Chapter 8

Present and Future Therapies for Alzheimer's Disease

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Additional information is available at the end of the chapter

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Abstract

Alzheimer's disease (AD) is an incurable, progressive neurodegenerative disorder and the most common type of dementia. Although four kinds of drugs are currently available for AD, these are symptomatic treatments and do not halt disease progression. Therefore, there is an urgent need for development of curative drugs for AD. Amyloid plaques are the main disease hallmark observed in AD brains. As amyloid-β (Aβ) is a major constituent of amyloid plaques, Aβ has been supposed to be pathogenic for AD (amyloid hypothesis). Thus, current, mainstream AD drug development is based around this hypothesis. In particular, both active and passive immunotherapies are aggressively employed. However, most clinical trials based on this hypothesis, including immunotherapies, failed to improve cognitive impairment in AD. Therefore, it is likely that AD onset is caused by factors besides Aβ. We have previously demonstrated that the intracellular domain of amyloid precursor protein (AICD) induces dynamic changes in gene expression and neuron-specific apoptosis, probably related to AD pathogenesis. Therefore, AICD may be a favorable target for AD therapies. In this chapter, current trials for AD therapies, especially immunotherapies targeting Aβ, are summarized. In addition, therapies targeting tau, another possible pathogenic molecule, are also described. Furthermore, we discuss the possibility of AICD as a novel therapeutic target for AD.

Keywords: Alzheimer's disease (AD), immunotherapy, amyloid precursor protein (APP), the intracellular domain of APP (AICD), tau, signaling

1. Introduction

Alzheimer's disease (AD) is an age-onset, incurable, neurodegenerative disorder and the most common form of dementia in elderly people worldwide. This disease presents as progressive memory loss, accompanied by cognitive impairment and behavioral abnormalities, caused by neuronal dysfunction and cell death of neurons. At present, only four kinds of drugs are

approved for the treatment of AD, all of which act as modulators of abnormal neurotransmitter systems: three cholinesterase inhibitors (donepezil, rivastigmine and galantamine) [1] and one N-methyl-D-aspartic (NMDA) glutamate receptor antagonist (memantine) [2]. Low levels of acetylcholine and dysfunction and loss of cholinergic neurons are observed in AD brains [3]; therefore, these cholinesterase inhibitors are thought to inhibit acetylcholine degradation, maintain it at high levels and restore the function of cholinergic neurons. NMDA glutamate receptors are excessively and continuously activated in AD brains, which may lead to memory disorder and excitotoxicity. Memantine, a NMDA receptor antagonist, suppresses this excessive activation and may improve cognitive function. These drugs are temporarily effective in improving cognitive function; however, they are symptomatic and unable to halt disease progression in AD. Therefore, there are currently many trials of curative treatments for AD underway.

Although current understanding of AD etiology is not sufficient for development of AD therapies, two pathological hallmarks are commonly observed in AD brains and thought to be related to AD pathogenesis: extracellular amyloid plaques, consisting of amyloid-β (Aβ) and intracellular neurofibrillary tangles, consisting of hyperphosphorylated tau proteins. Aβ peptide, a major constituent of amyloid plaques in AD, is generated from amyloid precursor protein (APP) through stepwise, proteolytic cleavage by β- and γ-secretases. Mutations not only in APP [4], but also in presenilin (PS) 1 [5] and PS2 [6, 7], both of which are catalytic subunits of γ-secretase complex, are known to be responsible for early onset familial AD (FAD). These mutations accelerate proteolysis of APP and accumulation of Aβ, leading to the formation of amyloid plaques. Therefore, it is generally believed that Aβ is a causative factor in AD, called the amyloid hypothesis [8, 9], and this forms the basis for current, mainstream AD drug development. Additionally, tau, a microtubule-associated protein, is thought to be another pathogenic agent and potential therapeutic target for AD. Tau proteins stabilize microtubules, and hyperphosphorylated tau disperses and destabilizes microtubules, potentially resulting in neurodegeneration.

Immunotherapy is a disease treatment designed to modulate an immune response against certain target molecule(s) and is widely used in a variety of diseases, such as cancers, autoimmune diseases and allergies [10]. In the field of AD, immunotherapies, especially those designed based on amyloid hypothesis, have been aggressively employed [11]. Other therapeutic approaches, including inhibition of β- and/or γ-secretases to reduce Aβ production, have mostly failed, so immunotherapies targeting Aβ have been much anticipated as curative treatments, and many clinical trials have been attempted. Although both active and passive immunotherapies, againsnt various species of Aβ, have been designed and tested in clinical trials, most of these trials have not met endpoints in terms of improving survival or cognitive impairment, even in the cases with marked clearance of amyloid plaques [12]. Recently, immunotherapies against tau have also been attempted [13]. Although neurofibrillary tangles are formed within neurons, and the mechanisms by which intracellular pathogenic tau proteins can be excluded/neutralyzed by immunotherapies are not fully elucidated, these therapies are also expected to improve AD symptoms.

