

Review

Molecular Mechanisms of Amyloid Oligomers Toxicity

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Abstract. Amyloid oligomers have emerged as the most toxic species of amyloid- β ($A\beta$). This hypothesis might explain the lack of correlation between amyloid plaques and memory impairment or cellular dysfunction. However, despite the numerous published research articles supporting the critical role $A\beta$ oligomers in synaptic dysfunction and cell death, the exact definition and mechanism of amyloid oligomers formation and toxicity still elusive. Here we review the evidence supporting the many molecular mechanisms proposed for amyloid oligomers toxicity and suggest that the complexity and dynamic nature of amyloid oligomers may be responsible for the discrepancy among these mechanisms and the proposed cellular targets for amyloid oligomers.

Keywords: Alzheimer's disease, amyloid, amyloid oligomers, amyloid toxicity

INTRODUCTION

The aggregation and accumulation of amyloid- β ($A\beta$) plays a significant role in the pathogenesis of Alzheimer's disease (AD). $A\beta$ oligomeric aggregates are believed to be the main toxic species and the causative agent underlying the pathological mechanism for AD, aggregating and accumulating within and around neurons. Excised from the amyloid- β protein precursor ($A\beta$ PP) by β - and γ -secretases, the $A\beta$ peptide has the intrinsic property of forming aggregates with β -pleated sheet structure [1]. The amyloid hypothesis has undergone several modifications, mainly concerning the type of $A\beta$ thought to cause AD: initially this was the amyloid plaque, followed by increased concentrations of $A\beta_{42}$, then

increased $A\beta_{42} : A\beta_{40}$ ratio, and finally oligomeric $A\beta$ [2]. Results from clinical trials have shown that removing plaques will not reverse the damage or stop AD [3, 4]. Recent evidence suggests that this toxicity may be linked to the aggregation state of the peptide, implicating oligomers, rather than insoluble fibrils, as the primary toxic species [5, 6]. While both are found in the brains of postmortem AD patients, soluble $A\beta$ oligomers are better correlated with disease severity than are the classic amyloid plaques containing insoluble $A\beta$ fibrillar deposits [7–9]. Furthermore, oligomers are found both extracellularly and intracellularly, and are capable of moving between the interior of the cell and the extracellular space [10, 11]. However, $A\beta$ oligomer structure, size, conformation, and interrelationships with other amyloid aggregates, as well as the exact mechanism of $A\beta$ oligomer-induced neurotoxicity, remain elusive [12–14]. Monomeric $A\beta$ undergoes conformation transitions and proceeds to form low molecular oligomers (dimer/trimer), and then soluble high molecular aggregates and progress to form

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spherical oligomers which are composed of 12 to 24 monomers, which prolong to protofibrils and finally become insoluble fibrils [15]. These various structures differ not only in aggregation state, but also in their toxic effects. Recently, many have reported that fibrils, which were once thought to exhibit the highest levels of toxicity, are actually second in toxicity to intermediate aggregates of A β (spherical oligomers and protofibrils) [14, 16, 17].

Our studies demonstrated the presence of a variety of A β oligomer conformations [15]. The different conformations can be produced by several pathways and simple manipulation of conditions in which A β aggregates, and underlines the complexity of the mechanism of oligomer formation [15, 16, 18–23]. Moreover, several studies suggest that oligomeric species differ not only in mechanism of formation, but also in mechanism of toxicity [24–26].

RECEPTOR-MEDIATED A β OLIGOMER NEUROTOXICITY

Extracellular A β oligomers bind the cell surface, leading to functional disruption of a number of receptors, including the N-methyl-D-aspartate receptor (NMDAR) [27] and others (Fig. 1A), resulting in synaptic dysfunction and neurodegeneration. A number of possible mechanisms and targets are under investigation, including the abnormal activation of signaling pathways.

Recently, Yamamoto et al. [28] suggested that A β oligomers induce nerve growth factor (NGF) receptor-mediated neuronal death. NGF can induce cell death through the p75 neurotrophin receptor (p75NTR), a member of the tumor necrosis factor receptor superfamily [29]. A previous report supports this concept, demonstrating that A β -derived diffusible ligands (ADDLs) potently alter NGF-mediated signaling in cultured cells [30]. Moreover, several studies suggested that A β toxicity is produced through the association with p75NTR [31–37]. Specifically, A β toxicity mediated by p75NTR depends on a death domain [38] in the cytoplasmic part of p75NTR molecules [37]. However, it has also been demonstrated that p75NTR promotes the survival and differentiation of vertebrate neurons, indicating that p75NTR might have diverse functions in both cell death and cell survival [39]. It should be noted that conflicting evidence also exists regarding the role of p75NTR against the toxicity of A β oligomers. Costantini and colleagues showed that soluble oligomers of

