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Molecular Mechanism Underlying A β Immunotherapy: Implications for the Toxic Action of A β Oligomers

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Abstract

Aβ immunotherapy brought us not only hope for but also led to greater attention to the mechanism underlying the clearance of amyloid β (Aβ), which provided fascinating insights into disease-relevant molecules such as toxic Aβ oligomers (AβOs). Accumulated lines of evidence indicate that AβOs play a causative role in the pathogenesis of Alzheimer's disease (AD), leading to a synaptic failure, which is considered a major cellular mechanism underlying the cognitive deficits in patients with mild cognitive impairment and AD. In this mini review, we focus on recent knowledge of the possible mechanisms underlying the action of the anti-Aβ antibody to clarify the toxic action of AβOs.

Keywords: Amyloid β (Aβ); Alzheimer's disease; Aβ oligomer, Neurotoxicity; Therapeutic antibody

Introduction

Cerebral amyloid diseases are considered part of an emerging complex group of chronic and progressive neurodegenerative entities collectively known as disorders of protein folding, the so-called "conformational diseases". In these diseases, normal molecules or their genetic variants self-assemble to form oligomers and/or fibrils that deposit in the brain parenchyma and are associated with cognitive deficits or dementia. Among them, amyloid β (Aβ) is identified as the major constituent of such fibrils in Alzheimer's disease (AD) [1,2]. It has been widely accepted that Aβ fibrils are relatively insoluble and resistant to proteolysis, which result in their marked accumulations as amyloid plaques mainly owing to a weak antigenicity or immunogenicity [3]. The dogma that the Central Nervous System (CNS) is an immune-privileged region with minimal immune surveillance supports the above-mentioned issue. Thus, no therapeutic intervention for the removal of deposited Aβ fibrils remained unexplored despite of this quite important issue to be considered. In 1999, we witnessed a striking paradigm shift with respect to our understanding of the efficacy of Aβ immunotherapy for AD [4]. Thereafter, significant efforts have been focused on the molecular mechanism responsible for immune-mediated Aβ depletion in the brain, which provided fascinating insights into disease-relevant molecules such as toxic Aβ oligoers (AβOs) [5]. Several major hypotheses have been proposed including microglia-mediated phagocytosis, peripheral sink, neonatal Fc receptor (FcRn)-mediated Aβ transport across the Blood-Brain Barrier (BBB), catalytic modifications of Aβ fibrils, intracerebral sequestration of Aβ in a monomeric state, and antibody-mediated neutralization of Aβ toxicity. However, molecular mechanisms underlying either the formation or clearance of AβOs remain unclarified. In this review, we will focus on AβO immunotherapy, with specific emphasis on the action of the anti-AβO antibody to clarify the toxic action of AβOs.

Central degradation of AβOs via microglia-mediated phagocytosis

The importance of this mechanism was pointed out by Aβ vaccine [4], which clears deposited fibrillar Aβ via an *in vivo* immune-mediated system. Some circulating anti-Aβ antibodies cross the BBB and activate Fcγ receptor (FcRγ)-mediated clearance of amyloid fibrils by microglia [6,7]. The direct *in vivo* evidence of this system was obtained by autopsy of cases who received clinical Aβ immunization, which showed that senile plaques are actually removed via microglial phagocytosis [8,9]. Owing to intraneuronal accumulation of AβOs [10-14], it is unlikely that microglia-mediated phagocytosis accounts for antibody-mediated degradation of AβOs. In support of this idea, the microglial response to 72D9 immunotherapy targeting AβOs remains unchanged compared with control IgG treatment despite the marked reduction of Gallyas-Braak-positive senile plaques in 3x-Tg AD mice [14]. These findings suggest that microglial phagocytosis is not a central mechanism of reducing AβOs.

Peripheral sink

DeMattos et al. [15] reported that the interaction of the anti-Aβ antibody with plasma Aβ generates a concentration gradient across the BBB, which promotes the efflux of brain Aβ into blood in passive immunotherapy. The same group confirmed that the measurement of brain Aβ efflux appears to be a useful tool to estimate on-going brain amyloid burden at a risk of AD [16]. This 'peripheral sink' theory brought us the new therapeutic concept that CNS Aβ clearance could be controlled by the modification of peripheral Aβ clearance, which drives the equilibrium from the brain to blood Aβ. Takamura et al. [13] reported that AβO immunotherapy results in the significant attenuation of extracellular and intraneuronal accumulation of AβOs, indicating that a similar scenario may take place. However, the physiological reliability of this issue has remained uncertain so far. Further study to clarify this issue is required.

