiation and/or progression of AD. Further studies suggested that protein citrullination (aka deimination), a post-translational protein modification that converts arginine to citrulline within proteins, may be involved in eliciting the production of brain-reactive autoantibodies[79].

Studies in animal models also support the pathogenic role of autoimmunity in AD. In a triple transgenic mouse model of AD, which develops both amyloid plaques and tau tangles, it was found that these mice exhibited manifestations of systemic autoimmune/inflammatory disease[80], including the elevation of autoantibodies. Further, the mice develop behavioral deficits in company with systemic autoimmune/inflammatory manifestations, prior to plaque and tangle pathology in the brain. These findings suggest a causal link between autoimmunity and abnormal behavioral function.

The pathogenic role of some specific autoantibodies has also been investigated. For example, it has been shown that autoantibodies to ATP synthase are not only indicative of AD but also pathogenic in AD[67]. ATP synthase autoantibodies were capable of inducing the inhibition of ATP synthesis, alterations of mitochondrial homeostasis and cell death by apoptosis in SH-SY5Y neuroblastoma cell line. Further studies *in vivo* showed that intracerebroventricular administration of ATP synthase autoantibodies purified from AD patients caused poor cognitive performance and pronounced cell damage in the hippocampus in mice[81]. In addition, specific autoantibodies to ceramide were found to increase amyloid plaque burden in a transgenic mouse model of AD[56].

Natural autoantibodies against Aβ are generally considered protective in AD[82-85]. Active and passive immunizations against Aβ have been explored as potential therapeutic approaches for AD (discussed below). However, these immunotherapies have been associated with severe side effects related to Aβ antibody-induced cerebral amyloid angiopathy (CAA) and perivascular inflammation[86-88]. Recent studies showed further evidence that Aβ autoantibodies causes CAA-related inflammation[89-90], similarly to what observed in Aβ-immunization trials. Thus, autoantibodies to Aβ could be pathogenic under certain conditions.

Therapeutic implications

Amyloid plaques and tau tangles are pathological hallmarks of AD. The fact that healthy humans naturally produce neuroprotective autoantibodies against Aβ and tau suggests the potential of preventing/treating AD by stimulating the production of such antibodies (active immunization) or directly administering these antibodies (passive immunization). Immunotherapy approaches for AD have been reviewed extensively in the literature[91-94]. Earlier efforts have been focused on targeting Aβ pathology. Remarkable successes of Aβ immunization in animal models led to subsequent human clinical trials. As mentioned above, although both Aβ vaccination and administration of monoclonal Aβ antibodies reduced the amyloid plagues in treated subjects, initial trials produced disappointing results due to the occurrence of severe adverse side effects and the failure of improving behavioral function. In light of these findings, many other trials (summarized in[93]) have been designed to use less inflammation-inducing strategies and to start at an earlier stage of the disease. Notably, treatment with intravenous immunoglobulin (IVIg), which contains natural Aβ-autoantibodies from healthy donors, has been shown to improve cognitive function without major side effects[95-98]. In addition, it has been reported that healthy humans produce catalytic autoantibodies that specifically hydrolyze Aβ and do not induce inflammatory reaction[99]. Thus, it is possible to develop a more effective IVIg formulation with catalytic autoantibodies to Aβ. Active research is ongoing in this aspect in preclinical animal models[100-101]. Adding the confidence on the therapeutic potential of Aβ autoantibodies, preliminary data from an early human clinical trial using

aducanumab (aka BIIB037), a natural antibody against Aβ oligomers and fibrils isolated from healthy humans, showed cognitive improvement in addition to the reduction of Aβ plague load in the brain[102]. Although preliminary, these results provide hope that natural human autoantibodies to Aβ could be an efficacious and safe therapeutic agent for AD.

Immunotherapies targeting tau, in particular phosphorylated tau, are being actively pursued[93-94]. It is postulated that anti-tau therapies may be more efficacious clinically than anti-Aβ therapies because tau pathology correlates better with cognitive impairment. Initial testing in animal models showed that active or passive tau immunization reduced tau pathology and improved cognitive function[103-104]. Further animal studies showed that anti-tau antibodies that blocked tau aggregation *in vitro* markedly reduced tau pathology and cognitive deficits *in vivo*[105], suggesting that immunotherapy specifically designed to block trans-cellular aggregate propagation of tau could be an effective therapy for AD. In addition, treatment with tau oligomer-specific monoclonal antibodies modulated both tau and amyloid pathology in a mouse model of AD[106], revealing an interesting reciprocal relationship between the two pathologies. Although some concerns have been brought up on tau immunization[107], numerous tau immunotherapy programs, including using human autoantibodies, are in clinical development[94]. Outcomes from these clinical programs are eagerly awaited with high expectations.