As outlined above, current mainstream AD drug development is based on the amyloid hypothesis. However, almost all trials targeting Aβ, including immunotherapies, have

failed to show efficacy in AD patients. Although genetic linkage analyses in FAD indicate that mutations in APP, PS1 and PS2 genes are linked to increased APP proteolysis and Aβ secretion, other fragments are also generated during the proteolysis of APP. For instance, extracellular fragments of APP are produced by β-secretase cleavage, and subsequent γ-secretase cleavage generates the intracellular domain (ICD) of APP (AICD) at the same time as Aβ. It is likely that these APP-derived fragments other than Aβ, contribute to AD pathogenesis [14].

γ-Secretase was originally identified as an APP-cleaving enzyme [15]. Although its biological roles are not fully characterized, γ-secretase is known to play a critical role in the regulation of Notch signaling [16, 17]. In canonical Notch signaling, γ-secretase cleaves Notch within its transmembrane domain to release the ICD of Notch (NICD), which immediately translocates to the nucleus and modulates expression of target genes through transcription factor binding. It was recently reported that many type-1 transmembrane proteins, besides APP and Notch, are substrates for γ-secretase, [18, 19] and their resultant ICDs can be detected in the nucleus. These observations suggest that the role of γ-secretase is to generate ICDs from its substrates to act as transcription factors [20–23]. Indeed, we have demonstrated that AICD alters the expression of a broad range of genes, leading to neuron-specific apoptosis, probably associated with AD pathogenesis [24, 25]. Based on these results, we propose that AICD may be a novel therapeutic target for AD [26].

In this chapter, current trials for AD therapies based on the amyloid hypothesis, especially immunotherapies against Aβ, are summarized. Other therapies, including immunotherapies against tau, are also described. Furthermore, we discuss the possibility of AICD as a novel therapeutic target for AD.

2. Aβ and amyloid hypothesis

APP plays a key role in AD pathogenesis [27, 28], although its physiclogical function has not been fully elucidated [29]. As previously described, because of the formation of amyloid plaques as one of the major hallmarks in AD, their main constituent, Aβ, is believed to be pathogenic.

Aβ is generated from APP through two stepwise enzymatic cleavages (**Figure 1(a)**). During the proteolytic process, APP is initially cleaved at either the *α*-site or the β-site, within its juxtamembrane domain, by *α*-secretase or β-secretase, respectively. Subsequently, both resultant membrane-tethered stubs are further cleaved at the γ-site and ε-site within the transmembrane domain by γ-secretase, resulting in the secretion of a non-amyloidogenic p3 fragment (in combination with *α*-secretase) or an amyloidogenic Aβ fragment (in combination with β-secretase). In both scenarios, AICD is simultaneously released from the cell membrane into the cytoplasm by γ-secretase cleavage. As mutation of APP, PS1 or PS2 genes in FAD accelerates proteolytic processing of APP and increases levels of Aβ, the amyloid hypothesis is believed to best explain the pathogenic mechanism of AD, and is the basis for most AD drug development.

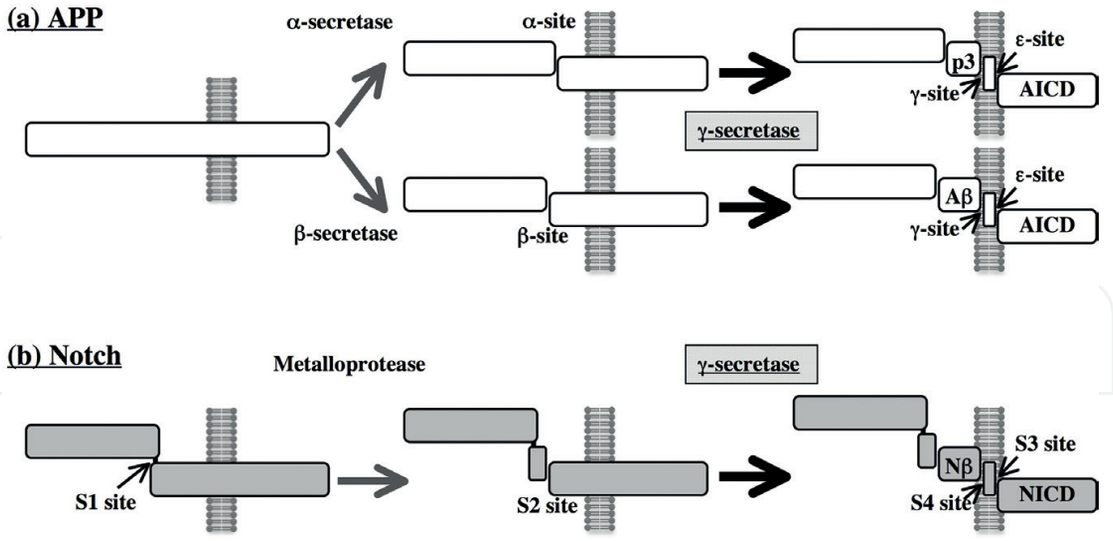

Figure 1. Proteolytic processing of APP and Notch. (a) After the cleavage of APP at the α-site or the β-site within its juxtamembrane domain by α-secretase or β-secretase, respectively, both remaining membrane-tethered stubs are further cleaved at the γ- and ε-sites within their transmembrane domains by γ-secretase. These sequential proteolytic reactions result in the secretion of either a non-amyloidogenic p3 fragment (α- and γ-secretase combination) or an amyloidogenic aβ peptide (β- and γ-secretase combination), and AICD (both combinations). (b) Notch is expressed on the cell surface as a heterodimer after cleavage at the S1 site by furin-like convertase. After the cleavage of Notch at the S2 site within its juxtamembrane domain by a metalloprotease, its remaining stub is further cleaved at the S3 and S4 sites within its transmembrane domain by γ-secretase, resulting in the production of NICD and Nβ fragment.

