Immunotherapy for Alzheimer’s disease

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Alzheimer’s disease (AD) is characterized by β-amyloid (Aβ) plaques consisted primarily of aggregated Aβ proteins and neurofibrillary tangles formed by hyperphosphorylated tau protein. Both Aβ and hyperphosphorylated tau are toxic both in vivo and in vitro. Immunotherapy targeting Aβ seems to provide a promising approach to reduce the toxic species in the brain. However, there is little evidence from clinical trials so far indicating the efficacy of Aβ immunotherapy in cognitive improvement. Immunization with tau peptides or anti-tau antibodies could remove the tau aggregates and improve the cognitive function in preclinical study, which provides a novel strategy of AD therapy. In this article, we will summarize the immunotherapeutic strategies targeting either Aβ or tau.

Keywords Alzheimer’s disease; immunotherapy; vaccine; β-amyloid; tau

Introduction

Alzheimer’s disease (AD) is the most prevalent type of dementia that affects more than 15 million people worldwide in 2010 (Alzheimer’s Association Report). Typical symptoms of AD patients are progressive memory loss, cognitive decline, and loss of functional abilities. AD is characterized by two pathological markers, β-amyloid (Aβ) plaques consisted primarily of aggregated Aβ proteins and neurofibrillary tangles (NFTs) formed by hyperphosphorylated tau protein. Aβ induces neurotoxicity through induction of apoptosis and inflammation, disruption of calcium homeostasis, oxidative stress, and activation of complement [1]. Recent reports indicated that oligomeric Aβ is more toxic compared with other forms, which reduces spine density and suppresses long-term potentiation [2]. Tau plays essential roles in Aβ-induced toxicity. Neurons from tau−/− mice were found to be resistant to Aβ-induced neurite degeneration compared with neurons from wild-type mice or mice expressing human tau [3]. Consistently, reduction of tau levels in AD model mice resulted in significant improvements in performance in spatial learning, and reduced premature mortality, hypoactivity, and excitotoxicity [4]. In addition, tau is involved in mitochondrial dysfunction in AD [5]. Therefore, prevention or reduction of production of toxic Aβ and tau species is supposed to be the primary strategy in therapy of AD.

Aβ is the product from the cleavage of amyloid precursor protein (APP). APP is cleaved by β-secretase and γ-secretase sequentially to generate Aβ. Inhibition of β/γ-secretase is thus a strategy to block generation of Aβ. The β-secretase or γ-secretase inhibitors have been pursued many years. However, a major obstacle of development of γ-secretase inhibitors is their toxicity. The toxicity of γ-secretase inhibitors comes from the fact that they usually inhibit other substrates in addition to suppressing the cleavage of APP. γ-Secretase has many substrates such as notch and β-catenin in addition to APP and is involved in multiple cell biology such as differentiation of neural precursor cells, neuroplasticity, calcium regulation, protein trafficking, and apoptosis [6–10]. Because the active site of BACE1 is broader and more open than many other aspartyl proteases, inhibitors aimed at the active site are relatively bulky compounds [11]. This feature limits many active-site inhibitors for consideration as AD therapeutics because the blood–brain barrier permeability of high molecular weight compounds is limited [12]. Thus, immunotherapy targeting the toxic Aβ and tau offers another opportunity for therapy of AD. In this article, we will review the immunotherapeutic approaches targeting Aβ or tau.

Mechanisms of Aβ Immunotherapy

The principle of immunotherapy in AD is to reduce the toxic Aβ plaques in the brain. Three mechanisms of immunotherapy in AD have been proposed: (i) activation of...
microglia; (ii) inhibition of aggregation of Aβ; and (iii) peripheral sink hypothesis that promotion of efflux of Aβ out of the brain is through disrupting Aβ equilibrium between the central nervous system (CNS) and plasma [13]. In this section, the three mechanisms will be discussed in detail.

