Binding Sites for Amyloid-β Oligomers and Synaptic Toxicity

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Cold Spring Harbor Perspectives in Medicine
www.perspectivesinmedicine.org

In Alzheimer's disease (AD), insoluble and fibrillary amyloid-β (Aβ) peptide accumulates in plaques. However, soluble Aβ oligomers are most potent in creating synaptic dysfunction and loss. Therefore, receptors for Aβ oligomers are hypothesized to be the first step in a neuronal cascade leading to dementia. A number of cell-surface proteins have been described as Aβ binding proteins, and one or more are likely to mediate Aβ oligomer toxicity in AD. Cellular prion protein (PrP^C) is a high-affinity Aβ oligomer binding site, and a range of data delineates a signaling pathway leading from Aβ complexation with PrP^C to neuronal impairment. Further study of Aβ binding proteins will define the molecular basis of this crucial step in AD pathogenesis.

As of 2016, an estimated 5.4 million Americans suffer from Alzheimer's disease (AD). The incidence of AD in the U.S. population is expected to increase to 13.8 million by 2050 (Prince et al. 2014). Current therapeutics are palliative, and no disease-modifying agents are known. Neuropathological findings of extracellular insoluble plaques of amyloid β (Aβ) and intraneuronal neurofibrillary tangles (NFTs) are diagnostic of disease and are used to determine disease severity (Hyman et al. 2012). Although the accumulation of insoluble Aβ peptides into plaques that are deposited throughout the brain is a hallmark of disease, levels of soluble Aβ oligomers (Aβo) have been shown to better correlate with disease severity (Lue et al. 1999; McLean et al. 1999). Additionally, Aβo have been ascribed the neurotoxic properties that trigger AD pathophysiology (Lambert et al. 1998; Walsh et al. 2002; Lesné et al. 2006; Shankar et al. 2008). Aβo have been shown in several tests to potently inhibit hippocampal long-term potentiation (LTP), increase dendritic spine loss, and impair learning and spatial memory in mice (Walsh et al. 2002; Cleary et al. 2004; Lesné et al. 2006; Lacor et al. 2007).

Given the extracellular localization of Aβ, it has long been suspected that a receptor(s) for Aβ is present at neuronal synapses. In the context of the current understanding of the role of Aβo in AD, such a receptor might include the following characteristics: a high affinity for Aβo; selectivity for oligomers over monomers; the ability to transduce extracellular events into intracellular changes, either directly or via coupling with other molecules; and the ability to ablate symptoms of disease upon genetic or pharmacological inhibition.

Editor: Stanley B. Prusiner
Additional Perspectives on Prion Diseases available at www.perspectivesinmedicine.org

 doi: 10.1101/cshperspect.a024075
Cite this article as *Cold Spring Harb Perspect Med* 2017;7:a024075

As research into the molecular mechanisms of AD progresses, an increasing number of cell-surface proteins are being identified as binding sites and potential receptors for Aβ. Although binding of Aβ to each of the receptors has previously been shown, and in some cases quantified, there has not been a direct comparison of the receptors' relevance to disease.

The literature describes direct binding of Aβ to cellular prion protein (PrP^C); neuronal acetylcholinergic receptor subunit α7 (nAchRα7); receptor for advanced glycation endproducts (RAGE); low-affinity nerve growth factor receptor ($p75^{NTR}$); Nogo-66 receptor 1 (NgR1); Ephrin type-B receptor 2 (EphB2); Fcγ receptor IIb (FcγRIIb); Leukocyte immunoglobulin-like receptor; subfamily B2 (LilrB2); sortilin; and insulin receptor (IR) (Fig. 1) (Du Yan et al. 1996; Kuner et al. 1998; Wang et al. 2000; Xie et al. 2002; Park et al. 2006a; Zhao et al. 2008; Laurén et al. 2009; Cissé et al. 2011a; Carlo et al. 2013; Kam et al. 2013; Kim et al. 2013). Additional receptors have been described as potentially mediating the effects of Aβ on neurons without addressing the presence or absence of a direct interaction between the two proteins. These potential receptors include sortilin-related receptor (SorLA, SorL1), EphA4, EphA1, epidermal growth factor receptor (EGFR), and sigma-2 receptor (σ_2R)/progesterone receptor

