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REVIEW

Amyloid beta receptors responsible for neurotoxicity and cellular defects in Alzheimer's disease

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Abstract Alzheimer's disease (AD) is the most common neurodegenerative disease. Although a major cause of AD is the accumulation of amyloid-β (Aβ) peptide that induces neuronal loss and cognitive impairments, our understanding of its neurotoxic mechanisms is limited. Recent studies have identified putative Aβ-binding receptors that mediate Aβ neurotoxicity in cells and models of AD. Once Aβ interacts with a receptor, a toxic signal is transduced into neurons, resulting in cellular defects including endoplasmic reticulum stress and mitochondrial dysfunction. In addition, Aβ can also be internalized into neurons through unidentified Aβ receptors and induces malfunction of subcellular organelles, which explains some part of Aβ neurotoxicity. Understanding the neurotoxic signaling initiated by Aβ-receptor binding and cellular defects provide insight into new therapeutic windows for AD. In the present review, we summarize the findings on Aβ-binding receptors and the neurotoxicity of oligomeric Aβ.

Keywords Amyloid beta · Alzheimer's disease · Aβ receptor · Neurotoxicity · Uptake · Mitochondria · ER stress

Introduction: Aβ oligomers in neurotoxicity

Extracellular plaques and neurofibrillary tangles (NFTs) are histological hallmarks found in the brains of patients with AD and are mainly composed of Aβ and tau proteins, respectively. AD is characterized by learning and memory deficits largely attributed to the neuronal degeneration and cell death of affected neurons in the hippocampus and cerebral cortex. Aβ is a 4-kDa peptide that is a proteolytic product of amyloid precursor protein (APP). The extracellular region of APP is cleaved by a group of metalloproteases called α-secretases and the remaining fragment undergoes intramembrane proteolysis by the γ-secretase protein complex [1]. This process generates the peptide fragment p3 that is not toxic. In contrast, APP is sequentially processed by β-site APP cleaving enzyme (BACE) and γ-secretase in AD brains [2]. This "amyloidogenic pathway" liberates Aβ, which is regarded as a main culprit in AD etiology because it forms insoluble deposits by self-aggregating. Mutations in APP and presenilin (PS), a catalytic unit of γ-secretase, elicit familial AD by driving the amyloidogenic pathway [3]. Cleavage of Aβ by γ-secretase determines its amino acid length from 37 to 43 amino acids long [4]. Among them, Aβ40 and Aβ42 are the major Aβ species. Longer Aβ42 is more prone to form aggregates than Aβ40 and is regarded as a major mediator of neurotoxicity. An elevated ratio of Aβ42 to Aβ40 is also found in AD brains [5]. Mutations located immediately after the C-terminus of Aβ induce greater Aβ42 production and result in familial AD [6, 7]. Together, strong evidence points to Aβ42 as the critical Aβ isoform in AD pathology.

Interestingly, recent reports support the idea that Aβ oligomers, which assemble with a few Aβ monomers less than 20, exert more toxicity to neurons than fibrillar Aβ deposits [8]. Aβ oligomers are produced in vitro by incubating synthetic Aβ under certain conditions [9, 10]. Although molecular features of synthetic Aβ oligomers are consistent and adjustable, oligomeric conformations

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differ from each other depending on the preparation conditions. Furthermore, it is unclear whether synthetic Aβ oligomers accurately reflect the features of Aβ found endogenously in AD brains, such as mutations in Aβ sequences, posttranslational modification including phosphorylation and pyroglutamylation, and interaction with divalent metal ion [11–13]. Nevertheless, physiological Aβ oligomers mimicking natural Aβ found in vivo can be prepared from cells and AD tissues. Mutant APP-expressing cells secrete Aβ oligomers that impair neurons and brain tissues [14]. Soluble Aβ oligomers extracted from the brains of AD mouse models and postmortem AD brain tissue also damage neurons [15, 16]. On the contrary, insoluble amyloid prepared from AD brains fails to impair neuronal function in brain slices, underscoring the role of soluble Aβ oligomers in AD pathology [16]. To delineate the mechanism(s) of Aβ neurotoxicity, we first provide an overview of Aβ-binding partners.