Activation of microglia-mediated clearance of Aβ
Microglia and astrocytes are the glial cells which play important roles in both the pathogenesis and immunotherapy of AD. The number of microglia and astrocytes is increased in the brains of AD patients. Both microglia and astrocytes are activated in response to Aβ. Activated microglia and astrocytes are found surrounded to amyloid plaques and to contain Aβ fragments [14]. Blocking activation of microglia and astrocytes has abolished their functions in the clearance of Aβ [15]. The recruitment of astrocytes to amyloid plaques is prompted by the chemokines chemokine (C–C motif) ligand 2 (CCL2) and CCL3, which are released by activated microglia [16]. Therefore, microglia plays a central role in the clearance of Aβ by glial cells. Activated microglia clears Aβ in different ways through expression of various molecules. For example, activated microglia promotes phagocytosis of fibrillar and oligomeric Aβ through expression of scavenger receptors (SRs) such as CD36, CD47, CD93, integrin-αβ, the class A macrophage SR, and SR class B type I. Activated microglia triggers phagocytosis of soluble Aβ via expression of heparan sulfate proteoglycans, insulin receptor, and serpin–enzyme complex receptor. Activated microglia degrades Aβ through the release of metalloproteinases and insulin-degrading enzyme [17]. Moreover, an Aβ-independent mechanism seems to be involved in the clearance of Aβ by activated microglia. Lipopolysaccharide (LPS) could induce the innate immune responses and therefore activate microglia. Enhanced clearance of Aβ has been seen in older APP transgenic mice injected with LPS intrahippocampally or intracranially [18–20]. The autopsy analysis of the brain from an AD patient who died from ischemia suggested that in the ischemic cortex, there is less amyloid plaque where microglia has been activated [21].

To be noted is that both LPS- and Aβ-activated microglia causes neuronal cell death in hippocampus [22]. When the activated glial cells fail to clear amyloid load in the brain, the inflammatory responses they induced would cause neurotoxicity, neurodegeneration, and neuronal death in the end [23]. Therefore, activation of glial cells plays a dual function in AD, and they act like a ‘double-edge’ sword.

On the basis of the essential roles of microglia in clearance of Aβ, one of mechanisms of immunotherapy is to promote the clearance of Aβ through activation of microglia. Anti-Aβ antibodies were adhered to cells which resemble activated microglia and monocytes after immunization with Aβ [23]. The in vitro experiments showed that most of the amyloid plaques were contained in phagocytic vesicles in the exogenous microglia in the presence of anti-Aβ antibody. It was also found that the phagocytosis of Aβ deposits was mediated by the fragment crystallizable (Fc) of the antibody [24]. These findings indicated that Fc receptor-mediated phagocytosis by microglia seems to be one of the mechanisms of clearance of Aβ by immunization. Consistently, there is less clearance of Aβ following injection of Aβ-specific antibody in animals where the function of microglia has been impaired [25]. However, it has been reported that antibodies without Fc have similar efficacy in the clearance of Aβ [26]. Wilcock et al. [27] have suggested that microglial activation-induced clearance of Aβ happens on the later phase. While in the early phase after application of Aβ antibodies, which primarily clear diffuse Aβ deposits, a mechanism independent on the activation of microglia has been involved.

Dissolution of Aβ aggregates and neutralization of Aβ oligomers
Another possible mechanism is that Aβ antibodies act as chaperones, leading to dissolution of amyloid fibrils through a direct effect on Aβ. The efficacy of a given Aβ antibody depends on the Aβ sequence element it binds to. It has been reported that the antibody recognizing the Aβ N-terminus is more effective than the one binding to the central residues of Aβ [28]. In addition, Aβ antibody could neutralize the synaptic toxicity caused by Aβ oligomers [29].

Peripheral sink hypothesis
The above two mechanisms require antibodies to enter the brain. Another mechanism indicates that antibody can result in the net efflux of soluble Aβ into the plasma from the brain. Acute administration of Aβ antibody caused a recovery of memory deficits without reducing the Aβ plaques in the brain, while the antibody–Aβ complex increased in the plasma [30].

It is important to note that these mechanisms are not mutually exclusive. Different antibodies may act through different mechanisms to different degrees. For example, antibodies which could not enter the brain may function as a peripheral sink. While antibodies binding to fibrillar Aβ may activate phagocytosis of glial cells or cause dissolution of amyloid fibrils, the isotype, epitope of the antibodies, and amyloid burden in the brain may influence the primary means of clearance or sequestration [13].