3. Secretase inhibitors

Several drugs to decrease and/or remove pathogenic Aβ and amyloid plaques have been developed. As Aβ is generated through proteolysis by β-secretase and γ-secretase, inhibitors for these enzymes were developed to decrease Aβ production [30].

β-Secretase is a type 1 transmembrane aspartic acid protease, also known as β-site APP cleaving enzyme 1 (BACE1). As human BACE1 knock-in mice showed accumulation of Aβ and, in an early study, BACE1-deficient mice did not display any abnormal phenotype, BACE1 inhibitors were expected to be safe therapeutic drugs for AD [31, 32]. LY2886721 was the first BACE1 inhibitor to reach Phase 2 clinical trials, but it was terminated due to liver toxicity [33]. Although other BACE1 inhibitors, such as MK-8931 and E2609, have been developed, and some are currently in clinical trials [34], recent studies have demonstrated that there are putative substrates for β-secretase besides APP [35], and adverse effects due to the inhibition of cleavage of these substrates should be of concern. In fact, further analyses of BACE1 knockout mice revealed several abnormal phenotypes such as axon guidance defects and hypomyelination [36]. Thus, it is likely that it will be difficult to inhibit the activity of β-secretase without side effects.

Inhibitors of γ-secretase (GSI) have also been developed to reduce levels of Aβ. Semagacestat was the first γ-secretase inhibitor to be taken into Phase 3 clinical trials; however, these trials were discontinued because patients showed worsened clinical measures of cognition and side effects such as increased risk of skin cancer and infections [37]. There are a large number of

membrane proteins that are substrates for γ-secretase [18, 19], and it is likely that GSIs will induce various adverse effects due to the inhibition of cleavage of other substrates, especially Notch. To date, GSIs that are selective for APP but not Notch (Notch-sparing GSIs) such as avagacestat, have been developed. Disappointedly, avagacestat failed to improve cognitive function and caused gastrointestinal and dermatological side effects [38].

γ-Secretase modulators (GSMs) are drugs that shift the γ-secretase cleaving site of APP and impair the production of the most toxic Aβ42 fragments, but do not affect other substrate cleavage. One such GSMs, tarenflurbil, was tested in Phase 3 clinical trials, but did not show beneficial effects in AD patients [39]. Recently, meta-analysis of pharmacological agents targeting γ-secretase have shown that these drugs increase risk of cancer and cognitive decline in AD patients, indicating that γ-secretase may not be an appropriate target for clinical treatment of AD [40].

4. Immunotherapies targeting Aβ

Besides the development of inhibitors for β- and γ-secretases, alternative attempts based on amyloid hypothesis have been made to remove soluble and/or insoluble Aβ utilizing immune responses. The first clinically relevant trial of immunotherapy directed towards Aβ was an active immunization using PDAPP transgenic mice, which overexpress mutant human APP with a valine to phenylalanine mutation at position 717 (V717F) under the control of a platelet-derived growth factor (PDGF) promoter. These transgenic mice, which exhibit accumulation of Aβ deposits at the age of 8–10 months, were immunized with Aβ, inducing high titers of Aβ-specific antibodies, resulting in the reduction and prevention of Aβ deposits [41, 42]. Based on these results, similar effects and clinical benefits were expected in human AD patients.

Active immunization with Aβ was the first immunotherapy performed in AD patients, who received full-length synthetic Aβ42 with QS-21 as the adjuvant (AN1792) [43–46]. A Phase 1 study demonstrated good safety and tolerability of this immunization. However, in Phase 2a, aseptic meningoencephalitis occurred in approximately 6% of AD patients treated with AN1792, probably due to a strong Th1 response, resulting in the termination of this trial [47]. Furthermore, follow-up assessments of the Phase 1 AN1792 study 6 years after immunization revealed that there was no evident difference in cognitive decline between the treatment group and the placebo group, although postmodern pathological studies of some of the treated patients showed marked clearance of amyloid plaques in the brain [48]. In addition, follow-up of the Phase 2a trial 4.6 years after immunization reported no significant difference in the majority of cognitive assessments between AN1792-treated and placebo groups [49].

To avoid an inflammatory T cell response, Aβ1–6 peptide, which is derived from the N-terminal Aβ-specific B cell epitope, coupled to a bacteriophage QB protein coat, was employed as an immunogen for active immunotherapy (CAD106). Phase 1 trials showed induction of anti-Aβ antibodies, safety and tolerability of this immunization, and no incidence of meningoencephalitis [50]. The Phase 2/3 clinical trial of CAD106 is currently ongoing.