Aβ-binding receptors in AD pathology

Because Aβ peptide is generated and released into extracellular region, it first challenges to generate toxic signal into neurons passing through plasma membrane. Aβ itself can directly bind to cell membranes and form ion channels or pores that induce membrane disruption and thus neuronal damage. Many observations show pore-like structure of Aβ in vitro and in the cell membrane of the AD brains and mice [17–20]. In addition, soluble Aβ oligomers, but not monomers or fibrils, increase membrane permeability and thus dysregulate Ca^{2+} signals for neurotoxicity [21]. More recently, emerging insight into the mechanistic link between Aβ and its binding proteins highlights the potential role of "Aβ receptors" in AD. A number of Aβ-binding proteins have been identified on the plasma membrane of neurons that may have an important role in Aβ-induced neurotoxicity. These proteins include the receptor for advanced glycation end products (RAGE), *N*-methyl-D-

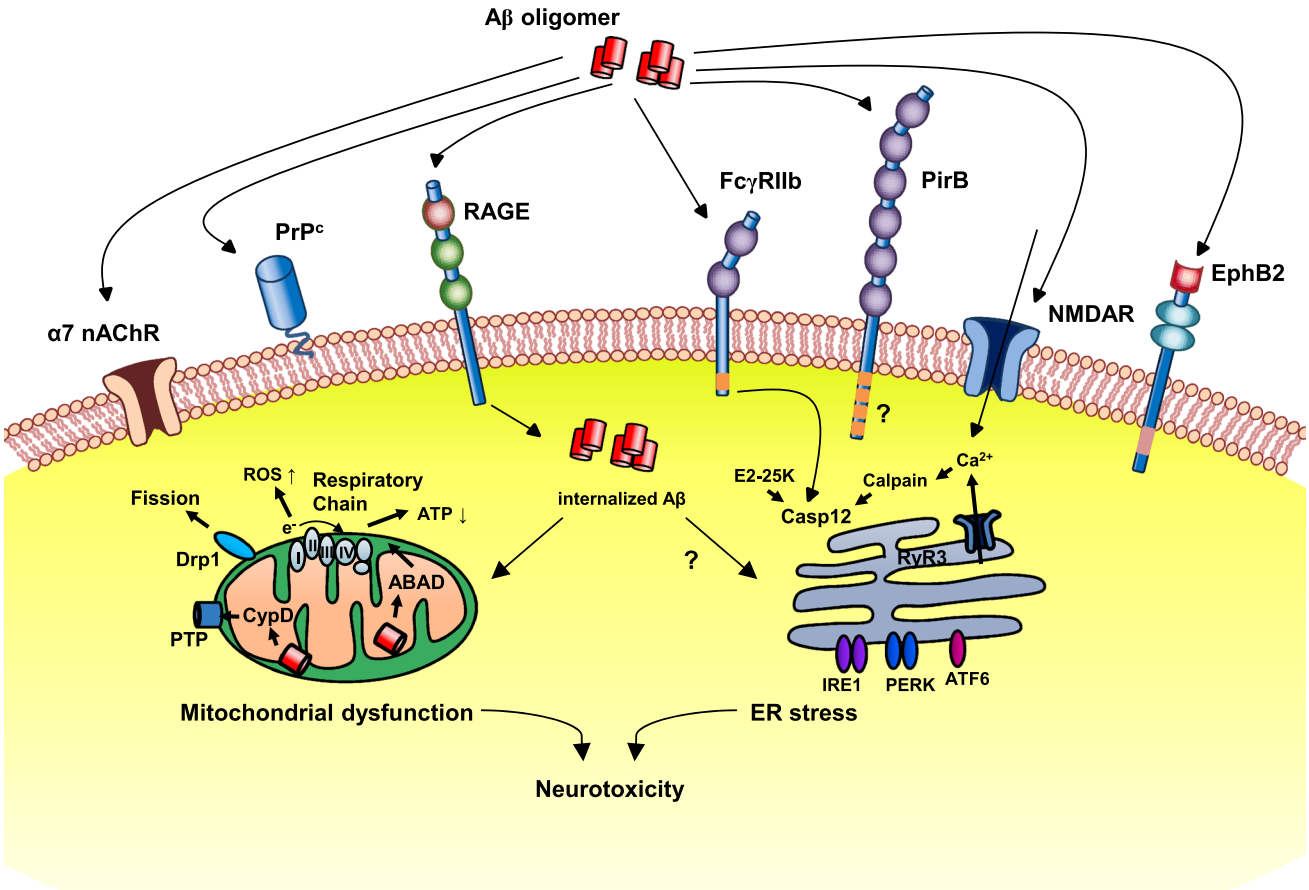

Fig. 1 Aβ-binding receptors in neurotoxicity. Aβ low-n or high-n oligomers bind to cognate Aβ receptors, such as RAGE, NMDAR (its direct binding is not clear), α7 nAChR, FcγRIIb, PirB, PrP^c, or EphB2. This Aβ-receptor interaction generates and transduces neurotoxic signal into neurons, which causes cellular defects, such as mitochondrial dysfunction and ER stress response. In addition, some Aβ receptors are most likely to internalize Aβ into neurons to display distinct cellular defect. Please see main text for details

aspartate receptor (NMDAR), α7-nicotinic acetylcholine receptor (α7 nAChR), cellular prion protein (PrP^c), ephrin type B receptor 2, immunoglobulin G Fc gamma receptor IIb (FcγRIIb), and paired immunoglobulin-like receptor B (PirB) (Fig. 1) [22–28].

RAGE