Types of Aβ Immunization
On the basis of the strategy of immunization, the immunization targeting Aβ includes active immunization and
passive immunization. Active immunization is the immunotherapeutic approach introducing an exogenous substance to stimulate the immune system to mount a response. The recipient is exposed to the antigen and generates the immune response which may take days/weeks or even longer time to develop, while the recipient always lasts for a long time or even lifelong. The active Aβ immunization is to immunize the individuals with synthetic Aβ peptide in adjuvant which is used to induce and boost the immunization. Passive immunization is the immunotherapeutic approach introducing exogenous antibodies directly into an animal or person to produce a benefit similar to that of active vaccination. In contrast to active immunity, passive immunity can occur immediately but only lasts for a short time, several weeks to 3–4 months at most. However, passive immunotherapy produces almost no Th1 cell response which has been extensively concerned in active immunization of Aβ [31]. In this section, we will discuss the active and passive immunization and some cases in clinical trials.

Aβ active immunization

**Preclinical studies of active immunization.** In 1999, Schenk et al. [32] first tried to immunize PDAPP mice with Aβ1–42 peptide. They found that prophylactic and therapeutic immunization reduced the density of amyloid plaques and the subsequent neuropathological changes such as neuritic dystrophy and astrogliosis. This was subsequently replicated in a variety of APP transgenic mice by different research groups [33–35]. On the basis of the promising results in transgenic mice, the clinical trial of AN1792 was carried out. However, this clinical trial was halted at phase IIa because a fraction of the immunized patients got meningoencephalitis. A T-helper (Th)1 cell epitope was found in Aβ1–42 peptide, which was responsible for meningoencephalitis induced by immunization with AN1792. Therefore, scientists began to search an ideal Aβ vaccine which could stimulate a Th2 immune response to generate robust anti-Aβ antibodies while avoiding a Th1 immune response. Amino acids 25 to 35 of Aβ mediated the toxic effects [36]. So these amino acids were always abscessed in later design of Aβ vaccines. Immunization with Aβ1–15 induced high titers of anti-Aβ antibodies [37,38]. Aβ deposition was reduced by a vaccine consisting of two copies of Aβ1–11 without causing an inflammatory response [39]. Frenkel et al. [35,40] first used only four amino acids: glu-phe-arg-his (EFRH) located at position 3–6 of Aβ via filamentous phage display on guinea-pigs and APP [V717I] transgenic mice. The EFRH phage evoked antibody responses which could prevent Aβ formation and aggregation. AffiRis has developed AFFITOPE vaccines composed of short peptides mimicking parts of the N-terminus of Aβ, which show no sequence identity with other human proteins. Immunization with AFFITOPE vaccines induces specific Aβ antibodies and exhibits beneficial function in preclinical study [41].

**Clinical trials of Aβ active immunotherapy.** AN1792, the first clinical trial of Aβ vaccine, was initiated in 2000 by Elan Inc. and Wyeth Inc. Small amount of AN1792 (human Aβ1–42) was injected with QS-21 adjuvant into 24 patients in the first stage. Seventy patients were injected with AN1792 + QS-21 plus polysorbate-80 preservative in the second stage. The results from two stages of phase I trial indicated that AN1792 had good safety and tolerability. Therefore, a phase IIa clinical trial began in September 2001. A total of 372 patients were enrolled. However, the trial was halted in January 2002, because 6% of the patients who have taken the vaccine developed aseptic meningoencephalitis. The later-on data analysis showed that the affected patients had different symptoms, duration, and severity of the meningoencephalitis. It seemed that the meningoencephalitis happened in the patients was not correlated with the times of injection of vaccine. Postmortem examination of the brain of one patient who developed meningoencephalitis after injection of AN1792 showed that cerebral white matter was extensively infiltrated by macrophages and T-lymphocytes, which could induce Th1-mediated cellular immune response. Activated Th1 cells produce pro-inflammatory cytokines such as interferon-γ and tumor necrosis factor-α and cause the inflammatory response [42–44]. Full-length Aβ1–42 contains epitopes that can induce Th1 immune response, which was later on thought as the biggest contributor to meningoencephalitis induced by vaccination of AN1792. In addition, polysorbate 80, a soluble agent widely used in many commercial products, was also considered as one of the possible factors causing meningoencephalitis [45,46]. Recent reports have found that polysorbate 80 can cause severe nonimmunologic anaphylactoid reactions [47,48].