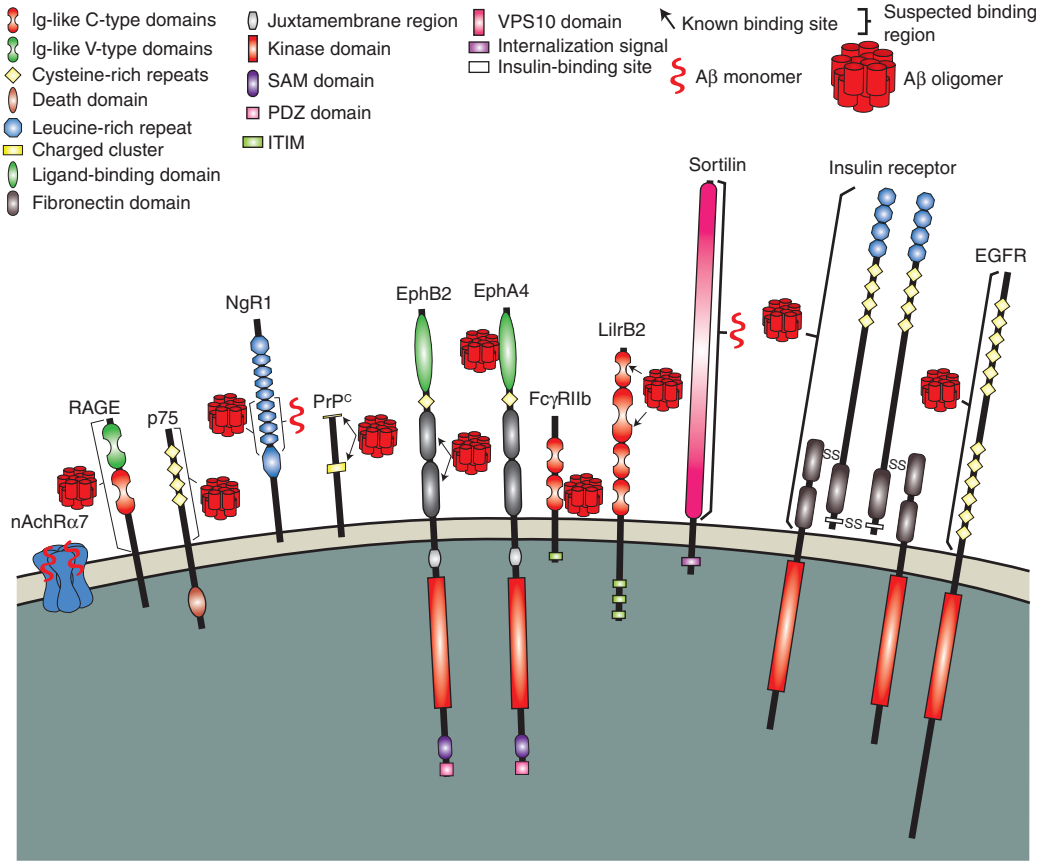

Figure 1. Putative receptors for Aβ, their binding sites, and species selectivity. Many cell-surface proteins have been reported to bind Aβ. Binding sites for Aβ monomers or oligomers are indicated with arrows when specific sites are known to mediate binding or with brackets when less information is available. Known domains of the proteins are also indicated. For details, see the text. SAM, Sterile α motif; VPS10, vacuolar protein sorting 10; ITIM, immunoreceptor tyrosine-based inhibitory motif; SS, disulfide bond; EGFR, epidermal growth factor receptor.

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membrane component 1 (PGRMC1) (Wang et al. 2012; Lambert et al. 2013a; Fu et al. 2014; Izzo et al. 2014a,b). Furthermore, much of the literature describing Aβ-receptor interactions has failed to characterize the physical nature of the Aβ species used, often not differentiating between monomers and oligomers. Further investigation into the nature of these interactions is needed to clarify the physiological relevance of various receptors for Aβ.

PrP^C AS A RECEPTOR FOR Aβo

PrP^C was identified as a high-affinity receptor for Aβo in an unbiased genome-wide screen of 225,000 cDNA clones from a mouse brain library (Laurén et al. 2009). In this screen, two independent clones encoding full-length mouse PrP^C ($mPrP^C$) were identified as capable of mediating binding of Aβo to cells. The affinity of Cos-7 cells transfected with $mPrP^C$ was identical to that of primary cultured hippocampal neurons, and $mPrP^C$ was shown to be highly selective for the oligomeric species of Aβ (Laurén et al. 2009). Direct binding of Aβ and PrP^C has been shown using co-immunoprecipitation of recombinant proteins in vitro, surface plasmon resonance (SPR), and immunocytochemistry (Laurén et al. 2009; Balducci et al. 2010; Um et al. 2012). PrP^C has been shown to be required for Aβo-induced inhibition of hippocampal LTP, loss of synapses and serotonergic axons, in vivo inhibition of LTP by human AD brain extract, and the early mortality phenotype observed in APPswe/Psen1ΔE9 (APP/PS1) transgenic mice (Laurén et al. 2009; Chung et al. 2010; Gimbel et al. 2010; Barry et al. 2011; Bate and Williams 2011; Freir et al. 2011; Resenberger et al. 2011; Kudo et al. 2012; Larson et al. 2012; Um et al. 2012, 2013; Fluharty et al. 2013; Ostapchenko et al. 2013; Rushworth et al. 2013; Dohler et al. 2014; Hu et al. 2014; Klyubin et al. 2014; Walsh et al. 2014). More critically, PrP^C is required for age-dependent memory dysfunction in APPswe/Psen1ΔE9 (Gimbel et al. 2010) and APPswe/Psen1M146L (Chung et al. 2010) AD model mice. However, certain forms of fibrillary Aβ (Aβf) inhibit LTP independent of PrP^C (Nicoll et al. 2013), and J20 mice do not require PrP^C for early-onset behavioral deficits (Cissé et al. 2011b).

PrP^C is a glycophosphatidylinositol (GPI) anchored protein localized to the postsynaptic density (PSD). To affect extracellular signals intracellularly, it was postulated that a transmembrane coreceptor for PrP^C exists. To identify this coreceptor, 61 transmembrane PSD proteins were screened for the ability to couple the exposure to Aβo with phosphorylation of Fyn, an event that does not occur in HEK293T cells but has been observed in the cortical neurons of mice (Um et al. 2013). mGluR5 was identified as capable of mediating phosphorylation of Fyn and several other biological responses to Aβo exposure, including induced calcium response, dendritic spine loss, and lactate dehydrogenase (LDH) release (Fig. 2) (Um et al. 2013). mGluR5 is a $G_{q/11}$-coupled G-protein-coupled receptor (GPCR). Its extracellular domain binds glutamate and modulates the responsiveness of NMDAR to glutamate. When mGluR5 binds extracellular glutamate, it activates phospholipase C, which leads to the cleavage of phosphatidylinositol 4,5-bisphosphate (PIP_2) into inositol 1,4,5-triphosphate (IP_3) and diacylglycerol (DAG). IP_3 binds IP_3 receptors on the smooth endoplasmic reticulum (ER), causing an increase in intracellular calcium. The increase in intracellular calcium couples with DAG to activate protein kinase C (PKC), leading to the phosphorylation of downstream targets of PKC (Conn and Pin 1997; Bruno et al. 2001). Intracellular calcium also binds calmodulin to activate Ca^{++}/calmodulin-dependent protein kinase II (CaMKII), which has been shown to participate in the hyperphosphorylation of tau observed in AD (Yamauchi 2005).

mGluR5 also couples extracellular Aβo with the intracellular nonreceptor tyrosine kinase Fyn in a PrP^C-dependent manner (Um et al. 2012, 2013). Aβo-PrP^C-mGluR5-Fyn signaling is responsible for a transient increase in NMDAR subunit 2B phosphorylation and surface localization that is succeeded by subunit dephosphorylation and NMDAR internalization (Um et al. 2012). Interestingly, Fyn activation and intracellular calcium release are independent processes. Pretreatment of cortical