RAGE is a multi-ligand receptor that binds to advanced glycation end product (AGE), amphoterin and S100/calgranulins [29], and AGE is observed in senile plaque and NFTs in AD brains [33]. RAGE is also known as a cell surface receptor for Aβ in neurons and microglia that mediates AD-related Aβ neurotoxicity, including oxidative stress, synaptic dysfunction, and eventually neuronal cell death [24, 30]. Indeed, the expression of RAGE is significantly increased in the brains of patients with AD, especially in blood vessels [24, 31, 32]. In genetic studies, AD mice (PDAPP J20) crossed with RAGE transgenic mice show early abnormalities in spatial learning and memory, while the mice harboring dominant-negative forms of RAGE are resistant to such neuropathological alterations [34]. RAGE also functions in Aβ transport across the blood–brain barrier (BBB) and Aβ accumulation in the brain by binding to soluble Aβ [31].

Treatment of AD mice with soluble RAGE or a RAGE-specific antibody not only improves impaired long-term potentiation (LTP) and cognitive dysfunction, but also prevents the entry of Aβ into the brain [31, 35]. Moreover, a multimodal RAGE-Aβ interaction blocker reduces the level of Aβ in the brain and neuroinflammatory response and thus prevents cognitive impairment in AD mice [36], indicating that the interaction between RAGE and Aβ is critical for AD pathogenesis. Currently, RAGE is considered as an advanced therapeutic target among Aβ receptors. The orally bioavailable and BBB-permeable PF-04494700, which inhibits the interaction between RAGE and Aβ, is tested for phase II clinical trial. Although low-dose (5 mg/day) test shows a good safety profile and decreased decline on the Alzheimer's disease assessment scale-cognitive (ADAS-cog) in mild AD patients, it still needs further investigation because of high dropout and discontinuation rates [37].