ACC-001 is a conjugate of multiple short N-terminal Aβ fragments (Aβ1–7), coupled to inactivated diphtheria toxin as a carrier. In two Phase 2 trials, ACC-001 was administered with or without QS-21 adjuvant to patients with mild to moderate AD [51]. ACC-001 administered with QS-21 elicited higher peak and sustained anti-Aβ IgG titers compared with ACC-001 alone. Exploratory cognitive evaluations did not show any difference or trends between treatment groups and placebo groups, and this immunotherapy was discontinued from clinical development.

A number of other active immunotherapies have being developed, such as ACI-24, UB-311, ABvac40, and Lu AF20513 [52]. ACI-24 is a liposome vaccine against tetra-palmitoylated Aβ1–15, which favors β-sheet structure, to induce antibodies specific to its conformation. UB-311 is a vaccine against Aβ1–14, formulated with CpG oligonucleotides and aluminum salt, which preferentially stimulates a Th2 regulatory response over a Th1 proinflammatory response. ABvac40 is a vaccine against multiple repeats of short Aβ C-terminus that is conjugated to keyhole limpet hemocyanin (KLH) and formulated with aluminum hydroxide. Lu AF20513 is a vaccine developed against three repeats of Aβ1–12 peptides interspersed with P30 and P2 T-cell epitopes of tetanus toxin to overcome weak immune response in the elderly by utilizing immunological memory generated by tetanus vaccination in childhood. These active immunotherapies are currently in the process of undergoing their respective clinical trials.

Although active immunotherapies are potentially cost-effective for long-term treatments, there are some limitations to this type of treatment. In elderly individuals over 65 years old, immune responses are generally weaker than in younger individuals, meaning active immunization may not induce sufficient production of antibodies specific for Aβ. In addition, active immunization could potentially induce autoreactive and/or unintended immune responses associated with severe adverse events, including the aseptic meningoencephalitis observed in AD patients treated with AN1792. Direct administration of passive immunotherapies, utilizing ready-made antibodies specific for Aβ, may be able to overcome these problems, if the Aβ-specific antibodies have no, or reduced, cross-reactivity to self-antigens. To this end, several human/humanized monoclonal antibodies (mAb) against various epitopes of Aβ have been developed for passive immunization. Generally, the N-terminus of Aβ is exposed when it forms aggregates, while its middle and C-terminal regions are not accessible for antibodies. Thus, it is likely that mAbs specific for Aβ N-terminus are effective for the removal of Aβ aggregates, and those specific for Aβ mid-regions or C-terminus are effective for prevention of aggregation and exclusion of monomeric Aβ. Two mechanisms have been suggested to explain the reduction of Aβ induced by mAbs [53, 54]: microglia activation through Fc receptors and the peripheral sink effect. Microglia are activated by administration of the mAb, through binding to the Fc receptor, and can recognize and clear amyloid plaques. The peripheral sink effect hypothesizes that there is a decrease of soluble Aβ in the circulation due to binding of mAb to Aβ that alters the equilibrium of Aβ between the brain and the periphery and might draw Aβ out of the brain.

Bapineuzumab is a humanized immunoglobulin (Ig) G1 of murine mAb 3D6, which recognizes the N-terminus of Aβ (Aβ1–5). This mAb binds fibrillar and soluble Aβ, and activates Fc receptor-mediated, microglial phagocytosis of Aβ deposits. Although some clearance of fibrillar Aβ was observed upon analysis with [^{11}C]-Pittsburgh compound B and positron emission tomography (PET) in a Phase 2 study [55], two large Phase 3 studies of bapineuzumab showed no clinical benefits [56], and these trials were terminated.

Solanezumab is a humanized monoclonal IgG1 of a murine mAb clone, m266, which binds the middle region of Aβ (Aβ16–26). This mAb recognizes soluble monomeric Aβ, not fibrillar Aβ. In two Phase 3 trials, solanezumab was administered to patients with mild to moderate AD, and no improvement on the primary endpoints was detected in these trials overall [57]. In contrast, subgroup analyses based on disease severity (mild or moderate) showed slowing of cognitive and functional decline in pooled mild AD patients [58]. However, in the next Phase 3 trial in patients with mild AD, solanezumab did not meet the primary endpoint and was abandoned as a treatment for mild AD [59].

Gantenerumab is a fully human IgG1, recognizing a conformational epitope on Aβ fibrils which encompasses both the N-terminal and middle regions of Aβ. Gantenerumab is thought to act mainly to disassemble and degrade amyloid plaques by supporting phagocytosis of microglia. In a Phase 3 study, no differences in efficacy measures were observed, and this clinical trial was stopped based on interim analysis for futility [60]. Despite the lack of a clinical benefit in subjects overall, gantenerumab showed a beneficial trend in the fastest progressors, especially with higher serum levels of gantenerumab, on post hoc subgroup analysis. Further Phase 3 clinical trials employing dose titration schemes are planned, and the degree of amyloid reduction and cognitive improvement by administration of high doses of gantenerumab will be assessed.

