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Anti-A β Antibodies in the Fighting with Alzheimer's Disease

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Abstract

Alzheimer disease (AD) is the most common form of dementia. Amyloid-β plaques have become main therapeutic targets on the basis of growing evidences. Despite hundred studies are designed in animals and humans, the success in this therapeutic approach is still a disappointment. In the present study, the affect mechanism of anti-Aβ antibodies, the type of antibodies and immunization, why despite numerous studies and the huge budget allocated for the researches of AD, the treatment success is limited also what is the last developments in the immunotherapeutic, are reviewed. The necessity of the early treatment of AD is stronger than ever. Therefore, the new studies which target to develop the new conformation specific antibodies and the new techniques that facilitate the crossing of these new conformation specific antibodies to central nervous system (CNS) through blood brain barrier (BBB) should be designed.

Keywords: Alzheimer disease; Antibodies; Pathogenesis; Immunization

Introduction

AD affect more than 5.4 million people in US currently [1], with about 11-16 million people expected to develop it by 2050 [2]. AD is 6th leading cause of death and the only reason of death among the top 10 that cannot be cured, prevented or even slowed in US [3]. Based on mortality data from 2000-2008, death rates have declined for most major diseases while deaths from AD have risen 66% during the same period. AD is significant economic burden for a country, the expenses of this disease not only include the cost of treatment, but also the lost productivity of patients and their caregivers, whom looking after chronically disabled family members. The costs of this disease for the USA estimated to be about $214 billion in 2014. If present trends continue, this cost will project to grow to $1.1 trillion per year by 2050- an overwhelming economic burden. Alzheimer's is a multifactorial neurodegenerative disease and is mainly characterized by amyloid beta (Aβ) deposition and neurofibrillary tangles. Hence, desired treatment is to prevent the accumulations of Aβ and neurofibrillary tangles in neurons. However, because Alzheimer's symptoms including memory, language and intellectual impairments appear after hippocampal Aβ deposition, when the patients are brought to the clinic it becomes too late for the treatment.

The conducted therapeutic studies in animals and humans have mainly focused on the clearance of Aβ burden in the brain to date. After years of disappointment, clinical-trial results released in Alzheimer's Association International Conference in Washington DC on 22 July 2015 showed small improvements in people with AD. But many researchers question whether these findings will hold up because every previous study investigated the efficacy of antibodies against Aβ senile plaques in brain has failed [4]. Many of novel therapeutic strategies targets the eradication of "amyloid cascade" [5,6] are based on the modulation of immune system. Animal studies in mouse models have shown great success of immunotherapy against Aβ senile plaques, however, the efficacious therapy with antibody for humans still remains as a challenge [7,8].

The Pathogenesis of Alzheimer's Disease

The pathologic signature of AD is the deposition of Aβ and tau. There are several hypothesis postulated for AD; Aβ [9], Tau [9] and Cholinergic [10]. The most favored one among them is Aβ cascade hypothesis [11]. The central idea in this hypothesis is that Aβ aggregation triggers the cytotoxic cascade that in turn leads to the tau accumulation. There is no suspect that Aβ hypothesis was strongly supported by numerous studies performed by advanced technologies, and the many of the current therapeutic studies designed are based on this hypothesis. However, when we look at the other face of the coin, this hypothesis may not be sufficient in the explaining of many aspects of AD pathology including the cognitive symptoms and selective vulnerability of cholinergic neurons. Therefore, when the literature is reviewed, the therapeutic strategies against the cognitive symptoms in Aβ hypothesis had the limited success is stand out [12]. The therapeutic strategy in this hypothesis is anti-Aβ antibody drugs. The first antibody trial against Aβ designed by Solomon et al. in cell-culture-based assays [13]. This initial study motivated next *in vivo* studies. Preliminary animal study demonstrated that anti-Aβ antibody, 3D6 (raised to $A\beta_1$-5), reduced Aβ burden by 86% in PDAPP mice [14]. In the same way, subsequent studies used anti-Aβ antibody reported the significant reduction in Aβ burden in mouse models of AD. However, to date, the trials of anti-Aβ antibodies in humans have not become successful as in the animal studies [15-17]. This is probably due to the removal of physiologic Aβ which is not involved in synaptotoxicity by the antibodies. The soluble oligomeric Aβ aggregates mainly contain two peptides (Aβ40, Aβ42) are formed from amyloid precursor protein (APP) by sequential proteolytic cleavages through two proteases; β-secretase and γ-secretase [18-20]. It is recognized that when APP is cleaved by β-secretase, the formed β-sheet formation shows neurotoxicity [21-23]. β-secretase is also known as β-site cleaving enzyme (BACE-1) [24]. When APP is sliced by BACE-1, amyloidogenic pathway is triggered, and as reaction products, APPβ and C-terminal fragment of APP (CTFβ) are generated. CTFβ is precursor membrane protein of γ-secretase which forms the final shape of Aβs (e.g.37-, 38-, 42-, or 43-mer) [25,26]. Recent discoveries indicate that Aβ42 plays the most critical role in AD pathogenesis [27]. The normal activity of γ-secretase requires the normal function of Presenilin 1 (PS1) and Presenilin 2 (PS2) genes [28].