NMDAR and α7 nAChR

Several reports suggest that Aβ interacts with NMDARs at postsynaptic terminals. Antibodies against the GluN1 or GluN2B subunit of NMDARs markedly block the binding of Aβ oligomer to neurons [38, 39] and Aβ oligomers partially colocalize with GluN2B subunits of NMDARs at the cell surface [13]. Indeed, through NMDAR activation, Aβ oligomers induce Ca^{2+} dysregulation, neuronal death [40], and synaptic dysfunction [41, 42]. However, it is still unclear whether Aβ directly binds to NMDAR subunits [43, 44]. In addition, Aβ oligomers promote the endocytosis of NMDARs, which requires the activation of α7 nAChR signaling [45]. The α7 nAChR is another candidate Aβ-binding receptor and binds to soluble Aβ with high affinity [23, 45]. The α7 nAChR mediates Aβ-induced tau phosphorylation via ERK and JNK [46]. Although α7 nAChR-expressing neuroblastoma cells are susceptible to Aβ-induced toxicity in vitro [47], the in vivo neurotoxic role of this receptor is inconsistent. For instance, α7 nAChR deficiency improves cognitive deficits and synaptic pathology in PDAPP J9 mouse model of AD, while it exacerbates AD pathology in Tg2576 mouse model [48, 49].

PrP^c

PrP^c was identified to have a high-affinity binding site for Aβ oligomers [25]. Subsequently, it was shown that PrP^c deficiency prevents Aβ oligomer-induced neuronal cell death [50] and inhibits Aβ oligomer-induced LTP blockade [25]. The role of PrP^c in the inhibition of LTP was also illustrated using synthetic Aβ oligomers called Aβ-derived diffusible ligands (ADDL) and Aβ oligomers derived from human AD brains [51, 52]. In addition, the deletion of PrP^c expression in APPswe/PS1ΔE9 mice rescues the loss of synaptic markers and the impairment of spatial learning and memory [53]. Further, treatment of APPswe/PS1 M146L mice with anti-PrP^c antibodies, which block the binding of Aβ oligomer to PrP^c, rescues the decreased synapse density and cognitive deficits [54].

Because PrP^c is anchored to the cell surface with a glycosylphosphatidylinositol anchor, Aβ-induced neurotoxic signaling is unlikely to be transduced only by PrP^c itself. Recently, the metabotropic glutamate receptor mGluR5 was identified as a neurotoxic mediator at the postsynaptic density that couples the Aβ–PrP^c complex with Fyn and disrupts neuronal function [55, 56]. Fyn interacts with and localizes tau to the dendritic compartment and facilitates NMDAR–PSD95 interaction, thereby mediating Aβ neurotoxicity at the postsynaptic membrane in AD [57]. In contrast, there is a report showing that PrP^c may not be essential for Aβ neurotoxicity. Kessels et al. [58] observed that PrP^c is not required for Aβ-induced synaptic depression, reduction in spine density, and blockade of LTP. In addition, the ablation or overexpression of PrP^c has no effect on the impairment of hippocampal synaptic plasticity in APPswe/PS1 L166P or PDAPP J20 AD mice [59, 60]. Further, cognitive impairment is not ameliorated in Aβ-injected mice lacking PrP^c [61]. Thus, the role of PrP^c in Aβ neurotoxicity remains controversial.

FcγRIIb and PirB

Recently, two immune receptors, FcγRIIb and PirB which were originally believed to function exclusively in the immune system, were shown to have neuropathic roles as Aβ receptors in AD brains [27, 28, 62]. Kam and Song et al. showed that FcγRIIb binds to oligomeric Aβ with high affinity ($K_d = 56.7$ nM) in vitro and in the brains of patients with AD. They also found that the expression of FcγRIIb is increased in the brains of AD mice and patients with AD and that FcγRIIb deficiency rescues Aβ-induced neurotoxicity, including cell death, decreased LTP, spine density, as well as memory impairment in AD mice (PDAPP J20). Inhibiting FcγRIIb–Aβ interaction using synthetic peptides also prevents Aβ-induced neurotoxicity in cultured neurons and memory impairment in the mice as assayed with intracerebroventricular-injection [27]. Similar to FcγRIIb, PirB deletion in mice suppresses the deleterious activity of Aβ oligomers on LTP and rescues impaired ocular dominance plasticity and behavioral deficits in AD mice (APP/PS1) [28].