Neonatal Fc receptor (FcRn)-mediated Aβ transport across the BBB

The *in vivo* relevance of neonatal Fc receptor (FcRn)-mediated Aβ transport across BBB has been confirmed in APP transgenic mice [17]. Bard et al. [6] reported that endogenous immunoglobulins in the brain parenchyma of aged PDAPP or non-Tg represent ~0.1% of serum endogenous immunoglobulins. Several other groups have also shown

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that ~0.023% to 0.11% of a peripheral dose enters into the brain [18-20]. Thus, this mechanism may play an important role in the clearance of soluble AβOs by the antibody that crossed the BBB. Considering the positive outcome of our *in vivo* immunotherapies [14], it is also reasonable to speculate that soluble AβOs are metabolized into plasma possibly by antibody-assisted removal via the BBB [17], whereby the conversion to insoluble AβOs and further development of amyloid plaques are effectively blocked [14]. Further study to clarify this issue is definitely required.

Catalytic modifications of Aβ assembly

Solomon et al. [21] reported that the anti-Aβ antibody is capable of dissolving already formed amyloid fibrils, which results in the marked decrease in the neurotoxicity of Aβ. The same group also showed the similar catalytic activity of the antibody towards fibrillar Aβ assembly [22-24]. Furthermore, they also showed that anti-aggregating antibodies against the EFRH residues located at positions 3-6 of the N-terminal Aβ peptide prevent self-aggregation [25] or resolve preformed aggregates [26] *in vitro* and *in vivo* [27].

In humans, polyclonal IgM antibodies purified from human sera showed Aβ hydrolytic activity, which prevents the formation of AβOs and Aβ fibrils [28]. Aging-induced synthesis of the catalytic antibodies to Aβ is indicative of the protective role of the immune system that counters the pathology associated with Aβ accumulation in the brain [28].

Intracerebral sequestration of Aβ in monomeric state

Yamada et al. [29] reported that monoclonal m266 with a high affinity for soluble Aβ may sequester soluble monomeric Aβ in the brain thereby preventing the formation of multimeric Aβ and related neurotoxicity. This concept was firstly reported by Solomon et al. [22,23] who showed that a monoclonal anti-Aβ antibody prevent samyloid fibril formation. However, monomeric Aß has normal physiological functions in the brain such as neuroprotection and modulation of LTP [30,31]. Although this strategy of targeting monomeric Aβ is theoretically relevant, it may interfere with these physiological functions. Therefore, intracerebral sequestration of AβOs in a nontoxic state should be considered.

Antibody-mediated neutralization of AβOs toxicity

The possible mechanisms underlying the neurotoxic action of AβOs have been postulated to involve neurotoxic ligands [32-41]. Regarding the above-mentioned action, *in vitro* experiments demonstrated that conformation-dependent antibodies successfully immunoneutralized the toxicity of AβOs [14,42-47]. Presently, no evidence is available showing that antibody-AβO interactions induce conformational changes that are not toxic. Immunotherapy using antibodies targeting AβOs is also sufficient to normalize cognitive behavior [13,14,46-49] and synaptic deficits [47]. Our *in vivo* experiment using antibodies specific for AβOs demonstrated that the direct sequestration of AβOs not only protected Tg2576 mice from memory deficits and postsynaptic impairment [13], but also reversed memory loss in 3x-Tg AD mice [14]. One of the unifying features is that specific control of extracellular AβOs results in a marked attenuation of intraneuronal accumulation of AβOs [13,14]. It has been shown that some of the AβOs are internalized by neuronal cells via transferrin-receptor-mediated endocytosis, causing neuronal death [50]. From a dual-function viewpoint (neurotoxicity and endocytosis), Takamura et al. [14] identified sortilin as a key molecule that regulates AβO-dependent neurotoxicity. As shown in Figure 1, sortilin forms a death signaling receptor with $p75^{NTR}$ in response to AβOs, inducing $p75^{NTR}$-mediated apoptosis via Go, c-Jun N-terminal kinase (JNK), NADPH oxidase, and caspase-3-released caspases [51]. Recently, Sotthibundhu et al. have