Crenezumab is a humanized mAb that recognizes multiple aggregated forms of Aβ, including its oligomers, fibrils and amyloid plaques. Its affinity for Aβ monomers is lower. This mAb uses an IgG4 backbone to activate microglial phagocytosis and to minimize inflammatory responses related to side effects, such as vasogenic edema. Phase 2 trials of crenezumab showed no clinical benefits at its endpoints. However, a post hoc subgroup analysis of the high dose group suggested that treatment with crenezumab attenuated cognitive decline in the milder subgroups. The Phase 3 trial of crenezumab in prodromal to mild AD patients at higher doses is in progress [61].

Aducanumab is a fully human IgG1 mAb generated from memory B cell libraries of healthy, aged individuals by screening for reactivity against aggregated Aβ. It is thought that immune systems of these donors without AD symptoms may be able to prevent AD, and that their antibodies can assist in removal of amyloid plaques. Aducanumab interacts with the N-terminal region (Aβ3–6) of aggregated Aβ, including soluble oligomers and insoluble fibrils, but not monomers. In a Phase 1b clinical trial, florbetapir (^{18}F) PET scans showed marked reduction of brain fibrillar Aβ in a dose- and time-dependent manner [62]. In addition, although this Phase 1b trial was not sufficient to detect clinical changes, exploratory analyses of clinical assessments revealed dose-dependent slowing of disease progression at 1 year. Based on these interim analyses, two identical Phase 3 trials were launched to evaluate the efficacy of aducanumab for slowing cognitive decline in patients with prodromal to mild AD.

BAN2401 is a humanized IgG1 mAb that selectively recognizes a specific conformation of large, insoluble Aβ protofibrils. A Phase 1 study of BAN2401 demonstrated its safety and tolerability [63], initiating a Phase 2 trial to evaluate its efficacy against cognitive impairment.

Ponezumab is a humanized IgG2 mAb that binds to the C-terminal region of Aβ (Aβ33–40). Although Phase 1 studies of ponezumab showed sufficient safety [64, 65], its Phase 2 trials revealed no significant cognitive improvement in patients with mild to moderate AD [66]. The development of ponezumab for AD was discontinued, although it is still in Phase 2 trials for cerebral amyloid angiopathy (CAA).

Several other mAbs for Aβ have also been developed, with some of their clinical trials currently in progress. In addition to these passive immunotherapies, another strategy of passive immunization is currently being investigated. Pooled human plasma antibodies are prepared from donated blood and administered intravenously to AD patients (IVIg). These preparations contain a small fraction of naturally occurring polyclonal anti-Aβ antibodies and are expected to result in Aβ clearance and/or prevention of Aβ aggregation. Several of these IVIg preparations, such as gammagard and gamunex, are currently being administered to AD patients in clinical trials. A Phase 3 study of gammagard, observed no beneficial effects despite a significant decrease in plasma Aβ levels [67]. Clinical trials of other IVIgs are still in progress.

Although most passive immunotherapies targeting soluble and/or insoluble Aβ have entirely failed to show clear beneficial effects in patients with mild to moderate AD, Phase 3 clinical trials of solanezumab suggested that earlier intervention with this drug during the disease course may provide beneficial effects [58]. Although Phase 3 trials of solanezumab in mild AD patients did end in failure, administration of solanezumab and gantenerumab in asymptomatic and very mildly symptomatic carriers of autosomal-dominant mutations in APP, PS1 or PS2 genes, as well as cognitively healthy subjects at risk of developing sporadic AD, is being tested as a secondary prevention method [68]. In addition, crenezumab is also being tested in presymptomatic carriers of the E280A mutation in the PS1 gene [69].

Thus, there are no drugs based on amyloid hypothesis, including immunotherapies targeting Aβ, that show clear efficacy in AD patients to date, although some clinical and prevention trials are still in progress. These results may suggest the necessity of approaches other than targeting Aβ to develop efficacious treatments for AD.

5. Therapies against tau

In addition to extracellular amyloid plaques, intracellular neurofibrillary tangles are generally observed in AD patients as another histopathological hallmark of AD brains, and may be linked to AD pathogenesis. Pathological neurofibrillary tangles are aggregates of paired helical filaments composed of hyperphosphorylated tau. Tau is a microtubule-associated protein and binds to microtubules through its C-terminal assembly domain, thereby stabilizing microtubules and promoting microtubule polymerization. In the brains of AD patients, tau proteins are abnormally hyperphosphorylated by several protein kinases, such as glycogen synthetic kinase-3 β (GSK3β). Hyperphosphorylated tau proteins are detached from microtubules due to their reduced affinity for tubulins, resulting in destabilization of cytoskeletal microtubules and the formation of neurofibrillary tangles. Thus, the hyperphosphorylated tau protein is thought to be another favorable target molecule for AD therapy.

Several compounds to inhibit hyperphosphorylation or aggregation of tau have been developed. Tideglusib is a small molecule that acts as an inhibitor of GSK3β and counteracts tau phosphorylation. In a Phase 2 trial tideglusib was reported to produce no clinical benefit in patients with mild to moderate AD [70]. Rember is a first generation drug designed to prevent tau aggregation and/or dissolve existing aggregates. It is a formulation of methylthioninium

chloride, known as methylene blue. Its second generation, TRx0237, a stabilized, reduced form of methylthioninium chloride, was developed to improve drug absorption. Phase 3 trials of TRx0237 are currently underway [71]. Several microtubule stabilizers, such as epothiline D and TPI287, have also been developed as AD drugs to counteract microtubule destabilization by tau hyperphosphorylation. Epothiline D has been discontinued for AD and TPI287 is in Phase 1 trials [72].