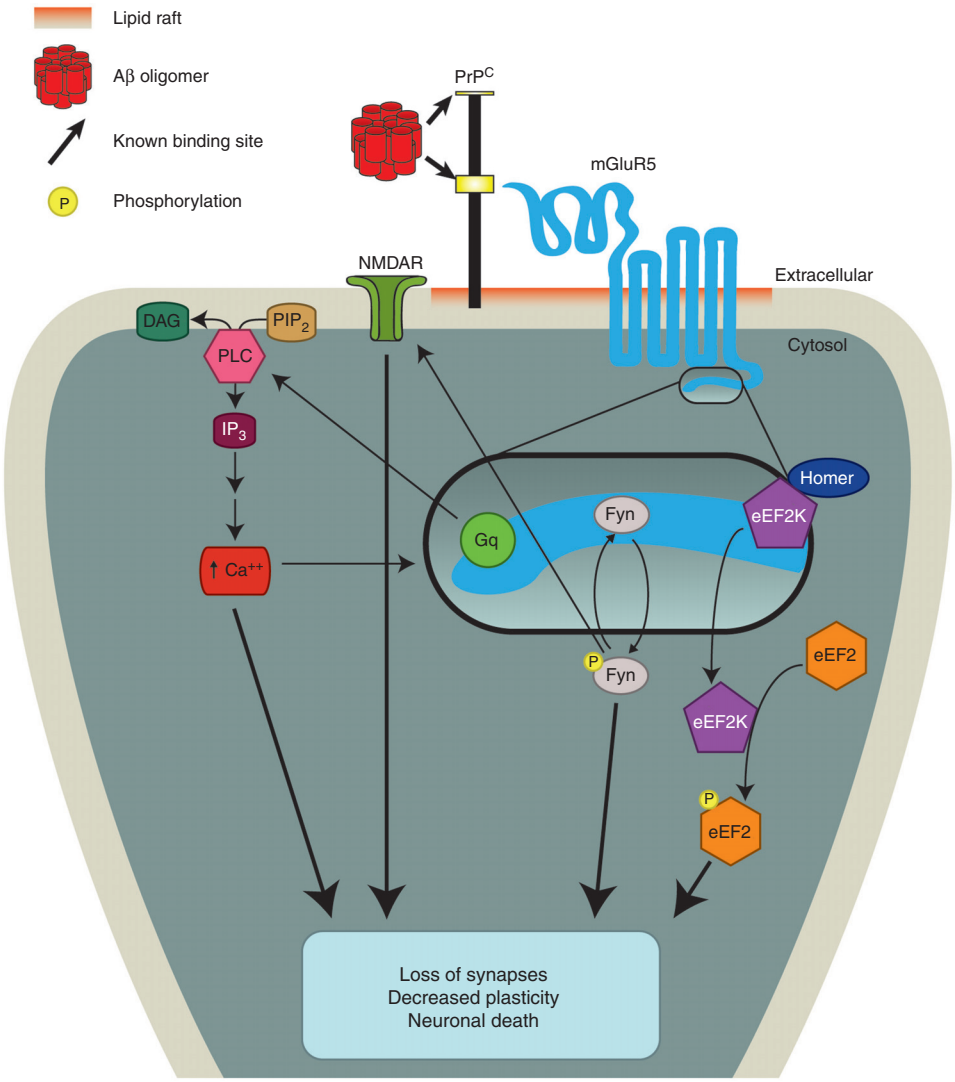

Figure 2. Intracellular consequences of Aβo binding to PrP^C. PrP^C and mGluR5 localize to lipid rafts (indicated in orange) in synapses. When Aβo bind PrP^C, signaling through mGluR5 causes increased intracellular calcium, increased phosphorylation of eEF2, changes in NMDAR activity and trafficking, and increased phosphorylation of Fyn. The net effect of these changes is a loss of synapses, decreased plasticity, and neuronal death. For details, see the text. (*Inset*) Expanded view of the C-terminal cytosolic domain of mGluR5. DAG, Diacylglycerol; PLC, phospholipase C; PIP_2, phosphatidylinositol 4,5-bisphosphate; IP_3, inositol triphosphate; Ca^{++}, calcium ion; NMDAR, *N*-methyl-D-aspartate receptor; eEF2K, eukaryotic elongation factor-2 kinase; eEF2, eukaryotic elongation factor-2.

neurons with thapsigargin reduced the calcium response induced by Aβo without affecting Fyn phosphorylation. Similarly, pretreatment with the Src family kinase inhibitor saracatinib inhibited the phosphorylation of Fyn without affecting the Aβo induced calcium response (Um et al. 2013). Investigation of the role of Fyn in Aβo signaling revealed that Fyn is required for the Aβo-induced desensitization of cortical neurons to NMDA, the internalization of NR2B subunits, LDH release, and dendritic spine loss (Um et al. 2012). Thus, PrP^C, mGluR5, and Fyn

mediate several of the Aβo-induced signs of AD (Fig. 2).

nAchRα7 BINDS Aβ TO SIGNAL THROUGH THE MAPK CASCADE

The characteristic loss of cholinergic neurons in the brains of AD patients has led to research investigating the role of cholinergic signaling in AD. nAchRα7 is a homomeric, ionotropic receptor for acetylcholine. Five α7 subunits assemble to form a ligand-gated ion channel that is unique among acetylcholine receptors for its high permeability to Ca^{++} (Hogg et al. 2003). Investigations into the interplay of cholinergic signaling and Aβ led to the proposal of nAchRα7 as a receptor for Aβ at the turn of the century (Wang et al. 2000). The same study also interrogated the affinity with which nAchRα7 binds Aβ using radiolabeled $Aβ_{1-42}$ ($Aβ_{42}$) in a competitive binding assay. Although unusual binding kinetics were observed for α7 antagonists methyllycaconitine (MLA) and α-bungarotoxin (α-BTX), the investigators observed binding kinetics indicative of two Aβ binding sites with affinities of 8 fM and 15 pM (Wang et al. 2000). It appears that these results were obtained using monomeric $Aβ_{42}$ and that oligomerization was not tested. When nAchRα7 was immunopurified from nAchRα7-expressing SK-N-MC cells, incubated with $Aβ_{42}$, and analyzed on western blot using antibodies against nAchRα7, a doublet band appeared. One band at ~52 kDa represented the nAchRα7 receptor. The second band at ~57 kDa appeared to represent $Aβ_{42}$-bound nAchRα7. The same ~57 kDa band was also present when the membrane was probed with an antibody against Aβ. The 5-kDa shift and $Aβ_{42}$ immunoreactivity of the 57-kDa band appears to represent the binding of a single $Aβ_{42}$ monomer to the receptor (Wang et al. 2000). Further binding studies from other groups have not been reported.

Additional work has linked nAchRα7 and intracellular signaling with Aβ binding to neurons. Rat hippocampal slices incubated with $Aβ_{42}$ showed increased phospho-ERK2, similar to slices incubated with nicotine (Dineley et al. 2001). Treating slices with $Aβ_{42}$ can desensitize nAchRα7, as showed by a lack of ERK2 activation in response to nicotine treatment following a 2-h incubation time with $Aβ_{42}$. Increased phospho-ERK2 in response to $Aβ_{42}$ or nicotine is also blocked by the nAchRα7 antagonist MLA, showing that activation of ERK2 is dependent on receptor activation (Dineley et al. 2001). Activation of ERK2 by $Aβ_{42}$ was also shown to be dependent on extracellular calcium (Dineley et al. 2001). Chronic activation of nAchRα7 causes upregulation of the receptor (Marks et al. 1983; Fenster et al. 1999). Similarly, there is an age-dependent increase in receptor level in the CA1 and dentate gyrus (DG) of Tg2576 transgenic AD-model mice. A negative correlation was described between the animals' performance in the Morris water maze probe trial and the amount of brain nAchRα7 (Dineley et al. 2001). In summation, it appears that $Aβ_{42}$ is capable of engaging nAchRα7 and stimulating receptor-dependent signaling through the MAPK pathway, although the specificity of the interaction for AD-specific conformations of Aβ is unclear.