Interestingly, these two proteins show similarity in their structure and in the binding affinity with Aβ oligomers. Both have immunoglobulin (Ig) domains on their extracellular regions and immunoreceptor tyrosine-based inhibitory motifs (ITIM) on their intracellular regions. FcγRIIb has two Ig domains and an ITIM, whereas PirB has six Ig domains and four ITIMs. FcγRIIb interacts with low-n oligomers via its second Ig domain and PirB binds to high-n oligomers via its first two Ig domains. Like FcγRIIb, PirB binds to Aβ with high affinity ($K_d = 110$ nM). One major difference between FcγRIIb and PirB is the requirement of ITIM in the neurotoxic signaling. While tyrosine phosphorylation in the ITIM of FcγRIIb mediates Aβ neurotoxicity, it is apparently not involved in Aβ signaling in the case of PirB. It will be interesting to examine this difference in ITIM to mediate the neurotoxicity.

Overall, we now require more detailed studies to clarify distinct roles and signaling of these Aβ receptors in Aβ neurotoxicity as well as their neuronal expression patterns. Unlike FcγRIIb and PrP^c that bind to Aβ low-n oligomers and high n-oligomers, respectively, other receptors have not been characterized for their binding preferences to those Aβ. The binding regions in the receptors as well as in Aβ have not been identified in most cases. In addition, a possibility for protein–protein interaction among those receptors that may function together in Aβ neurotoxicity or for the roles of those receptors in various cell types remains to be addressed.

Cellular defects in Aβ neurotoxicity

Endoplasmic reticulum stress response for Aβ toxicity

ER senses and responds to various changes in cellular circumstances to maintain the protein folding capacity through the unfolded protein response (UPR) [63]. The UPR is a cellular recovery system in response to ER stress and relieves ER overload. The UPR is composed of three main pathways induced by inositol requiring kinase 1 (IRE1), protein kinase R-like ER kinase (PERK), and activating transcription factor 6 (ATF6). Among the three arms of UPR, PERK phosphorylates eukaryotic translation initiation factor 2 subunit α (eIF2α) and this phosphorylation prevents recycling of the eIF2 complex to its active GTP-bound form [64], lowering overall protein translation and ER overload. On the other hand, prolonged activation of PERK elicits cell death by expressing C/EBP-homologous protein that inhibits the transcription of anti-apoptotic B cell lymphoma 2 (Bcl-2) [65]. Therefore, tight regulation of the PERK pathway is required for appropriate modulation of ER stress. The effect of the PERK pathway on AD pathogenesis is controversial. Administration of salubrinal, a selective inhibitor of protein phosphatase 1 that counteracts PERK by dephosphorylating eIF2α, is protective against Aβ neurotoxicity [66, 67]. On the contrary, forebrain-specific knockout of PERK in APP/PS1 AD mice recovers cognitive defects [68]. The latter study identified systematic aspects of the PERK pathway on protein translation, especially synaptic proteins, reflecting different patterns of UPR modulated by the duration of Aβ toxicity.

In AD, the ER in neurons is also burdened by other pathologic conditions, such as Ca^{2+} dysregulation. Because the function of ER chaperones is affected by ER Ca^{2+} level, disrupted ER Ca^{2+} triggers ER stress [69]. These features are connected to genetic factors of AD. For example, mutant PS1 upregulates ER ryanodine receptor 3 (RyR3), which mediates ER Ca^{2+}-induced Ca^{2+} release; mutant PS1-expressing PC12 cells and cortical neurons exhibit increased levels of RyR3 and concomitant enhanced responses to intracellular Ca^{2+} [70]. The increased expression of RyR3 is also seen in AD model mice harboring mutant PS1 [71]. Interestingly, the level of RyR3 is elevated in TgCRND8 mice containing no PS mutation but KM670/671NL and V717F mutant APP transgenes [72]. In addition, Aβ neurotoxicity is prevented by decreased expression of RyR3 through X-box binding protein 1 (XBP1), which undergoes alternative splicing by IRE1 during ER stress [73]. It is likely that PS and Aβ regulate the expression of RyR3 to affect ER stress responses. In addition to ER RyR3, inositol 1, 4, 5-tri-

phosphate receptor (IP3R) is also linked to ER Ca^{2+} release by Aβ [74].