CAD106 is an immunotherapeutic vaccine consisting of the Aβ1–6 peptide and the QB virus-like particle. Preclinical studies have showed that CAD106 induced anti-Aβ antibodies and reduced amyloid accumulation without stimulating T cells and causing microhaemorrhages (CAD106; http://www.clinicaltrials.gov/). In phase I clinical trial conducted by Novortis Inc., 58 mild-to-moderate AD patients were allocated into two cohorts based on the dosage of immunized CAD106. In cohort one, 24 of 31 patients were immunized with 50 μg CAD106. In cohort two, 22 of 27 patients were given 100 μg CAD106. The patients in both cohorts received three subcutaneous injections. CAD106 induced a substantial anti-Aβ IgG/IgM response without eliciting Aβ-specific T-cell response. However, 56 of 58 patients were reported to get mild adverse events, such as nasopharyngitis, fatigue and headache in cohort one CAD106-treated patients and injection...
site erythema, chills, fatigue, injection site pain, fever, and headache in cohort two CAD106-treated patients. Nine vaccinated patients experienced serious adverse effects such as trauma, aorta stenosis, fainting, and chest pain. Nevertheless, there was no proof that these adverse effects were relevant to the vaccine. The total plasma A\textbeta concentration increased and free A\textbeta in plasma decreased in parallel, indicating binding of the antibodies to A\textbeta in vivo. However, no statistically significant differences in cerebrospinal fluid (CSF) biomarkers have been observed between CAD106-treated and placebo-treated patients, which may be due to the limited sample size and short exposure to antibodies (\sim 100 days) [49]. Long-term studies with larger study populations are needed to further confirm the safety and efficacy of CAD106 in AD (NCT01097096 and NCT01023685).

AFFITOPE vaccines (AFFITOPE AD01 and AD02) are composed of 6-amino acid peptides mimicking parts of the native A\textbeta42. They are foreign to the human immune system and therefore easier to elicit an immune response. AFFITOPE vaccines are highly specific. They only target the N-terminus of A\textbeta in a way that the peptide sequence is only recognized if its N-terminus is free, thus preventing the cross-reactivity with APP. Both AFFITOPE AD01 and AD02 vaccines exhibited beneficial effects when administered to APP transgenic mice including reduced cerebral A\textbeta load, improved AD-like neuropathology and cognitive function. Both vaccines showed a favorable safety profile in Phase I clinical trial [41]. The Phase II trial is currently recruiting participants (NCT01117818).

Other vaccines which contained the B-epitope of A\textbeta were developed and under clinical trials such as ACC-001 developed by Elan Corporation Inc. (NCT00955409, NCT01238991, and NCT00960531) and V-950 developed by Merck Inc. (NCT00464334).

DNA vaccine is a novel vaccine which could induce both cellular and humoral immune response. Compared with other vaccines, DNA vaccines have several advantages. They are easier to design and to make large-scale production. They are more stable than other vaccines that require cold storage. DNA vaccines also seem to have a good safety. There are nearly one hundred types of DNA vaccines on clinical trial. None of them has been reported to show any side effects so far [50].

DNA vaccine has been used in immunotherapy of AD based on the principle to elicit Th2-mediated immune response but avoid Th1-mediated immune response. Qu et al. generated a plasmid encoding the A\textbeta1–42 gene with the control of synthetic promoter SP72. Gene gun immunization of either BALBc/wild-type or APPswe/PSEN1 transgenic mice effectively elicited humoral immune responses without significant T-cell-mediated immune responses to the A\textbeta peptide [51]. A similar DNA vaccine was designed, which contained two plasmids, an activator plasmid encoding the yeast GAL4 transcription factor and a responder plasmid encoding three repeats of open reading frame for A\textbeta1–42, for which expression is driven by binding of GAL4 to UAS (upstream activating sequences) [52]. Immunization of wild-type mice with this vaccine elicits a Th2-type immune response and no cellular immune response has been observed.