RAGE AND Aβ

RAGE was first identified by its ability to bind glycated proteins. Soon thereafter, neuronally expressed RAGE was shown to bind the neurite growth-promoting protein p30/amphoterin (Neeper et al. 1992; Schmidt et al. 1992; Hori et al. 1995). The latter discovery implicates RAGE in neuronal plasticity with the potential for aberrant receptor activity to adversely affect neuronal health. The increased binding of Aβ to vasculature in AD brains and the high-affinity binding of Aβ to endothelial cells suggest that an endothelial receptor for Aβ exists (Du Yan et al. 1996). Interestingly, the affinity of cultured endothelial cells and cultured rat cortical neurons for Aβ was found to be similar: 40 ± 9.8 nM and 55.2 ± 14.6 nM, respectively (Du Yan et al. 1996). The investigators speculated that the same protein might mediate Aβ binding in both cell types. Using extracts of bovine lung tissue rich in endothelial cells and ^{125}I labeled Aβ, RAGE was identified as the receptor

responsible for Aβ binding to endothelial cells. Additional binding studies showed that binding of ^{125}I labeled Aβ to RAGE was inhibited by the addition of human AD brain extract, an antibody targeting RAGE, and soluble RAGE (sRAGE) comprised of the extracellular and transmembrane domains (Du Yan et al. 1996). RAGE was also shown to mediate the transport of Aβ across the blood–brain barrier (BBB) (Deane et al. 2003). When wild-type (WT) mice were peripherally infused with ^{125}I labeled Aβ, uptake into the brain was eliminated in RAGE knockout (KO) animals and inhibited by co-infusion of sRAGE. Strikingly, daily peripheral administration of sRAGE to the J20 mouse model of AD from 6 to 9 mo of age resulted in a 78% decrease in total brain Aβ and a 72% decrease in $A\beta_{42}$ compared with non-treated transgenic controls (Deane et al. 2003).

RAGE was shown to be essential for several physiological consequences of Aβ infusion, including decreased cerebral blood flow and increased expression of the stress/inflammation markers tumor necrosis factor α (TNF-α), interleukin 6 (IL-6), and heme oxygenase 1 (HO1) (Deane et al. 2003). To further investigate the effects of RAGE on the aspects of AD recapitulated in transgenic mouse models of the disease, hAPP transgenic AD model mice were crossed with mice overexpressing either RAGE or a dominant negative RAGE (DN-RAGE) that lacked the cytosolic domain (Deane et al. 2003). Transgenic hAPP animals overexpressing RAGE but not DN-RAGE showed both earlier onset and increased severity of AD pathology, including increased astrocytosis and microgliosis, increased nuclear translocation of nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB), and decreased acetylcholinesterase activity and synaptophysin staining in the hippocampus. In the radial-arm water maze, double-transgenic mice overexpressing functional RAGE showed a deficit at 3–4 mo of age, whereas both hAPP single-transgenic and hAPP/DN-RAGE mice showed no deficit until 5–6 mo. At 5–6 mo of age, all hAPP genotypes had memory and spatial learning deficits; however, the hAPP/RAGE animals performed the worst, and the hAPP/DN-RAGE animals made significantly fewer errors than hAPP single-transgenic and hAPP/RAGE double-transgenic animals. Several intracellular consequences of RAGE overexpression were identified in hAPP/RAGE animals at 3 mo of age. Protein extracts from the hippocampi of these animals showed increased activation of p38, ERK1/2, and cAMP response element-binding protein (CREB). In addition, CaMKII activity was increased in the hippocampi of double-transgenic mice 14- to 16-mo-old but not in hAPP or hAPP/DN-RAGE animals. In another study of APP transgenic mice, the absence of RAGE slowed but did not prevent the accumulation of Aβ plaque and failed to rescue behavioral deficits (Vodopivec et al. 2009). Currently available data describe a role for RAGE in which the receptor interacts with Aβ with physiological consequences as well as describes a mechanism by which RAGE facilitates or enhances the effects of AD transgenes in mice. A clinical trial was completed for a small-molecule inhibitor of the RAGE-Aβ interaction (Galasko et al. 2014). Interim analysis determined that the results met the criteria for futility, and treatment was discontinued. There was evidence that low-dose therapy may have had some benefit.

p75^{NTR} MEDIATES CELLULAR TOXICITY OF Aβ

p75^{NTR} is a cell-surface transmembrane protein that contains an extracellular nerve growth factor (NGF) binding domain and a cytoplasmic death domain. NGF binds to p75^{NTR} with context-dependent effects on cell proliferation (Rabizadeh et al. 1994; Frade et al. 1996). Alternatively, Aβ binding to p75^{NTR} consistently produces negative effects on cell viability. Interestingly, the expression of p75^{NTR} has been found to be threefold higher in the brains of AD patients and is particularly enriched in the cholinergic neurons of the nucleus basalis, a part of the brain particularly susceptible to neurodegeneration (Woolf et al. 1989; Mufson and Kordower 1992). Multiple investigations have shown that ^{125}I-labeled Aβ physically interacts with p75^{NTR} by use of co-immunoprecipitation from immortalized cell lines, primary cultured

neurons, and transfected cell lines (Yaar et al. 1997; Kuner et al. 1998). Binding of ^{125}I Aβ to p75^{NTR} was inhibited by incubation of cells with NGF or nonlabeled Aβ (Yaar et al. 1997; Kuner et al. 1998). Reports of the affinity of this interaction are all in the low nanomolar range (Yaar et al. 1997; Kuner et al. 1998). An approximately twofold higher affinity of p75^{NTR} for monomeric Aβ compared with what the authors call an aggregated preparation was observed (13 nM and 23 nM, respectively) (Yaar et al. 1997). Aβ binding to p75^{NTR} leads to NF-κB nuclear translocation and subsequent degradation of DNA via a pathway that is dependent on NF-κB (Kuner et al. 1998). Aβ exposure also resulted in decreased cell counts in cultures of PC12 and fibroblast cells expressing p75^{NTR} but not in those lacking the receptor (Rabizadeh et al. 1994; Yaar et al. 1997).