Another factor involved in Aβ neurotoxicity and mediating ER stress is ER-resident caspase-12. Sustained ER stress over the capacity of UPR induces cell death independent of typical intrinsic cell death pathways. While ER stress as well as Aβ stimulates murine caspase-12, cell death-inducing stimuli usually do not. Primary neurons from caspase-12-knockout mice show resistance to Aβ neurotoxicity [75]. Mechanistically, proteolytic activation of caspase-12 is achieved by the Ca^{2+}-activated protease calpain and tumor necrosis factor-associated factor 2 under IRE1 [76, 77]. In response to Aβ-induced ER stress, E2-25K, an E2 conjugating enzyme in ubiquitin–proteasome system (UPS), activates calpain to process caspase-12 [78]. Unlike in rodents, however, caspase-12 in the human genome cannot be translated due to a frame-shift mutation and premature stop codon in the transcripts of all variants [79]. Interestingly, sequence comparison analysis among caspases illustrates that human caspase-4 is a homolog of murine caspase-12 with 57 % sequence identity. Consistently, human caspase-4 was shown to be involved in intracellular Aβ-induced neuronal cell death with ER stress [80]. Like caspase-12, human caspase-4 is activated by calpain through increased intracellular Ca^{2+} triggered by Aβ [78, 81]. It is now clear that the prolonged and aberrant ER stress response mediates Aβ neurotoxicity by triggering Ca^{2+} dysregulation and ER caspase activation.

The studies on Aβ receptors that induce neurotoxic ER stress, deregulation of Ca^{2+} flux, and ER-caspase activation have not been active yet, while these signals are strengthened by the interaction of Aβ with its receptors. Currently, limited information on the receptors is available. For Ca^{2+} dysregulation and ER stress, it was reported that Aβ oligomers induce plasma membrane localization of the GluN2B subunit of NMDAR and leads to Ca^{2+} dysregulation and neuronal death through activation of the ionotropic glutamate receptors [40]. Aβ oligomer also leads to clustered assembly of mGluR5 cluster, which is possibly mediated by interaction with PrP^c [56, 82]. In addition, FcγRIIb was recently shown to play an essential role in the activation of ER-resident caspase-12 during Aβ neurotoxicity [21].

Mitochondrial dysfunction

Mitochondria generate cellular energy in most cells, and in neurons, mitochondria use glucose sources almost exclusively. Interestingly, mitochondrial defects are found in the neurons of patients with AD and in many cases of Aβ-treated neural cells and AD mice, and the key enzymes involved in glucose metabolism and the respiratory chain in mitochondria are impaired. For example, the enzyme activities of pyruvate dehydrogenase and α-ketoglutaraldehyde dehydrogenase in the citric acid cycle and cytochrome C oxidase, and the expression of respiratory chain complexes I, IV, and V are all reduced [83–87]. However, it is uncertain what causes their reduction in the mitochondria of AD neurons. In addition, the expression of enzymes mediating antioxidant functions like catalase is also altered [88]. All these features are associated with metabolic abnormalities of mitochondria, impairing energy production frequently observed during AD pathogenesis.

The presynaptic terminal demands high levels of energy required for sustained neurotransmitter release [89] and requires well-organized Ca^{2+} regulation machinery for activity-dependent synaptic transmission [90]. To meet these challenges, neuronal mitochondria are moved to the synapse by anterograde axonal transport and build a synaptic mitochondrial pool [91]. Therefore, tight regulation of anterograde mitochondrial axonal transport is critical for adequate synaptic output as well. Consequently, dysfunction of axonal transport is coupled with many neurological disorders and Aβ often induces impairment of anterograde mitochondrial movement [92, 93]. While it is not much known, Aβ likely inhibits axonal transport through NMDA receptor and glycogen synthase kinase 3β (GSK3β) [94] and impairs cargo recognition of microtubules by phosphorylating kinesin light chain through casein kinase 2 [95]. Collectively, these studies delineate the role of Aβ in the failure of axonal delivery of mitochondria in AD pathogenesis.