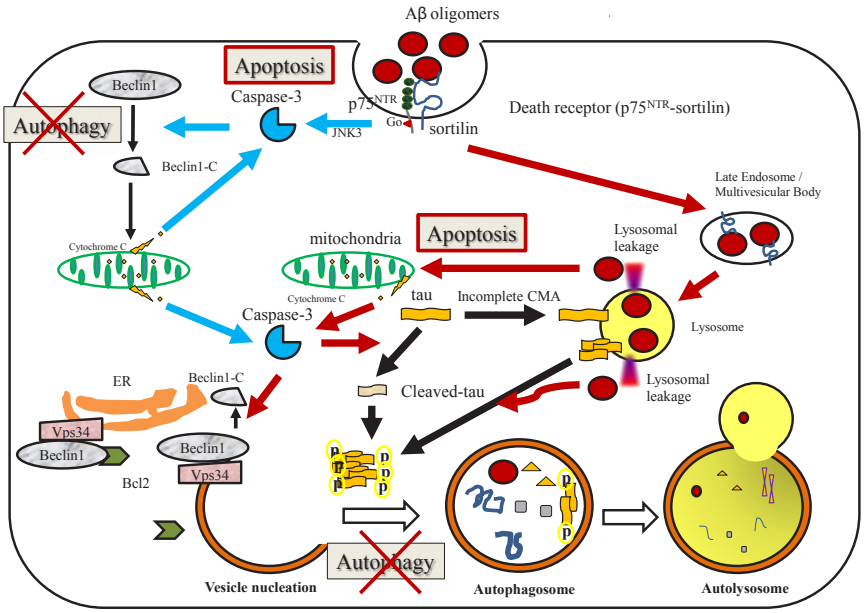

Figure 1: Schematic representation of molecular interconnections responsible for the toxic action of Aβ oligomers (AβOs).
In the presence of AβOs, $p75^{NTR}$-sortilin death receptors are formed on the neuronal membrane [14], inducing $p75^{NTR}$-mediated apoptosis via Go, c-Jun N-terminal kinase 3 (JNK3), caspase-3-released caspases [51].The activated caspase-3 cleaves Beclin1, which attenuates the autophagy, whereas the resulting Beclin1-C causes mitochondria-mediated apoptosis [53-58]. Sortilin induces endocytosis of AβOs [14] into lysosomes [65], resulting in lysosomal leakage [12] and the subsequent mitochondrial apoptosis [12]. In addition to the cleavage of Beclin1 [53-58], the resulting activated caspase-3 causes the cleavage of tau [61-63], followed by tau assembly [64,65] and phosphorylation [11,14,60]. Incomplete chaperone-mediated autophagy of tau [64] also induces the generation of amyloidogenic fragments that can self-assemble and phosphorylated by AβOs leaked from lysosomes.

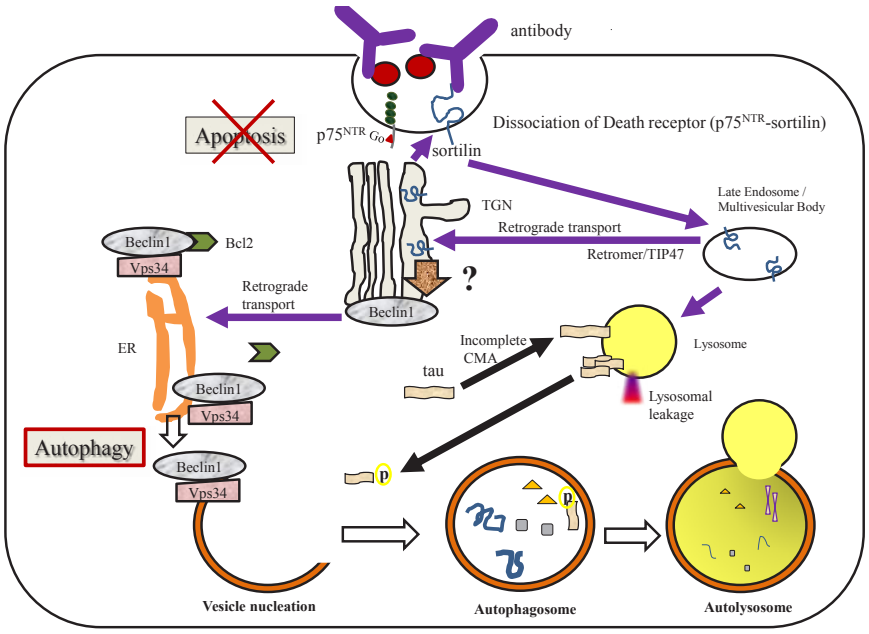

Figure 2: Schematic representation of molecular interconnections responsible for the therapeutic action of anti-AβO antibodies. Immunoneutralization of extracellular AβOs by an antibody interrupts the association between p75^{NTR} and sortilin, inhibiting p75^{NTR}-mediated apoptosis [14]. In contrast, sortilin not only maintains physiological levels of lysosomal sorting pathways [65], but also induces Beclin1 [14]. A hypothetical model shows that sortilin may govern the supply of Beclin1 via retrograde transport [67] from TGN to ER, which contributes to the physiological levels of autophagy. In the absence of p75^{NTR}-mediated apoptotic signalling and endocytosis-mediated AβOs, the formation of phosphorylated, truncated tau assemblies suppressed, and the assemblies can be disposed of via autolysosomes.