A β exert cytotoxic activity independent of p75NTR and that the expression of p75NTR exerts a protective role against the toxic activity of soluble oligomers. The authors also concluded that this role is due to an active function of the juxtamembrane sequence of the cytoplasmic region of p75NTR and that the protective function is mediated by phosphatidylinositol 3-kinase (PI3K) activity [37]. In another study, it was observed that low levels of extracellular A β increase the levels of p75NTR in primary cultures of human neurons. Unexpectedly, it was found that p75NTR protects primary human neurons against A β -induced toxicity [40]. These opposite conclusions imply that the signaling pathways of p75NTR are complicated and that the functions of p75NTR vary depending on several factors.

Other reports on neuronal receptor-mediated toxicity mechanisms have shown that A β disturbs NMDAR-dependent long-term potentiation induction *in vivo* and *in vitro*. Furthermore, these studies suggest that A β specifically interferes with several major signaling pathways downstream of NMDAR, including the Ca²⁺-dependent protein phosphatase calcineurin, Ca²⁺/calmodulin-dependent protein kinase II (CaMKII), protein phosphatase 1, and cAMP response element-binding protein (CREB) (reviewed in [41]). In another study of downstream NMDAR effectors, Zhao et al. determined that low molecular weight oligomeric A β could also inhibit CaMKII and thereby disrupt the dynamic balance in place between protein kinase and phosphatase, presumed to be critical during synaptic plasticity [42]. In another study, it was found that ADDLs stimulated excessive formation of reactive oxygen species (ROS) through a mechanism requiring NMDAR activation. ADDL binding to neurons was reduced and ROS formation was completely blocked by an antibody to the extracellular domain of the NR1 subunit of NMDARs [43]. The authors showed that the mechanism of ADDL-stimulated ROS formation requires ADDL targeting and activation of NMDARs, leading to a rapid increase in neuronal calcium levels. Taken together, these observations suggest that dysregulation of NMDAR function induced by ADDL binding to neuronal synapses may lead to synaptic mitochondrial dysfunction and excessive ROS formation.

Shankar and coworkers found that A β oligomers decrease spine density through a pathway that requires NMDA-type glutamate receptors (NMDARs), calcineurin, and cofilin. These results suggest that A β oligomers mimic a state of partial NMDAR blockade, by reducing NMDAR activation, reducing