Besides the impairment in metabolism and axonal transport, alteration in structural dynamics of mitochondria is also observed in AD. In most studies, Aβ shortens mitochondrial length and increases the amount of fragmented mitochondria by modulating the expression of mitochondrial fusion/fission-related proteins [96, 97]. In the brains of patients with AD, phosphorylation and S-nitrosylation of dynamin-related protein 1 (DRP1), which is a critical factor for mitochondrial fission, is increased, likely impacting mitochondrial structure [96, 98]. In addition, mortalin seems to function in Aβ-mediated mitochondrial fragmentation and dysfunction through DRP1 [99]. On the other hand, a recent report showed an opposite result that elongated mitochondria may contribute to neurodegeneration [100]; mislocalization of DRP1 triggered by tau-mediated F-actin stabilization leads to elongated mitochondria to promote neurodegeneration. This inconsistent effect of mitochondria dynamics on the neurotoxicity needs to be clarified. In addition, coupling of Aβ membrane receptors to mitochondrial damage remains to be addressed.

Intracellular Aβ and neurotoxicity

For a long time, extracellular Aβ generating neurotoxic signals through the aforementioned receptors has been blamed as the major cause of AD. However, a growing body of evidence suggests that intracellular accumulation of Aβ also has a potential role in AD pathogenesis. Aβ immunoreactivity was first observed inside neurons with the neurofibrillary tangles of both patients with AD and normal individuals [101]. Intracellular Aβ is widely detected in patients with mild cognitive impairment, AD [102] and down's syndrome [103]. The accumulation of intracellular Aβ precedes the formation of Aβ deposits and the development of pathologies in these diseases [104]. Consistently, accumulation of intracellular Aβ appears prior to neuronal degeneration and neurofibrillary tangle formation in AD mice, including APP/PS1 [105], 3xTg-AD [106], and 5xFAD [107]. Especially, age-related loss of synaptophysin-immunoreactive presynaptic boutons within the hippocampus occurs before extracellular Aβ deposits are observed in APP/PS1 mice [108]. In addition, intraneuronal accumulation of Aβ is also observed in 4-month-old 3xTg-AD mice which have no detectable Aβ plaques and hyperphosphorylated tau yet but are in the beginnings of cognitive deficits [109], implicating that accumulation of the intraneuronal Aβ is an early event in the progression of AD.

Receptors for Aβ internalization

Because APP localizes to several subcellular compartments, including ER, endosomes, and plasma membrane, Aβ could accumulate intracellularly after its production inside cells. However, it is known that most Aβ produced at the plasma membrane or secretory vesicles is secreted extracellulary [110]. Thus, it is reasonable to believe that the main source of the intracellular Aβ pool would result from internalization of the extracellular Aβ, though clear evidence for this is insufficient yet. As a possible way for the internalization of Aβ, it was shown that Aβ might directly interact with lipids, cholesterols, or proteoglycans in extracellular regions and that membrane-bound Aβ oligomers are recruited into lipid rafts by a fyn-dependent manner [11, 112, 113]. In addition, reduction of cellular cholesterol and sphingolipid levels decrease Aβ uptake [114]. More directly, treatment of lipid raft-dependent endocytosis inhibitor or inhibition of clathrin-dependent endocytosis decreases Aβ uptake [47, 115, 116]. Collectively, such direct interaction with lipid rafts and clathrin-mediated endocytosis may provide way(s) for Aβ uptake.