Concluding remarks

Autoantibodies are ubiquitous in the serum of humans. The level of autoantibodies depends on the age, gender, and disease status of the subjects. Some of the autoantibodies have been found to be specifically associated with AD, which may facilitate the establishment of blood-derived diagnostic/prognostic biomarkers for AD. In particular, the new "autoantibomic" techniques using protein or peptide/peptoid arrays show great promise for the diagnosis of AD. Some autoantibodies have been shown to contribute to the pathogenic process of AD, whereas others have been demonstrated to exert neuroprotective effects, providing a remarkable opportunity for developing effective autoantibody-based immunotherapies for AD. Thus, it appears that autoantibodies serve as a double-edged sword in AD (***Fig. 2***). Further studies are warranted to harness the unique and beneficial

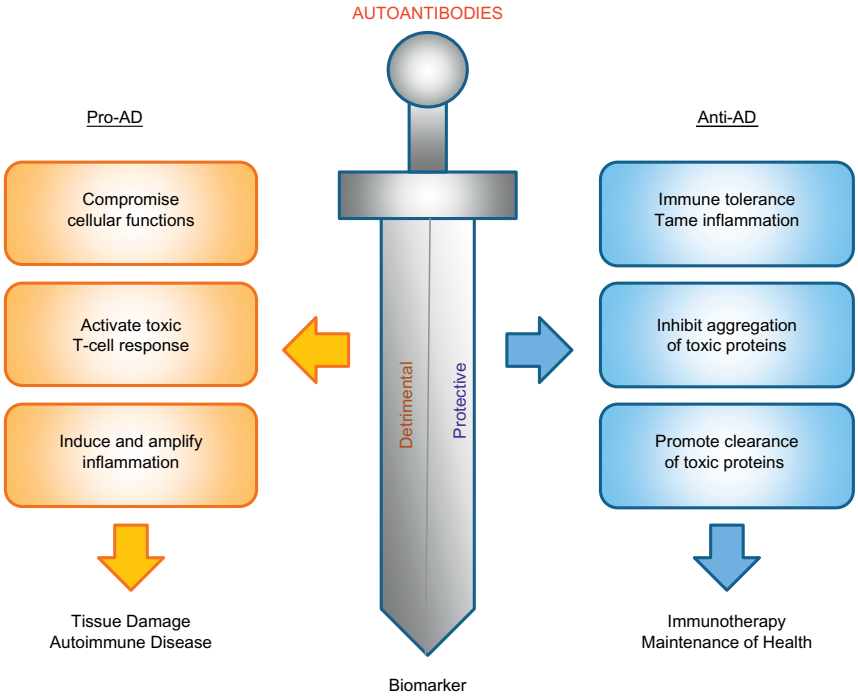

Fig. 2. **Potential roles of autoantibodies in Alzheimer's disease.** Like a double edged sword, autoantibodies could exert both detrimental and protective effects. Under pathological conditions, autoantibodies interfere with cellular function and trigger severe inflammatory response, causing brain tissue damage and autoimmune disease. Under physiological conditions, autoantibodies confer immune tolerance, attenuate inflammation, and facilitate the clearance of toxic proteins. These beneficial effects of autoantibodies have provided the basis for developing anti-Aβ and anti-tau immunotherapies. However, the exact roles of many autoantibodies are currently unknown. Some autoantibodies are specifically associated with the status of the disease and thus may serve as diagnostic/prognostic biomarkers for Alzheimer's disease.

power of autoantibodies for the diagnosis and the treatment of AD.

Acknowledgements

This work was supported in part by grants from the National Institute of Health (HL117652) (to JW) and the Academic Health Center (Faculty Research Development Program) of the University of Minnesota (to LL and JW).

Abbreviations

AD, Alzheimer's disease; APP, amyloid-β precursor protein; AT1R, angiotensin 2 type 1 receptor; Aβ, amyloid-β protein; BBB, blood-brain barrier; CAA, cerebral amyloid angiopathy; CSF, cerebrospinal fluid; DA, dopamine; ELISA, enzyme-linked immunosorbent assay; GFAP, glial fibrillary acidic protein; GM1; monosialotetrahexosylganglioside; 5-HT, hydroxytryptamine; Ig, immunoglobulin; IVIg, intravenous immunoglobulin; MCI, mild cognitive impairment; NMDAR, N-methyl-D-aspartate receptor; oxLDL, oxidized low-density lipoproteins; PL, anti-phospholipids; RAGE, receptors for advanced glycosylation end products; R-RAAs, redox reactive autoantibodies.

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