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On the other hand, APP is cleaved by α-secretase to produce C-terminal fragment (CTFα) and secreted APPα (sAPPα). This is non-amyloidogenic pathway, resulting in the production of smaller APP fragments. The expression of smaller APP fragments is observed in almost all human organs. Even the products of non-amyloidogenic pathway (neurotrophics) may acts as a growth factor for neurons [29]. In clinic trails, anti-Aβ antibodies for Aβ clearance has been intensively examined for years [30], however, limited symptomatic benefits have been obtained. When the low success was noted by scientists, anti-Aβ approach was requisitioned whether it is the best way in the fighting with AD or not. This requisitioning motivated to develop the conformation specific antibodies target only synaptotoxic Aβ oligomers.

Aβ Immunotherapy

The antibodies which include Aβ sequences activate microglia to phagocyte the amyloid plaques. The antibody activation procedure divided into two;

Active immunization

In 1999, Schenk et al. [31] firstly administrated synthetic Aβ42 to animals and observed a reduction in the plaque area. There was something attracts the attention of scientists in the most of animal trails that while cognitive symptoms were not recovered despite the reduction in the plaque area, the reduction in Aβ oligomer provide the recovery of cognitive impairments [32]. That indicated Aβ oligomers are more optimal targets in the symptomatic treatments of AD. Therefore, the development of highly sensitive oligomer-specific antibodies is indispensable.

There might be also unintended results of the antibodies. For example; in the clinic trail of Elan and Wyeth in 2001, aseptic meningoencephalitis was observed in 6% of the patients [33]. In addition to this, the follow up studies demonstrated that antibodies may not provide cognitive recovery [34]. This was likely due to the unintended removal of physiologic Aβ42; Soscia et al. [35] reported that Aβ42 may be found in the immune system as an antimicrobial protein, or due to strong response of T-helper lymphocytes are over activated by vaccine adjuvants (surface-active saponin adjuvant QS-21) [36].

Passive immunization

Active Aβ immunization cause strong and long lasting response with only a few injections. In contrast, passive Aβ immunization is mild effective even in elders whose pro-inflammatory reactions are normally stronger [37]. There are some advantages of passive immunization over active immunization; passive immunization can be halted at any time wanted in the case of adverse reactions and the antibodies can be only targeted to the agents of interest such as toxic Aβ peptides [36].

Despite the fact that the mechanisms of Aβ immunization are shed light in large and anti-Aβ antibodies hinder Aβ deposition in the mouse models, the success which is expected has could not get in clinic trails (some of the results of active and passive trails is shown in table 1). We indicated the possible reasons of this problem above that the treatment is too late to recover the neurons from neurodegeneration [38,39]. Therefore, it is needed to develop highly sensitive oligomer-specific antibodies for the purpose of early diagnosis. In recent years, studies focus on the development of new antibodies could be effective in humans. So far, over 600 antibodies against Aβ have been deposited in Alzforum (http://www.alzforum.org/), and most of these were dependent on the Aβ sequence.