Alternatively, Aβ can actively be uptaken by Aβ-binding proteins, including α7 nAChRs, LRP1, and RAGE. Intracellular Aβ colocalizes with α7 nAChRs in AD brains and overexpression of α7 nAChR in neuroblastoma cells leads to intracellular accumulation of Aβ [47]. LRP1, a classic endocytosis receptor that uptakes extracellular ligands, also internalizes Aβ into cultured neurons [116] and AD mice [117]. Interestingly, LRP1 cooperates with PrP^c to internalize Aβ oligomers for cytotoxicity [118]. In addition, RAGE colocalizes with intraneuronal Aβ in the hippocampus of AD mice and RAGE-knockout neurons display reduced uptake of Aβ [119]. However, the route of Aβ uptake into neurons is still unresolved. While Aβ internalized by RAGE accumulates in mitochondria and thus induces mitochondrial dysfunction, Aβ internalized by other receptors, such as α7 nAChRs, localizes to endosomal or lysosomal compartments [47, 119, 120].

Moreover, whether the receptors responsible for Aβ uptake in neurons or non-neurons function for either Aβ neurotoxicity or clearance remains to be further clarified. For example, microglial Toll-like receptor (TLR) 2 and 4 are also known as potential Aβ receptors which directly interact with Aβ and mediate microglial activation [121, 122]. These interactions can lead to either neuronal death through TLR-mediated neuroinflammatory response or neuroprotection by clearing the intracellular Aβ after its uptake [123, 124]. Unlike neuronal Aβ receptors whose inhibition prevents neuronal uptake of Aβ and neurotoxicity, the destructive mutation of TLR4 in AD mice exhibits a decrease of Aβ uptake in microglia and an increase of Aβ deposits in brains, thus leading to cognitive dysfunction [125, 126]. In addition, similar function of TLR2 in Aβ phagocytosis is shown in TLR2-deficient AD mice which accelerate memory impairments with the increases of Aβ load [122, 127]. Thus, Aβ receptors found in different cell types display distinct functions in the progression of AD pathogenesis.

Cellular defects by intracellular Aβ

How the intraneuronal accumulation of Aβ causes neurotoxicity and AD neuropathology is largely unknown. Most studies indicate that intracellular Aβ leads to the malfunction of many intracellular organelles. The stable expression of human intracellular Aβ increases the number of Golgi apparatus elements, lysosomes, and lipofuscin bodies in the hippocampus of APP/PS1 double mutant transgenic rats [128]. Endosomal and lysosomal accumulation of Aβ leads to increase of lysosomal membrane permeability, resulting in the release of lysosomal proteases, especially cathepsins, to trigger neuronal cell death [129]. Mitochondria are another subcellular compartment for Aβ accumulation and neuronal dysfunction in AD [130, 131], as damaged and dysfunctional mitochondria are frequently observed in the AD brain. In particular, interactions between Aβ and mitochondrial resident

proteins, such as Aβ-binding alcohol dehydrogenase (ABAD) and cyclophilin D, were reported to mediate mitochondrial and neuronal stress exerted by Aβ [130, 131]. In addition, intraneuronal Aβ42 accumulates in multivesicular bodies (MVB) in transgenic mice and AD brains and thus impairs the MVB sorting pathway in AD [102, 132]. Intracellular Aβ is also observed in the nucleus and increases neuronal apoptosis [133]. Because of these compelling findings, it is now crucial to uncover the receptors driving Aβ internalization and the pathological significance of the internalized Aβ, in parallel to the intense study on Aβ receptors for neurotoxic signaling cascade.

Concluding remarks

Extracellular Aβ interacts with several recently identified receptors to transduce neurotoxicity in cultured neurons and AD mice. With recent advances in identifying those receptors, we now better understand the neurotoxicity of Aβ which elicits diverse cellular defects, including ER stress and damage to mitochondria. However, the connection of those receptor functions to the cellular defects, the signal selectivity and cell-type specificity of the receptors, and cooperative interactions among the receptors need more characterization. In addition, a role of intracellular Aβ in neurotoxicity and AD pathogenesis, which further complicates AD pathogenesis, remains ripe for investigation.

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Conflict of interest The authors declare that they have no conflict of interest.

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