DNA vaccine can be modified to express a fused protein that would induce a Th2 immune response. Movsesyan N. et al. developed a pMDDC-3A\textbeta1–11-PADRE vaccine that had three copies of the self-B cell epitope of A\textbeta1–42 (A\textbeta1–11) and a non-self T-helper cell epitope (PADRE). Immunization of the 3 \times Tg-AD mice induced a Th2 immune response and reduced the A\textbeta accumulation. The pMDDC-3A\textbeta1–11-PADRE vaccine reduced the glial activation without increasing the risk of microhemorrhages [39]. Apoptosis can stimulate humoral and Th2-biased cellular immune responses. A DNA vaccine-encoding A\textbeta in conjunction with an attenuated caspase was immunized in TgCRND8 transgenic mice. The DNA vaccine reduced A\textbeta load significantly though it generated lower titers of A\textbeta antibodies [53]. These studies showed that DNA vaccine seems to be a good approach in immunotherapy of AD as it induces generation of A\textbeta antibodies without causing Th1-mediated immune responses seen in vaccination with A\textbeta peptides. The major problem of DNA vaccines is that they have showed low immunogenicity when tested alone in human clinical trial. A significant effort has been made to develop methods of enhancing the immune response to plasmid DNA and to enable its general use as a method of immunization in humans, such as by modifying immunization routes, adjuvant, and construction of DNA plasmids [50]. However, the clinical trial of DNA vaccine in therapy of neurological diseases is restricted in multiple sclerosis. No clinical trial of DNA vaccine in AD therapy has been conducted yet.

A\textbeta passive immunization

Preclinical studies of passive immunization. M266, a monoclonal antibody binding to the central domain of A\textbeta, reduced A\textbeta deposits in the brain and reversed memory deficits in object recognition and hole board learning of PDAPP mice when administrated peripherally [30,54,55]. However, m266 did not bind to A\textbeta deposits in the brain. The reduction of A\textbeta deposits in the brain was correlated with the magnitude increase of plasma A\textbeta, indicating that administration of m266 changed A\textbeta equilibrium between the CNS and the plasma. Some A\textbeta antibodies were shown to bind to A\textbeta deposits and reduce the plaques via activation of microglia. However, passive immunization of A\textbeta antibodies was also showed to cause microhaemorrhage [56,57]. A modified antibody with minimized interaction with Fc-\gamma receptors and complement protein has been
shown to reduce microhemorrhage, though with a moderate efficacy, in the reduction of Aβ deposits [58].

Clinical trials of Aβ passive immunization. Bapineuzumab is a humanized anti-Aβ monoclonal antibody against Aβ1–5. Phase II studies showed that immunization of bapineuzumab significantly reduced cerebral Aβ levels, CSF hyperphosphorylated-tau, and total tau levels compared with placebo-treated patients [59–61]. However, the patients with administration of bapineuzumab did not show significant cognitive, functional, or clinical benefit. A post hoc analysis on APOEε4 carriers and non-carriers suggested that the benefits of bapineuzumab may be limited to non-carriers alone. High-dose of bapineuzumab showed adverse effects. About 10% bapineuzumab-treated patients developed vasogenic cerebral edema. Half of these patients developed transient clinical symptoms, including headache, confusion, vomiting, and gait disturbance. These patients recovered both clinically and radiographically after lowering the dosage [60]. Several large phase III trials to check the cognitive efficacy and long-term safety and tolerability of bapineuzumab in AD patients are underway (NCT00667810, NCT00996918, and NCT00998764).