NgR1 BINDS AMYLOID PRECURSOR PROTEIN (APP) AND Aβ AND REGULATES α- AND β-SECRETASE PROCESSING OF APP

A pathological feature of AD is the presence of neuritic plaques. At the periphery of these plaques, neurites are described as dystrophic and feature tortuous neurites harboring increased amounts of synaptophysin (Lombardo et al. 2003). These dystrophic neurites may be the result of the dysregulation of neurite sprouting, a process regulated in part by NgR1 (Chen et al. 2000; GrandPre et al. 2000; Prinjha et al. 2000; Fournier et al. 2001). NgR1 and APP colocalize on the surface of Cos-7 cells overexpressing both proteins as well as in primary culture of dorsal root ganglia expressing endogenous levels of the proteins. Furthermore, the two cell-surface proteins show a physical association, as they co-immunoprecipitate from transfected cell lines and both rat brain homogenate and membranes treated with a crosslinking agent. NgR1 staining of human brain sections revealed that in patients with AD, NgR1 is enriched in the vicinity of Aβ plaques (Park et al. 2006a). Accordingly, in vitro binding studies using cell culture, as well as those using purified proteins, show that NgR1 binds Aβ monomers and oligomers with an affinity of ∼60 nM (Park et al. 2006a).

The intracerebroventricular infusion of NgR(310)ecto-Fc in APP/PS1 transgenic mice reduced total brain Aβ, Aβ plaque burden, and the number of dystrophic neurites (Park et al. 2006a). Expectedly, genetic deletion of NgR1 in APP/PS1 mice resulted in worsening of the pathology: increased total brain Aβ, increased Aβ plaque burden, and increased dystrophic neurites (Park et al. 2006a). Peripheral treatment of APP/PS1 transgenic mice with the soluble ectodomain of NgR1 (NgR(310)ecto-Fc) also altered the clearance of Aβ. Treatment resulted in a reduction of total brain $Aβ_{40}$ and $Aβ_{42}$, and of plaque Aβ to ∼50% of nontreated transgenic mice (Park et al. 2006b). The number of dystrophic neurites detected and the degree of astrogliosis were also decreased in treated transgenic mice (Park et al. 2006b). The effects of NgR(310)ecto-Fc treatment had functional consequences as well. Treatment halted the progression of a learning deficit in APP/PS1 animals as measured by the radial-arm water maze. Importantly, treated animals began to show improvement in learning, whereas the performance of nontreated control animals continued to decline (Park et al. 2006b). The data show that NgR1 levels modify the metabolism of APP and Aβ, and that there is a functional benefit from NgR(310)ecto-Fc administration.

Eph RECEPTORS AND Aβ

The receptor tyrosine kinase EphB2 regulates surface levels of NMDA receptor via Src family kinases and the phosphorylation state of NMDA receptor subunits. Examination of brains from AD patients has revealed decreased hippocampal expression of NMDA receptor subunits (Ikonomovic et al. 1999). EphB2 is also diminished in the hippocampi of AD patients (Simón et al. 2009). Furthermore, exposure of primary neurons to Aβo resulted in decreased expression of EphB2 (Cissé et al. 2011a). Investigation into the relationship between Aβo, EphB2, and NMDA receptor subunit expression led to the discovery that Aβo directly bind the fibronectin repeats of the extracellular domain of EphB2 (Cissé et al. 2011a). The two proteins co-immunoprecipitated from cell-free

systems as well as homogenates of primary neurons (Cissé et al. 2011a). The dissociation constant (K_D) for this interaction was not reported. Hippocampal LTP is depressed in hAPP transgenic mice. However, when a lentiviral vector expressing EphB2 was injected into the hippocampi of hAPP mice, LTP was restored to that of wild type. The same treatment also rescued behavioral deficits in the Morris water maze, novel object/place recognition, and passive avoidance tests (Cissé et al. 2011a).

EphA4 binding to ephrin A4 leads to receptor activation and autophosphorylation at tyrosine 602 (Fu et al. 2014). This activation leads to cyclin-dependent kinase 5 (CDK5)-dependent RhoA activation and consequent dendritic spine retraction (Fu et al. 2006; Bourgin et al. 2007; Richter et al. 2007). EphA4 has also been found to be dysregulated in the hippocampi of human AD patients as well as AD model mice (Simón et al. 2009; Fu et al. 2014). EphA4 was shown to bind Aβ in a cell-free pull-down assay. Furthermore, treatment of WT hippocampal slices exposed to Aβ with Fc-EphA4 or a peptide inhibitor of the EphA4 ligand-binding domain, KYL, restored synaptic activity to normal. The same effect was seen for hippocampal slices from APP/PS1 mice treated with either KYL or lentiviral shRNA against EphA4, injected into the CA1 region (Fu et al. 2014).

A third Eph receptor family member, EphA1, has repeatedly been identified by genome-wide association studies (GWAS) as a potential risk-modifying locus for AD (Hollingworth et al. 2011; Naj et al. 2011; Lambert et al. 2013a). No additional information regarding the ability of this receptor to mediate the effects of Aβ is available.

FCγRIIb AND Aβo

FcγRIIb is predominantly expressed in B cells, macrophages, and neutrophils, wherein the binding of antigen-bound IgG complexes transduces an inhibitory signal resulting in inhibition of the B-cell-mediated immune response (Wu et al. 2009; Wu et al. 2013). This negative feedback mechanism has been implicated in preventing autoimmune responses. Accordingly, FcγRIIb KO mice show autoimmune disorders (Takai et al. 1996; Bolland and Ravetch 2000; Katz 2002; Pritchard and Smith 2003). FcγRIIb and its family members are also known to be expressed in the nervous system on non-immune cells, and further investigation of their function is needed (Nakamura et al. 2007).