6. Immunotherapies targeting tau

Various forms of pathogenic tau proteins may also become targets for immunotherapies. Two mechanisms for recognition of intracellular tau proteins/neurofibrillary tangles by anti-tau antibodies have been proposed. First, pathogenic tau proteins are supposed to be propagated from one cell to the next. Experiments with P301S transgenic mice, which express human mutant P301S tau, causing inherited frontotemporal dementia and development of filamentous tau inclusions, revealed that injection of brain extracts from P301S mice into the brains of wild-type human tau-expressing mice induced assembly of wild-type tau into filaments [73]. This pathological abnormality spread from the injection site to adjacent regions, suggesting extracellular transmission of tauopathy between cells. If certain pathological forms of tau can spread and induce abnormal assembly of normal tau in AD brains, it is therefore expected that anti-tau antibodies could bind to tau outside of cells and prevent the spread of tauopathy, resulting in the inhibition of disease progression. Second, anti-tau antibodies may be translocated inside neurons. It has previously been shown that neurons can take up anti-tau antibodies via clathrin-dependent low affinity FcγII/III receptors-mediated endocytosis and that these now-intracellular antibodies can bind to pathological tau within the endosomal-lysosomal system, promoting the clearance of pathological tau [74]. Thus, immunotherapies against pathological tau are hoped to be efficacious as AD treatments, and several active and passive immunotherapies, targeting various forms of pathological tau, have been developed.

AADvac-1 is an active vaccine consisting of a synthetic tau peptide (amino acids 294–305) coupled to KLH that is a carrier, with aluminum hydroxide as an adjuvant. The short tau domain synthesized for this vaccine is essential for pathological tau-tau interaction. A Phase 1 trial of AADvac-1 showed a good safety profile and excellent antibody response [75]. A Phase 2 trial is currently in progress.

In another Phase 1 study, ACI-35, which is a liposome-based vaccine consisting of a synthetic tau peptide (amino acids 393–408) phosphorylated at S396 and S404, is being tested in patients with mild to moderate AD [76].

Several humanized anti-tau mAbs are currently being tested in clinical studies as passive immunotherapies against tau. RG7345 is a humanized mAb specific for the tau phospho-epitope pS422, which is critical for binding to microtubules. Tau phosphorylated at S422 is prominent in early stages of AD and persists until late-stage disease, making it an attractive target for antibody therapeutics. RG7345 was tested in a Phase 1 trial but was subsequently discontinued [77].

BIIB092 is a humanized IgG4 mAb specific to extracellular, N-terminal fragments of tau (eTau), originally isolated from neuronal cultures using induced pluripotent stem cells derived from FAD patients. Since eTau is supposed to be involved in the spread of tauopathy, BIIB092 is expected to neutralize eTau propagation. Phase 1 trials of this mAb showed a dose-dependent accumulation in serum and CSF and marked reduction of CSF eTau, and a Phase 2 trial is planned [76].

ABBV-8E12 is a humanized mAb that recognizes an aggregated, extracellular form of pathological tau, and, thus, has the potential to stop or slow the propagation of tau pathology observed in AD and other tauopathies. Since a Phase 1 study showed an acceptable safety and tolerability profile of single doses, two Phase 2 trials to assess the efficacy and safety of multiple doses are in progress [76].

Although there have not yet been any successful clinical trials of immunotherapies targeting tau, many researchers have recently focused on the tau protein as a target molecule for AD treatment because of the failure of most clinical trials based on the amyloid hypothesis. However, since both the mechanism of transmission of tauopathies among cells, and that of antibody-uptake in neurons, have not fully been characterized, further studies to elucidate these mechanisms will be required in order successfully to design immunotherapies targeting tau.

7. γ-Secretase-regulated signaling and AICD

Since amyloid plaques, a major histopathological hallmark observed in AD, are thought to be a pathogenic factor in AD, Aβ, a main constituent of amyloid plaques, has long been thought to be a prime therapeutic target for AD. However, as mentioned, no clinical trials targeting Aβ have shown any efficacy in terms of cognitive improvement in progressing AD to date, and it is likely that there may be another mechanism that leads to the onset of AD.

As described above, genetic mutations in genes coding APP, PS1 and PS2 cause early onset of FAD. Since these genes are all associated with APP processing and Aβ production, and amyloid plaques are observed in the brains of both FAD and sporadic AD patients, the amyloid hypothesis, that Aβ is toxic for neurons and pathogenic in AD, has been widely accepted. Although several clinical trials of drugs targeting Aβ, including immunotherapies, are still in progress, no trials to date have succeeded in improving cognitive decline and/or behavioral abnormalities, even in the cases with marked reduction of soluble and insoluble Aβ. In addition to the failures of these clinical trials, several questions regarding amyloid hypothesis in AD have been raised. For example, amyloid plaques are often detected in the brains of healthy elderly people with no AD symptoms [78]. In addition, Aβ-overexpressing transgenic mice did not show any neurodegeneration although these mice exhibited Aβ deposition mimicking amyloid plaques observed in AD brains [79]. These observations suggest that Aβ has no neurotoxicity or pathogenicity in AD. Based on the FAD genetic analysis described above, it still seems likely that APP itself and/or its proteolysis contributes to AD pathogenesis, and it is possible that an APP-derived fragment other than Aβ, is the cause of AD [14].