Solanezumab is a humanized version of the mouse antibody 266 against Aβ13–28. In contrast to bapineuzumab that binds to amyloid plaque more strongly, solanezumab selectively binds to soluble Aβ with little to no affinity for the fibrillar form. The data from the phase II clinical trial indicated that CSF and plasma levels of Aβ1–42 were increased by solanezumab in a dose-dependent manner, whereas the plaque burden in the brain showed no significant change in posterior cingulate binding with treatment from 4′-dimethylamino-phenyl)-6-iodo-imidazo-[1,2-a]pyridine (IMPY)-single photon emission computed tomography imaging. The plasma Aβ1–42 was associated with the magnitude of IMPY. These results indicated that similar to m266, solanezumab promoted clearance of Aβ via a peripheral sink mechanism. There is no cognitive improvement observed with administration of solanezumab in phase II clinical trial. In a phase II study enrolling 52 patients, there is no evidence of meningoencephalitis, microhemorrhage, or vasogenic edema [62,63]. In another phase II study including 33 Asian patients, a fraction of patients has been reported to get mild or moderate adverse effects. One patient got pain in extremity, though it was unrelated to solanezumab. In contrast to bapineuzumab, there is no evidence to date that APOEε4 genotype alters the efficacy or side effect profile of solanezumab [62]. Solanezumab has been recently progressed to phase III clinical testing (NCT01127633).

IvIg is a pooled mixture of natural human immunoglobulins obtained from the blood of thousands of healthy donors that has been proved for more than decades by the United States Food and Drug Administration for the treatment of immune deficiency disorders and other indications but not AD. IvIg contains Aβ antibodies (those recognizing Aβ oligomers and fibrils, among others). IvIg has been shown to interfere with the oligomerization and fibrilization of Aβ, to protect neurons from Aβ-mediated toxicity and to promote Aβ clearance from the brain [64]. In a pilot study of intravenous injection of five patients with IvIg for 6 months, total CSF Aβ levels significantly decreased, the plasma Aβ levels increased, whereas cognitive function improved in the AD patients [65]. However, in another 18-month clinical study in which IvIg was applied to AD patients for 6 months, discontinued, and then resumed for another 9 months, CSF Aβ decreased significantly at 6 months, returned to baseline after washout and decreased again after IvIg was readministered for an additional 9 months. Plasma Aβ levels increased transiently after each infusion. Mini-mental state scores increased by an average of 2.5 points after 6 months, returned to baseline during washout and remained stable during subsequent IvIg treatment. IvIg infusions were well tolerated and no serious adverse events occurred during the 18 months of study [66].

Several other Aβ antibodies are under clinical trials. PF-04360365 (Ponezumab), targeting Aβ33-40, is under phase II clinical trial (NCT00722046 and NCT00945672). MABT-5102A, which binds to Aβ monomers, oligomers and fibrils with equal affinity, and GSK-933776, R-1450 (gantenerumab) are currently recruiting participants for phase II trial (NCT01342926, NCT01224106, NCT01343966, NCT01397578).