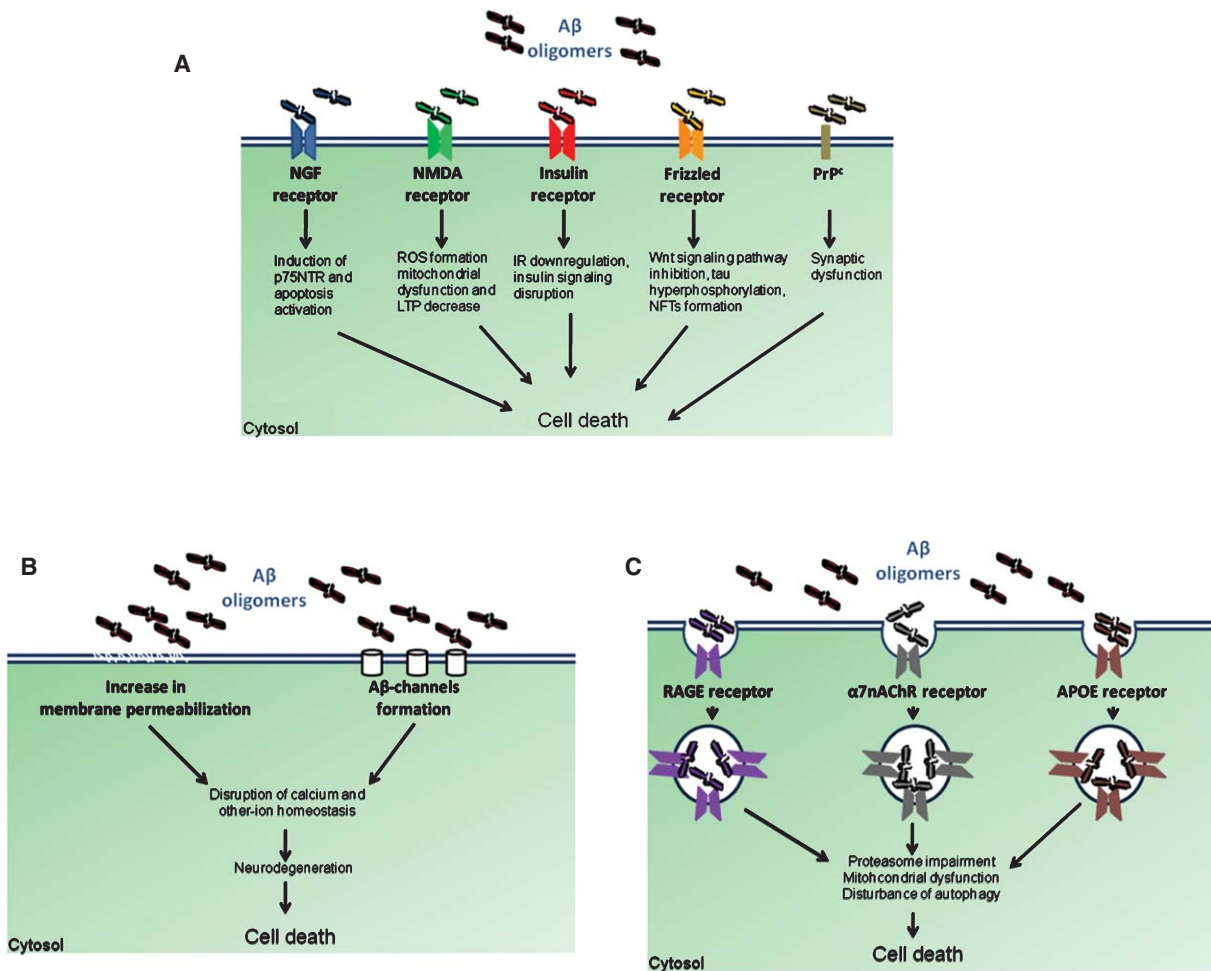


Fig. 1. A) A β oligomer neurotoxicity can be mediated through their ability to bind multiple receptors leading to the activation of various signaling pathways. Two possibilities may explain the lack of receptor specificity: 1) A β oligomers are indeed “sticky” as have been reported having a detergent-like quality, making it easier for them to be promiscuous in their interactions; and 2) oligomers are heterogeneous as indicated by colors and each oligomeric species has high affinity to a specific receptor or membrane protein. B) A β oligomers insertion in the membrane and the subsequent formation of ion channels or pores lead to neurodegenerative processes. C) The intracellular accumulation of A β oligomers and other aggregates cause many key pathological events of AD, including proteasome impairment, mitochondrial dysfunction, disturbance of autophagy, the production of reactive oxygen species, lipid peroxidation, disruption of lysosomal membrane, and breakdown of many cellular processes.

NMDAR-dependent calcium influx, or enhancing NMDAR-dependent activation of calcineurin [44]. It has also been shown that signal transduction by neuronal insulin receptors (IRs) is strikingly sensitive to disruption by soluble A β oligomers. In a recent study, it was found that ADDLs caused a rapid and substantial loss of neuronal surface IRs specifically on dendrites bound by ADDLs. Removal of dendritic IRs was associated with increased receptor immunoreactivity in the cell body, indicating redistribution of the receptors [45]. The results presented by the authors identify novel factors that affect neuronal IR signaling

and suggest that insulin resistance in AD brain is a response to ADDLs, which disrupt insulin signaling. Townsend and colleagues found that soluble A β binds to IR and interferes with its insulin-induced autophosphorylation. Taken together, these data demonstrate that physiologically relevant levels of naturally secreted A β interfere with IR function and prevent the rapid activation of specific kinases required for long-term potentiation [46]. De Felice et al. also suggest that ADDLs caused major downregulation of plasma membrane IRs, via a mechanism sensitive to CaMKII and casein kinase II inhibition [47].

Magdesian et al. showed that A β oligomers bind to the Frizzled (Fz) cysteine-rich domain at or in close proximity to the Wnt-binding site and inhibit the canonical Wnt signaling pathway [48]. Wnts are secreted glycoproteins that bind to and signal through Fz receptors and mediate cell-cell communication [49]. Wnt signaling regulates a variety of critical biological processes, including development, cell movement, cell polarity, axon guidance, and synapse formation [50]. Magdesian and colleagues concluded that A β oligomers bind to Fz receptors, producing the inhibition of Wnt signaling, which causes tau phosphorylation and neurofibrillary tangles; that suggests a Wnt/ β -catenin toxicity pathway [48].