Conformation Specific Antibodies to Aβ Plaques

Despite the fact that there are many conformation specific antibodies to Aβ, the successful study reported is minute amount even in animal; I shortly summarize a few here;

Anti-ADDLs antibodies

This antibody was generated by Lambert et al. [40] to hinder the production of ADDL. ADDL is derived from Aβ42 by the proteases. It blocks LTP by binding synaptic terminals. The therapeutic benefit has not been reported [40,41].

Grafted amyloid-motif antibody

Even if the "grafting" approach was introduced by Tessier et al. [42], the real architects of this idea were Moroncini et al. [43]. This idea is based on the development of sequence and conformation-specific antibody leads the degradation of Aβ plaques by microglia. Although Ladiwala et al. [44] demonstrated the efficiency of grafted amyloid-motif in reducing the accumulation of Aβ42, generally, this motif has not been preferred in the clinic trails because the grafted motif in this type of antibodies includes C-terminal region of Aβ fibril which react with fibrils as well as Aβ oligomer. That is because grafted amyloid-motif antibody makes nonpathogenic Aβ fragments (p3) a target for microglia.

αAPF and A11 antibodies

These antibodies generated by Kayed et al. [45]. A11 is an oligomer specific antibody that only recognizes Aβ oligomers (prion peptides, α-synuclein and polyglutaime). This was the first antibody which only targets the intermediates of Aβ aggregation. Then Kayed and colleagues produced αAPF as a second generation of A11.

Anti-globulomer antibody (A-887755)

A-887755 is the most promising antibody in animal studies but its efficiency has not been evaluated in clinic trails yet. A-887755 was discovered by Hillen et al. [46] against synthetic oligomer (globulomer) using a truncated peptide (Aβ20-42) [47]. A-887755 could discriminate among senile plaques, monomers, fibrils and oligomers were shown in immunoprecipitation studies. In addition, it was reported that A-887755 had rescued cognitive impairment in AD mice.

Conclusion

The results of old and novel anti-Aβ antibody studies indicate that immunotherapeutic approach is still a disappointment for AD. The growing evidence has started to persuade that targeting amyloid plaques may not be an appropriate treatment option in cases in which the plaques are already formed in brain.

The most important factor has delayed the acceptance of failure of the antibodies is the success of animal studies. Therefore, recent studies have focused to understand the reason of differences. Two hypotheses postulated to explain the reason of limited success in human. The restricted cross of antibodies to central nervous system through Blood Brain Barrier (BBB). BBB controls the passage of nutrients, hormones and drugs from the blood into the brain. The passage of the most of substances include monoclonal antibodies to brain is prevented by BBB. Recent studies showed that 0.1% of anti-Aβ antibodies can cross BBB [48]. The beginning of treatment is too late because the patients are brought to the clinic after the appearance of cognitive symptoms which indicate already amyloid deposition.

A few studies reported that Anti-Aβ antibodies for the treatment of

Anti- Aβ antibody trails			
Trail	**Stage**	**Status**	**Aβ target**
ACC-001	Phase II	Not reported, finishing	Aβ1-6-QS21
AN1792	Phase II	(2000-2002) halted, no improvement, encephalitis 6%	Aggregated Aβ1-42,QS21,Polysorbate80
CAD106	Phase I	Aβ titers, no change biomarkers	Aβ1-6/Bacteriophages QB
IVIG Gammagard	Phase III	No improvement, data not released	Naturally occurring anti- Aβ
IVIG Octopharma	Phase II	Safe, no improvement	Three different doses of naturally occurring anti- Aβ
Bapineuzomab AAB-001	Phase II	No clinic improvement	Humanized 3d6, anti- Aβ1-5, six infusions, different dosages
Solaneuzumab	Phase III	No improvement overall	Humanized mAb266 anti-Aβ16-24
Source: http://www.clinicaltrials.gov.			

Table 1: Active and passive antibody trails.

AD continues to show small promise, however, the necessity of the early treatment of AD is stronger than ever. The general consensus among the scientists that the treatment of individuals with AD ought to begin prior to onset of symptoms and the development of new strategies and methods to improve the cross of antibodies to brain is needed.

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