Co-immunoprecipitation experiments using cell lysates, human AD brain extract, and recombinant proteins each showed that FcγRIIb physically interacts with Aβo. Additionally, the dissociation constant for the binding of synthetic Aβo to recombinant FcγRIIb ectodomain was measured at 56 nM monomer equivalents (Kam et al. 2013). Aβo-induced neuronal death, decreased synaptophysin staining, and decreased dendritic spine density in primary hippocampal neurons were each rescued by either FcγRIIb KO, incubation with soluble FcγRIIb ectodomain, or overexpression of the FcγRIIb I232T loss-of-function mutant (Kam et al. 2013). When neurons were exposed to Aβo, there was an FcγRIIb-dependent increase in c-Jun N-terminal kinase (JNK) activity, which resulted in activation of c-Jun (Kam et al. 2013). Interestingly, the expression of FcγRIIb promoter-driven luciferase was also increased by Aβo exposure. The JNK inhibitor SP6000125 prevented Aβo-induced increase in luciferase expression as well as increased expression of FcγRIIb in the neuroblastoma-derived SH-SY5Y cell line. Inhibition of JNK also prevented Aβo-induced cell death in cultures of primary hippocampal neurons (Kam et al. 2013). Furthermore, loss of FcγRIIb prevented the upregulation of the ER stress markers 78 kDa glucose-regulated protein (GRP-78) and CCAAT/enhancer-binding protein (C/EBP) homologous protein (CHOP) in response to Aβo (Kam et al. 2013). Pretreatment of immortalized hippocampal neurons (HT22) with the selective eIF2α inhibitor salubrinal abrogated cell death in response to Aβo treatment (Kam et al. 2013). Transgenic AD model mice as well as WT mice injected intracerebroventricularly with synthetic Aβo showed inhibition of LTP. In both contexts, loss of FcγRIIb prevented LTP depression. Additionally, investigation into memory recall and learning in the same models

showed that FcγRIIb KO animals performed the same as WT controls in the Y-maze, novel object recognition, and passive avoidance tests (Kam et al. 2013). These data indicate that Aβo binds FcγRIIb and activates intracellular signaling cascades. Furthermore, the physiological consequences of this interaction correspond to some of the phenotypes of human AD.

LilrB2 BINDS HIGH-*N* Aβo

LilrB2 is a transmembrane receptor for major histocompatibility complex (MHC) class 1 molecules on antigen-presenting cells. LilrB2 is found on immune cells, and when engaged with an MHC class 1 molecule, transduces an inhibitory signal that prevents an immune response. This activity is implicated in limiting autoreactivity, as MHC class 1 molecules often present epitopes from normal intracellular proteins, which should not elicit an immune response (Pruitt et al. 2014). The murine ortholog of this gene is the paired immunoglobulin-like type 2 receptor B (PirB). In addition to MHC ligands, PirB expressed in neurons can interact with myelin inhibitor proteins and can regulate synaptic plasticity (Syken et al. 2006; Atwal et al. 2008; Huebner et al. 2011; Bochner et al. 2014).

Based on the role of PirB in brain plasticity, a physical interaction between LilrB2 and Aβo was assessed and shown to occur by co-immunoprecipitation and immunocytochemistry (Kim et al. 2013). Using an alkaline phosphatase assay, the K_D of Aβo binding to LilrB2 transfected HEK293 cells was measured as 250 nM monomer equivalents (~1 nM oligomer) (Kim et al. 2013). Minimal binding of monomeric Aβ was observed. The same group mapped the Aβo binding site(s) using deletion mutants. Deletion of the two N-terminal immunoglobulin (Ig) domains of LilrB2 nearly abrogated binding, whereas absence of the two most C-terminal domains did not affect binding. Thus, the two most N-terminal Ig domains of LilrB2 and PirB are necessary and sufficient for Aβo binding. When investigating the functional role of LilrB2 in AD models, the murine ortholog PirB was the focus of investigation. Genetic deletion of PirB restored LTP in the striatum radiatum that was lost in WT hippocampal slices exposed to Aβo (200 nM monomer equivalent). It was also discovered that the actin depolymerizing factor cofillin is activated in brains of APP/PS1 mice as well as in WT cortical neurons treated with Aβo. Neither of these effects was observed in the absence of PirB (Kim et al. 2013). Activation of cofillin is mediated by protein phosphatase 2A (PP2A) and calcineurin via dephosphorylation of cofillin at serine 3 (Meberg et al. 1998; Oleinik et al. 2010). Cofillin, PP2A, and calcineurin have previously been shown to connect Aβo exposure with dendritic spine loss and thereby implicate Aβo-LilrB2/PirB signaling with another hallmark of AD (Shankar et al. 2007; Li et al. 2009).

SorLA

SorLA (SorL1) was first implicated in AD following a microarray screen of lymphoblasts derived from 14 patients with probable or definite AD. The screen was done in two cohorts, and it was found that the expression of SorLA decreased 1.8- and 2.5-fold in the Alzheimer's populations compared with controls, respectively. Protein changes were confirmed by immunohistology (Scherzer et al. 2004). More recently, GWAS has implicated SorLA (SorL1) in AD risk (Lambert et al. 2013b).

The primary function of SorLA lies in trafficking APP through the endocytic and secretory pathways (Lane et al. 2012). Accordingly, the majority of SorLA expressed in cells is localized to endosomes and the trans-Golgi network (TGN). Less than 10% of total SorLA is found at the plasma membrane (Jacobsen et al. 2001; Offe et al. 2006). β-secretase also localizes to endosomes. These organelles harbor the same acidic environment that has been shown as necessary for amyloidogenic processing of APP (Vassar et al. 1999; Huse et al. 2000). Thus, SorLA appears to shuttle APP to the site of β-secretase cleavage. The exact mechanism by which inhibition or loss of SorLA function contributes to AD is not yet well defined. The back-and-forth trafficking of APP and its metabolites between endosomal compartments and the TGN may serve to sequester Aβ within cells.

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Furthermore, the interaction between SorLA and APP appears to inhibit cleavage of APP by β-secretase (Spoelgen et al. 2006; Willnow and Andersen 2013). Impairment or loss of SorLA function in either of the described roles would be expected to increase the secretion of Aβ. Accordingly, genetic deletion of SorLA in mice results in a dramatic increase in Aβ (Andersen et al. 2005, 2006; Rohe et al. 2008). There is currently no evidence to suggest that SorLA interacts with Aβo to mediate their toxic effect on neurons. However, it does appear that SorLA plays an intimate role in the generation of Aβ and its delivery to the extracellular space.

SORTILIN

Sortilin is a type 1 transmembrane protein with structural similarity to SorLA and is also a member of the vacuolar protein sorting 10 protein (VPS10P) domain receptors. Sortilin acts as a receptor for both pro-nerve growth factor (pro-NGF) and pro-brain-derived neurotrophic factor (pro-BDNF) and functions in the cell-death-inducing signaling of these molecules (Nykjaer et al. 2004). In the case of pro-NGF, sortilin is an essential co-receptor and pairs with $p75^{NTR}$ to mediate the cell-death signal (Nykjaer et al. 2004). Sortilin is also the major neuronal binding site for extracellular progranulin, implicated in frontotemporal lobar degeneration (Hu et al. 2010). Recently, sortilin has been shown to be critically important to the clearance of Aβ from the extracellular space via uptake by neurons (Carlo et al. 2013). Interestingly, apolipoprotein E (ApoE) was shown to be crucial to sortilin-mediated Aβ clearance. However, ApoE-independent, direct binding of $Aβ_{40}$ to sortilin was also observed using SPR. The apparent K_D of this interaction was measured to be 800 nM monomer equivalents (Carlo et al. 2013). A physical interaction between sortilin and $Aβ_{40}$ is apparent, although functional information is lacking. The paper that examines the direct interaction using SPR does not distinguish monomer from oligomer Aβ, and $Aβ_{42}$ was not reported. Further investigation of the functional role of this interaction in AD is necessary.