Tau Immunotherapy

The NFTs, formed by aggregation and accumulation of the microtubule-associated protein (tau), are pathological hallmark of AD. Increased levels of tau oligomers have been detected in the very early stage of AD, when NFTs and individual manifest clinical symptoms of AD have not been observed [67]. Like Aβ, soluble tau aggregates are the most toxic and pathologically significant tau species. Tau oligomers induced cell death, synaptic and mitochondrial dysfunction and memory impairment [68,69]. Therefore, clearance of oligomeric tau is another strategy in AD therapy. However, this seems difficult because soluble tau aggregates locate inside neurons. Nevertheless, two reports on tau immunotherapy indicated targeting tau with either a vaccine or antibodies could remove intracellular tau [70,71]. Novak [70] immunized transgenic rats with recombinant misfolded truncated tau before neurobehavioral alterations. The immunization reduced the levels of both the phosphorylated and non-phosphorylated soluble misfolded tau proteins, and delayed the onset of severe sensorimotor deficits in transgenic rats, without obvious harmful side effects. Asuni et al. [71] immunized P301L...
tangle model mice with an adjuvant peptide corresponding to residues 379–408 of tau, with phosphorylation of Ser396 and Ser404, two phosphorine residues commonly associated with NFTs (Tau379–408[P-Ser396,404] in short). Specific tau antibodies have been induced. They passed the blood–brain barrier, bound to pathological tau, reduced tau aggregation, and delayed progression of the tangle-related behavioral phenotype. The immunotherapy was more effective in the early stages of functional impairments. This may indicate that the immunization becomes less efficient when the rate of tau aggregation increases. In htau/presenilin 1 transgenic mice, which express human non-mutant tau and PS1 M146L mutation on tau knockout background, immunization with Tau379–408[P-Ser396,404] peptide reduced pathological tau in the brain and prevented cognitive decline [72]. Immunization of the wild-type mice with full-length recombinant tau protein, however, induced the occurrence of NFT-like structures, axonal damage, gliosis, and neurological deficits such as a limp tail and limb paralysis. Mononuclear infiltrates without demyeliation was also observed in the immunized rat brain. These results raised a potential risk in tau immunotherapy [73]. Although immunization with the phosphorylated truncated tau did not show serious adverse effects in the animal studies, it has significant potential risks as these phosphorylation sites are mainly associated with matured meta-stable tangles. An optimal vaccine should target early stages of tangles (pre-filament tau species) rather than just targeting matured meta-stable tangles. Prefilament-specific phosphorylation sites have yet to be conclusively identified [74]. Paired helical filament (PHF) 1 is a monoclonal antibody targeting phosphoserine in positions 396 and 404 of the tau. Immunization of JNPL3 model mice with this antibody reduced the tau aggregation and improved the functional impairments. However, this passive immunization seems to be less effective than active immunization. The higher injection frequency of active immunization is a possible reason. Otherwise, the polyclonal response to the tau immunogen results in generation of antibodies that target a larger portion of the tau molecule than PHF1 [75]. The mechanisms underlying tau immunotherapy remain elusive. It has been postulated that tau antibodies possibly function without entering the neurons. They could change the equilibrium between the intra- and extra-cellular aggregates, which has been demonstrated for Aβ [74]. Another possibility is that tau antibodies prevent and clear tau aggregates intracellularly, which has been supported by the recent finding that tau antibodies can be internalized, most likely by endocytosis [76].

Perspectives

As discussed previously, the reason for failure of AN1792 was that the full-length Aβ peptide contains the epitopes which caused Th1-immune response. This caused the development of active Aβ vaccines which contain the B-cell epitopes. The results from several clinical trials have shown no serious adverse effects so far. However, the barriers of development of active Aβ vaccines is the hypoactivity of immune systems in the elderly patients. Developments of new adjuvants that specifically boost Th2 response are helpful. The passive immunization with monoclonal Aβ antibodies has received a lot of attention. Some of them showed promising results in terms of reduction of pathological markers. However, none of them have provided sufficient evidence in improvement of cognition. Large scale of phase III clinical trial designed for evaluating the efficacy of Aβ immunotherapy in cognition will give us the final answer.

Vaccination with tau peptides or tau antibodies in preclinical studies represents a novel strategy in immunotherapy of AD. However, the potential risks of tau immunotherapy need further validation. Moreover, the synergic roles of Aβ and tau in the pathogenesis of AD remain elusive. Some studies indicated that abnormality of tau appears earlier than Aβ. Aβ and tau contribute to the pathogenesis of AD through different and independent mechanisms. Whether targeting Aβ or tau alone is efficient enough in therapy of AD remains unknown. A combinational immunotherapy of Aβ and tau may need to be addressed.

The basis of immunotherapy is to reduce the toxic Aβ species and phosphorylated tau. However, once the amyloid plaques form, they are very hard to disrupt. Some Aβ antibodies could solubilize amyloid plaques, while it may generate more toxic oligomeric species. The oligomerization of Aβ and the phosphorylation of tau appear at very early stage of AD, even before the appearance of the clinical symptoms. Immunization at the early stage is more effective for the therapy of AD. However, there is still a lack of biomarkers of early diagnosis of AD. Development of specific markers for diagnosis of AD and evaluation of therapeutic efficacy of immunotherapy are a major hurdle to be addressed.

Immunotherapy is an approach of therapy of AD. The final results of some clinical trails will come out in 2 or 3 years. Development of small compounds targeting Aβ and tau is another opportunity of AD therapy. The pathology of AD is the disruption of synaptic plasticity and neuronal loss. Prevention of disruption of synaptic plasticity and neuronal loss, in addition to targeting Aβ and tau is another strategy.

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