γ-Secretase has been primarily characterized as an APP cleavage enzyme, and is thought to play a role in AD pathogenesis [15]. Although the physiological functions of this enzyme have not been

fully elucidated, it is well known that γ-secretase plays a central role in the regulation of Notch signaling (**Figure 2**) [16, 17]. In the canonical Notch signaling pathway, Notch is cleaved at its S2 site within the juxtamembrane domain by metalloproteases after the binding of ligands on neighboring cells to Notch. Subsequently, the remaining membrane-associated, C-terminal fragment is further cleaved at S3 and S4 sites within the transmembrane domain by γ-secretase, resulting in the release of the ICD of Notch (NICD) into the cytoplasm. NICD immediately translocates to the nucleus where it binds to a CSL transcription factor (CBF-1/RBP-jκ in mammals, Suppressor of Hairless in *Drosophila*, Lag-1 in *Caenorhabditis elegans*) [16, 80] and a mastermind-like (MAML) protein [81] to form a complex. In this process, a co-repressor in this complex is substituted with a co-activator, such as p300 and P/CAF [82], and the resultant complex induces expression of certain target genes such as Hes [83]. In this way, γ-secretase plays a regulatory role in Notch signaling.

Recently, many type-1 transmembrane proteins have been reported as substrates for γ-secretase [18, 19]. Interestingly, the proteolytic processing of some of these substrates, including APP, is very similar to that of Notch, and several of these ICDs have been detected in the nucleus. These observations suggest that some of these substrate proteins possess γ-secretase-regulated signaling mechanisms similar to Notch signaling [20–23]. Indeed, we have previously demonstrated that Delta, a ligand of Notch, possesses a γ-secretase-regulated signaling mechanism similar to Notch [84]. The ICD of Delta acts as a transcription factor through binding to Smad, a transcription factor in the TGF-β/activin signaling pathway, and modulates expression of target genes. These findings indicate that γ-secretase functions as a signaling regulator by generating ICDs of substrate membrane proteins, which then act as transcription factors in the nucleus.

AICD is generated through a proteolytic process similar to NICD (**Figure 1 (a)** and **(b)**), and it is possible that APP has a γ-secretase-regulated signaling mechanism similar to Notch [20–23]. We have previously demonstrated that AICD may act as a transcriptional factor, leading to neurodegeneration potentially related to AD pathogenesis. To examine the function of AICD, we used a teratocarcinoma P19 cell line, which can differentiate into neurons through stimulation with all-*trans* retinoic acids (RA), overexpressing AICD (AICD/P19). Although undifferentiated AICD/P19 cells were morphologically the same as control P19 cells, induction of AICD/P19 cells into neurons caused neuronal cell death with characteristic features of apoptosis, while control P19 cells differentiated normally into neurons [24]. In addition, DNA

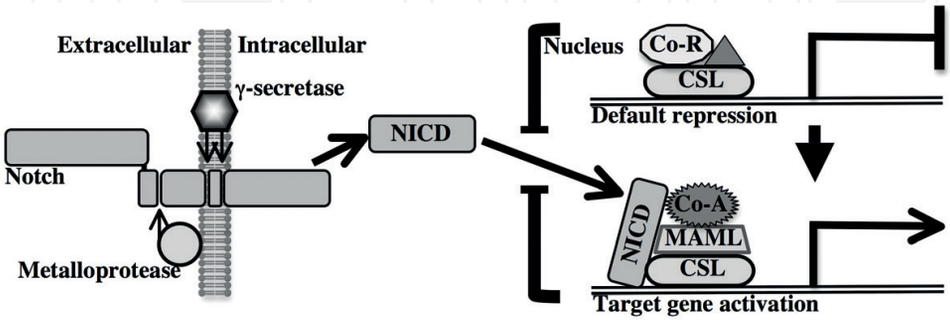

Figure 2. Notch signaling. When Notch binds to its ligand, Notch is cleaved at the S2 site by metalloproteases. Then, its remaining stub on the membrane is further cleaved at the S3 and S4 sites by γ-secretase, resulting in the release of NICD into cytoplasm. Immediately, NICD translocates to the nucleus and binds to the CSL transcription factor and MAML. During this process, the co-repressor(s) (Co-R) dissociate from this complex and the co-activator(s) (Co-A) is recruited. Finally, the resultant NICD-complex promotes the transcription of target genes as an activator.

microarray analyses with these cells revealed that AICD dramatically altered expression of numerous genes, possibly due to function of AICD as a transcription factor [25]. Although genes with altered expression were not directly related to the apoptotic cascade, it is likely that such dynamic alteration in the expression of many genes would disturb homeostasis in neurons, leading to neuron-specific apoptosis. Thus, AICD has a γ-secretase-regulated mechanism similar to Notch and may have potential as a therapeutic target in AD.