NEURONAL INSULIN RECEPTOR

The appearance of central nervous system insulin resistance and decreased glucose metabolism are early signs in the course of AD. Investigation into a possible interaction between the insulin receptor (IR) and Aβ revealed that 20 μM (monomer equivalents) $Aβ_{40}$ or $Aβ_{42}$, but not the reverse peptide, was capable of displacing insulin binding to IR. However, the inhibitory constants for $Aβ_{40}$ and $Aβ_{42}$ were reported as ~25 and 8 μM, respectively, which calls the physiological relevance of this inhibition into question (Xie et al. 2002). Importantly, the same group showed that co-incubation of affinity-purified IR with 50 μM $Aβ_{40}$ significantly inhibited autophosphorylation of IR (Xie et al. 2002). A separate group went on to show that this inhibition is dependent on NMDA receptor activity (Zhao et al. 2008). It was also found that phosphorylation of Akt serine 473, an important step in negative feedback on IR, was increased on exposure to Aβ (Zhao et al. 2008). A critical observation is that despite the ability of biotin-Aβ to immunoprecipitate IR from hippocampal neurons and vice versa, not all IR-expressing cells exposed to Aβ showed binding of Aβ when examined by fluorescence immunocytochemistry (Zhao et al. 2008). These observations suggest a potential co-receptor or receptor complex that is differentially expressed in neurons (Zhao et al. 2008). Despite significant evidence in support of an interaction between Aβ, IR, and downstream signaling, the nature and function of the interaction remains unclear.

EGFR

The evidence for EGFR's role in AD comes from a study in which a synergistic impairment of learning and memory was observed in *Drosophila melanogaster* co-overexpressing Aβ42 and EGFR (Wang et al. 2012). Interestingly, treatment of APP/PS1 mice with the EGFR inhibitor gefitinib rescued deficits in escape latency and time in target quadrant in the Morris water maze test (Wang et al. 2012). Additionally, $Aβ_{42}$ was detectable in samples immunoprecipitated with anti-EGFR from Cos-7 cells

transfected with both EGFR and $A\beta_{42}$ (Wang et al. 2012). Although these findings are interesting, a key question that remains unanswered is whether the aberrant regulation of EGFR is a cause or consequence of disease.

σ_2R/PGRMC1

Exposure of primary neurons to Aβo results in increased exocytosis (Liu and Schubert 1997). By functionalizing this observation in a screening system, Izzo et al. (2014a) identified several molecules capable of preventing Aβo binding to neurons. These same compounds showed high affinity and selectivity for the σ_2R/PGRMC1 receptor in a counter-screen of 100 receptors and enzymes expressed in the CNS (Izzo et al. 2014b). Furthermore, the compounds inhibited the binding of receptor-selective ligands (Izzo et al. 2014b). Based on this information, the authors concluded that σ_2R/PGRMC1 is a direct physical interactor for Aβo (Izzo et al. 2014a,b). Surprisingly, a 28% knockdown of σ_2R/PGRMC1 resulted in a 91% decrease in Aβo binding (Izzo et al. 2014b). To probe the role of σ_2R/PGRMC1 in AD model phenotypes, APPswe/Ldn mice were treated with Aβo-σ_2R/PGRMC1 antagonists, and memory was assessed. Following 6 weeks of treatment, transgenic mice displayed improved performance in the Morris water maze probe trial (Izzo et al. 2014a). Although the presently available data describe σ_2R/PGRMC1 as a mediator of some AD mouse phenotypes, distinction between the protein's role as a direct Aβo receptor versus an indirect regulator of other binding sites requires further investigation. Study of σ_2R/PGRMC1 null mice crossed with AD model mice will provide additional critical information.

EVALUATING PATHOPHYSIOLOGICAL ROLES OF DIFFERENT Aβo BINDING SITES

Among the growing number of putative receptors for Aβ, the quality of evidence supporting each is highly variable (Tables 1 and 2). The most complete functional dataset exists for PrP^C as an Aβo receptor that mediates synaptic damage (Table 2). Although it seems unlikely that any single receptor would be responsible for all of the intracellular effects of extracellular Aβ, it is important to critically evaluate the physiological relevance of any interaction with Aβ.

Aβ SPECIES SPECIFICITY

Aβo are now widely held to be the toxic species responsible for AD pathology (Klein et al. 2001; Haass and Selkoe 2007). In contrast to oligomers, the concentration of monomeric species in the cerebrospinal fluid decreases at the onset and progression of disease (Motter et al. 1995; Strozyk et al. 2003). Given this understanding, a protein that is suggested to act as a receptor for Aβ in neuronal disease manifestations should be highly selective for Aβo over monomers. If a putative receptor does not discriminate between oligomeric and monomeric species, it becomes difficult to explain why the severity of disease correlates with oligomers and why there is no phenotype in healthy adults continually exposed to monomeric Aβ for decades. At the very least, a receptor that does not discriminate between oligomers and monomers would need to be shown to engage augmented signaling cascades in an Aβ-conformation-specific manner.

The literature describes many different oligomeric assemblies that appear to consist of anywhere from 2 to >100 Aβ monomers per oligomer (Yaar et al. 1997; Lesné et al. 2006; Laurén et al. 2009; Cissé et al. 2011a; Kam et al. 2013). Although definitive structural information about Aβo from diseased brain is lacking, it is expected that the various oligomeric assemblies generate unique structural features, each capable of unique and discriminating interactions with putative receptors. This prediction would lead to the expectation that each receptor selectively interacts with a specific subset of the Aβ pool. When *Prnp* is deleted, there is a 50% reduction in the binding of synthetic Aβo to mouse hippocampal neurons (Laurén et al. 2009). Further, it has been shown that PrP^C is capable of binding 50% of the Aβo present in human AD brain extracts (Kostylev et al. 2015). The finding that only half of Aβo binding to neurons is lost in $Prnp^{-/-}$ neurons could be explained by two mechanisms: PrP^C may com-