provided evidence of a direct link between p75^{NTR} signaling and Aβ1-42-induced toxicity in hippocampal neurons *in vitro* and in cholinergic basal forebrain neurons *in vivo* [52]. During such apoptotic processes, activated caspases also result in the production of C-terminal fragment of Beclin1 (Beklin1-C) [53,54]. Beclin1 cleavage inactivates the autophagic function of Beclin1, whereas Beklin1-C acquires apoptosis-inducing activity by translocating from the cytosol to the mitochondria, accelerating apoptosis probably via the enhancement of the release of cytochrome C [55-57]. Indeed, the caspase-induced cleavage of Beclin1 was observed in the AD brain [58]. In contrast, a new mouse model expressing only AβOs in neurons provides evidence of caspase-3 activation in the brain via lysosomal leakage and mitochondrial dysfunction [12]. Thus, the sortilin-mediated endocytosis of AβOs may induce lysosomal leakage, followed by mitochondrion-mediated apoptosis [12] and the attenuation of autophagy via the cleavage of Beclin1 [55-58]. Because Beclin1 has multiple binding partners, the composition of proteins in the Beclin1 complex determines its function [59]. Thus, the decreased availability of Beclin1 may result in the destabilization of the complex and impair the formation and/or maturation of autophagosomes [59], followed by the accumulation of intraneuronal AβOs [14]. Recently, the relevance of such a pathway has been proved in the AD brain [58]. Taken together, anti-AβO antibodies can prevent the interaction between extracellular AβOs and sortilin, and sortilin-p75^{NTR} death signaling receptor formation [14] (Figure 2).

Antibody-mediated neutralization of tau toxicity

Our *in vivo* experiment demonstrated that 72D9-immunized 3x-Tg AD mice with improved cognition showed lower levels of AT8-positive tau and fewer NFT-bearing neurons than control IgG2b-treated controls [14].To the best of our knowledge, this is the first description of a direct link *in vivo* between endogenous AβOs and NFT formation. In support of this finding, Jin et al. showed that natural exogenous Aβ dimers isolated from the AD brain are sufficient to induce AD-type tau hyperphosphorylation followed by neuritic dystrophy [60]. Of note, Aβ accumulation triggers caspase 3/7 activation, leading to tau cleavage, followed by hyperphosphorylation and NFT formation [61]. A similar scenario is also reported [62]. Furthermore, Dolan et al. [63] showed that impaired autophagy causes intraneuronal accumulation of caspase-cleaved tau, leading to neuronal degeneration in AD. From these points of view, AβO-induced apoptosis (p75^{NTR}- and/or lysosomal leakage-mediated) or autophagic reduction [14] via Beclin1-mediated cleavage may contribute to the accumulation of tau, leading to hyperphosporylation and NFT formation (Figure 1). Incomplete Chaperon-Mediated Autophagy (CMA) of tau generates an amyloidogenic fragment that promotes aggregation, which also induces lysosomal leakage [64]. Sortilin-mediated endocytosis of AβOs may induce lysosomal leakage, promoting hyperphosphorylation of tau assembly (Figure 1). Therefore, the antibody can prevent tau toxicity via specific control of extracellular AβOs through the inhibition of p75NTR-mediated apoptosis and/or sortilin-mediated endocytosis of AβOs, which cause lysosomal leakage, mitochondrial apoptosis, and/or hyperphosphorylation of tau assembly.

Conclusion

We herein summarize the current knowledge on the possible action of antibodies targeting AβOs. As shown in Figure 2, the anti-AβO antibody induces the dissociation of sortilin from p75^{NTR} by neutralizing extracellular AβOs, which attenuates several steps of a cascade responsible for neuronal death (Figure 1). Under these conditions, sortilin maintains physiological levels of lysosomal sorting pathways [65] (Figure 2). Recent studies in our laboratory revealed that the knockdown of sortilin results in a marked decrease in Beclin1, indicating that sortilin acts as a Beclin1 inducer. Of note, the majority of Beclin1 localizes to the *Trans*-Golgi Network (TGN), whereas

some endogenous Beclin1 localizes to the Endoplasmic Reticulum (ER), which leads to the speculation that Bcl2 redistributes of Beclin1 away from TGN to ER [66]. It is possible that sortilin up regulates this retrograde transport pathway and maintains physiological levels of autophagy. Furthermore, a marked attenuation of sortilin-mediated endocytosis of AβOs results in the depletion of AβOs, which accelerate the phosphorylation of tau assembly; this depletion rescues the autophagy system from excessive load for degradation. Because AβO immunotherapy is promising for preemptive disease-modifiers, more research aiming at a deeper understanding of the molecular mechanisms underlying the action of AβOs and/or antibodies targeting AβOs is definitely required.

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