Figure 3 shows a diagram of APP signaling model. To prevent AICD-induced neurodegeneration, several strategies are possible: (1) reduction of AICD generation, (2) prevention of AICD translocation to the nucleus and (3) removal of AICD in the cytoplasm.

To reduce AICD generation, inhibitors of β- and/or γ-secretases would be an obvious choice. However, these enzymes have many substrates, and it is highly possible that inhibition of these other proteolytic reactions may induce an adverse reaction [18, 19, 35].

To translocate to the nucleus, AICD must bind to the adaptor protein Fe65 [85, 86], and it is likely that this binding is regulated by phosphorylation/dephosphorylation at T668 within AICD [87]. Phosphorylation of T668 interferes with the interaction between AICD and Fe65, and AICD is constitutively phosphorylated at T668, impairing its translocation to the nucleus. Phosphorylated AICD remains in the cytoplasm and is rapidly degraded by the proteasome and/or insulin-degrading enzyme (IDE) [88], suggesting that AICD is not toxic in the brains of healthy individuals. When AICD is dephosphorylated by phosphatases, or kinase phosphorylation of AICD is decreased, non-phosphorylated AICD can bind to Fe65 and translocate to the nucleus where it may act as a transcriptional factor, leading to neuronal cell death [89]. Therefore, it is thought that drugs that can modulate AICD phosphorylation by either decreasing dephosphorylation activity or restoring/increasing phosphorylation activity on AICD, preventing its translocation into the nucleus, are potential future AD treatments. Alternatively, removal of cytoplasmic AICD prior to its nuclear translocation is another potential treatment avenue, and, in this regard, drugs that upregulate the activity of AICD degrading enzymes, such as IDE, may also be efficacious.

From an immunotherapy perspective, if anti-AICD antibodies can be taken up into neurons as described in the section of 'Immunotherapies targeting tau' [74], immunotherapies targeting AICD may also act to remove intracellular AICD and/or prevent its translocation to the nucleus.

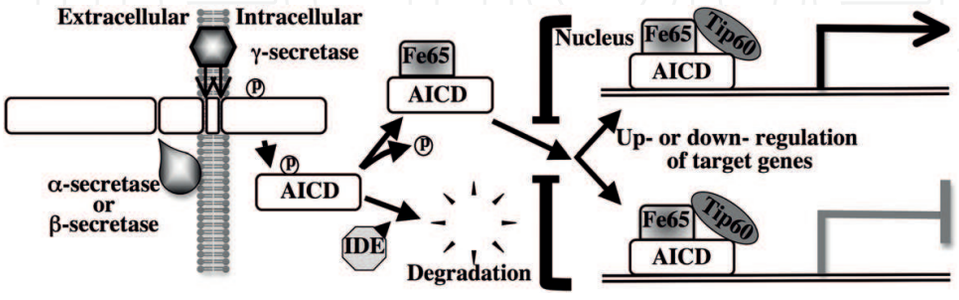

Figure 3. APP signaling model. Most APP proteins on the membrane are phosphorylated at T668 within AICD in neurons. After the removal of APP ectodomain by α-secrease or β-secretase, AICD is released by γ-secretase from the cell membrane into the cytoplasm. Then, phosphorylated AICD stay in the cytoplasm and quickly degraded by the proteasome and/or insulin-degrading enzyme (IDE). Dephosphorylated AICD can bind to Fe65 and then translocate into the nucleus. In the nucleus, AICD/Fe65 complex further binds to the histone acetyltransferase Tip60, and acts as a transcriptional regulator for up- or downregulation of target genes.

Thus, AICD may be a pathogenic agent in AD and has potential as a novel therapeutic target.

8. Conclusion

AD is an age-related, incurable, neurodegenerative disease and the most common type of dementia in elderly people. Increasing numbers of people suffer from this disease, but very few treatments are available, all of which are only symptomatic. Therefore, there is urgent need for development of curative AD therapies.

Although the precise mechanism underlying AD pathogenesis has not been elucidated, Aβ, a major constituent of amyloid plaques commonly observed in AD brains, is considered to be pathogenic. Most AD drugs have been designed in accordance with this 'amyloid hypothesis'.

Based on the amyloid hypothesis, immunotherapy was expected to be a powerful approach to remove and decrease pathogenic Aβ, and many trials of both active and passive immunotherapies targeting Aβ have been attempted. However, these immunotherapies targeting Aβ have totally failed to show efficacy, even in cases with marked clearance of amyloid plaques. Therefore, Aβ may not be the pathogenic entity in AD. At present, several immunotherapies targeting another possible pathogenic agent, tau, are also being tested.

Since it is highly possible that an APP-derived fragment, probably one other than Aβ, is responsible for AD pathogenesis, we have focused on AICD. According to our observations, AICD induces neuron-specific apoptosis, and has potential as a therapeutic target in AD. Based on our findings, the most important step in designing a drug against AICD, is likely preventing its translocation to the nucleus. This step may also help to remove pathogenic intracellular AICD. Taken together, it is hoped that AICD, and other promising target molecules, as well as Aβ and tau, will be further explored, and that efficacious treatments for AD will be established in the near future.

Conflict of interest

The authors have declared that no conflict of interest exists.

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