Table 1. Characteristics of reported receptors for Aβ

Receptor	Impetus for investigation	Estimated affinity for monomers	Estimated affinity for oligomers	Evidence for interaction
PrP^C	Unbiased screen	>1000 nM monomer	50–100 nM monomer	CoIP, SPR, ICC
nAchRα7	Expressed in brain regions susceptible to degeneration, has a role in calcium homeostasis	8 fM, 16 pM monomer	Unknown	RLBA, CoIP, IHC
RAGE	Aβ binding to endothelial cells	50 nM monomer	Unknown	RLBA
$p75^{NTR}$	Increased expression in neurons disposed to neurodegeneration	13 nM monomer	23 nM monomer	CoIP
NgR1	Plasticity changes in neuritic plaques	60 nM monomer	60 nM monomer	ICC
EphB2	Decreased expression in the hippocampus of human AD brain	Unknown	Present, not measured	CoIP
EphA4	Role in dendritic spine retraction	Unknown	Present, not measured	CoIP
FcγRIIb	Upregulated in microarray of Aβ-treated cortical neurons	Unknown	57 nM monomer	CoIP, ICC, SPR
LilrB2	Ocular dominance plasticity	Minimal	250 nM monomer	CoIP, ICC
Sortilin	Sequence similarity to SorLA	800 nM monomer	Unknown	SPR
IR	Altered cerebral glucose metabolism	Unknown	8 μM monomer	RLBA, CoIP
EGFR	Behavioral screen	Unknown	Present, not measured	CoIP
σ_2R/PGRMC1	Screen for compounds capable of correcting the increased exocytosis induced by exposure to Aβ	Unknown	Unknown	ICC

CoIP, Co-immunoprecipitation; SPR, surface plasmon resonance; ICC, immunocytochemistry; IHC, immunohistochemistry; RLBA, radioligand binding assay.

pete with other receptors for free Aβo and thereby additional receptors titrate Aβ away from PrP^C and/or PrP^C interacts with a specific population of PrP^C-interacting Aβ. Although some putative receptors have shown selective binding to oligomers, as shown in Table 1, others show no selectivity, and for many, the question remains unanswered.

FUNCTIONAL EFFECTS OF RECEPTOR ENGAGEMENT

In the course of characterizing a cell-surface protein as a receptor for the disease-causing ligand, it is important to investigate and describe the downstream consequences of Aβo exposure. Given the large number of putative receptors, it is important to show that the protein of interest is specifically responsible for these effects. The most rigorous method for such a demonstration is to show the absence of response in models lacking the receptor of interest. A less stringent method would be to use receptor-specific ligands capable of preventing or disrupting binding of Aβo to neurons. Table 2 summarizes the evidence for each reported receptor's role in mediating the toxic effects of Aβ. The quality of data ascribing a pathological role to each receptor is variable; however, data for PrP^C, FcγRIIb, and LilrB2 include the rescue of synapse loss and neuronal plasticity when the genes encoding these receptors are disrupted. Furthermore,

Table 2. Functional roles of putative Aβ receptors

Receptor	Knockout or knockdown decreases Aβ binding to neurons?	Knockout or knockdown rescues synapse loss?	Knockout or knockdown restores plasticity?	Knockout or knockdown rescues memory/learning deficits?
PrP^C	Yes	Yes	Yes	Yes
nAchRα7	Unknown	Unknown	Unknown	Unknown
RAGE	Unknown	Unknown	Unknown	No
$p75^{NTR}$	Unknown	Unknown	Unknown	Unknown
NgR1	Unknown	Unknown	Unknown	Unknown
EphB2	Unknown	Unknown	Yes (lentiviral treatment rescues LTP deficit)	Yes (lentiviral treatment rescues LTP deficit)
EphA4	Unknown	Yes	Yes	Unknown
FcγRIIb	Unknown	Yes	Yes	Yes
LilrB2	Unknown	Unknown	Yes	Yes
Sortilin	Unknown	Unknown	Unknown	Unknown
IR	Unknown	Unknown	Unknown	Unknown
EGFR	Unknown	Unknown	Unknown	Unknown
σ_2R/PGRMC1	Yes	Unknown	Unknown	Unknown

loss of these receptors ameliorates deficits in learning and memory observed in mouse models of AD (Gimbel et al. 2010; Kam et al. 2013; Kim et al. 2013). Downregulation of EphB2 is also shown to be responsible for memory and learning deficits, which are rescued by bilateral injection of Lenti-EphB2 in the dentate gyrus of AD model mice (Kim et al. 2013).

REVERSIBLE BINDING OF Aβ

The kinetics of Aβo binding to neurons show saturable binding to a single site. Furthermore, this binding has been shown to be subject to inhibition (Laurén et al. 2009; Izzo et al. 2014a). Thus, binding of Aβo to any purported receptor should be subject to prevention or disruption. This attribute has been observed in simplified systems for PrP^C (Laurén et al. 2009), RAGE (Deane et al. 2012), $p75^{NTR}$ (Yaar et al. 1997; Kuner et al. 1998), IR (Xie et al. 2002), and in primary culture of hippocampal neurons for σ_2R/PGRMC1 (Izzo et al. 2014a). The most thorough investigations into the binding of Aβ to a potential receptor will also provide information about the mechanism of the interaction, such as the number of binding sites on the receptor and the domain(s) of the receptor that are necessary and/or sufficient for the interaction. Aβ-receptor interactions, including known interacting species of Aβ as well as the domains of each receptor responsible for the interaction, are summarized in Figure 1.

CONCLUDING REMARKS

The ultimate goal of identifying a cell-surface receptor for Aβo is to identify and map the intracellular signaling cascade that mediates the synaptotoxic effects of Aβo. As described above and summarized in Table 2, information regarding intracellular signaling in response to Aβo binding to neurons is highly variable between receptors. An example of a receptor for which the downstream signaling cascade has been thoroughly investigated is PrP^C. As diagrammed in Figure 2, much is known about the intracellular consequences of Aβo binding that ultimately give rise to synapse loss and decreased neuronal plasticity. It is important to advance our understanding of each Aβo-receptor interaction to better understand the contribution of each putative receptor to disease. A thorough understanding of which putative receptors are relevant to human disease as well as the mechanisms by which they lead to the pathophysiology of AD will facilitate the develop-

ment of disease-modifying therapeutics capable of augmenting the progression of this devastating disease.

ACKNOWLEDGMENTS

This work is supported by grants from the National Institutes of Health, the BrightFocus Foundation, the Alzheimer's Association, and the Falk Medical Research Trust to S.M.S. S.M.S. is a cofounder of Axerion Therapeutics, which seeks to develop PrP-based therapeutics for Alzheimer's disease.

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Cold Spring Harb Perspect Med 2017; doi: 10.1101/cshperspect.a024075 originally published online December 9, 2016