A recent study by Lauren et al. [51] identifies the cellular prion protein (PrP^C) as an A β oligomers-receptor. The authors demonstrated that PrP^C is a mediator of A β oligomer-induced synaptic dysfunction and that A β oligomers bind with nanomolar affinity to PrP^C, but the interaction does not require the infectious PrP^{Sc} conformation. The binding of A β oligomers to PrP^C receptor may disrupt the interaction between PrP^C and co-receptor, such as NMDAR. Despite the fact that A β oligomers have been strongly implicated in neuronal dysfunction and neurotoxicity in AD, the signal transduction mechanisms involved in the neuronal impact of A β oligomers remain to be fully elucidated. A major unknown is the identity of the neuronal receptor(s) that binds A β oligomers and mediates neuronal dysfunction. As we described above, several studies postulate a great number of possible receptors involved in the toxicity of A β oligomers, but some of these studies are contradictory. The final identification of a highly specific receptor(s) for A β oligomers would provide considerable insight into mechanisms of pathogenesis and might reveal novel opportunities for the development of strategies to combat AD.

CELLULAR MEMBRANE AND A β OLIGOMERS TOXICITY

The maintenance of plasma membrane integrity is critical for cell viability, since the membrane controls the exchange of materials between the cell and its surrounding environment. An increase in membrane permeability and intracellular calcium concentration has long been associated with amyloid pathogenesis, although questions remain as to the mechanism underlying these observations [52, 53]. One explanation for the molecular mechanism of neurodegeneration induced by A β specifically is channel formation and

disruption of calcium homeostasis. Arispe and coworkers demonstrated the incorporation of A β peptides into artificial lipid bilayers to form cation-specific channels [54, 55]. Furthermore, others reported cytosolic calcium elevations as a result of this channel formation by A β , but also by other amyloid-forming proteins [56]; the results of this study strongly suggest that incorporation of A β into membranes and the subsequent pore formation may be the primary events in A β neurotoxicity. Specifically, the authors suggested that after being incorporated into the membrane, A β will change its structure and accumulated A β become aggregated on the membranes. They also suggested the possibility that the ratio of cholesterol to phospholipids in the membrane alters membrane fluidity and therefore affects the process. Micro-circumstances on the membranes, such as the presence of rafts, may influence this process [56]. These data and other reports culminated in what came to be known as the “channel hypothesis”, implicating amyloid peptide channels in the pathogenic ion dysregulation observed in degenerative disease [57, 58]. In this respect, A β may share this mechanism of toxicity with the similar mechanism underlying the toxicity of various antimicrobial or antifungal peptides, such as alamethicin, gramicidin, magainin 2, and melittin, which also exhibit channel forming ability and cell toxicity [59]. Once A β channels are formed on neuronal membranes, the disruption of calcium and other-ion homeostasis may promote numerous degenerative processes, including free radical formation [60] and phosphorylation of tau [61], thereby accelerating neurodegeneration. The free radicals also induce membrane disruption, by which unregulated calcium influx is amplified and a vicious circle is initiated. We recently demonstrated the presences of these A β pores in human cases of AD [62, 63].

In contrast to the amyloid channel hypothesis, recent data suggest that homogeneous solutions of amyloid oligomers increase the conductance of artificial lipid bilayers, but do not exhibit channel-like properties. Specifically, the conductance changes observed did not occur in discrete steps; rather, oligomers appeared to enhance ion mobility across the lipid bilayer independently [64]. This increased conductivity was not ion specific, and thus has the potential to depolarize the membrane and lead to cellular dysfunction. A growing body of evidence points to membrane permeabilization by amyloid oligomers as a common mechanism of pathogenesis in amyloid-related degenerative diseases [13, 19, 64–77]. These studies suggest that membrane permeabilization caused by amyloid oligomers is due

to defects in the lipid bilayer, rather than the formation of discrete proteinaceous pores. In accordance with this observation, a study by Demuro et al. showed that amyloid oligomers consistently produce rapid and dramatic elevations in Ca^{2+} , whereas equivalent concentrations of monomers or fibrils do not. The action of amyloid oligomers appears to involve a channel-independent disruption of the integrity of both plasma and intracellular membranes [68]. The authors propose that amyloid oligomers exert an immediate action by increasing the permeability of the plasma membrane and subsequently penetrate cells, as proposed previously [78], where they similarly disrupt intracellular membranes to cause leakage of sequestered Ca^{2+} . In another study we reported that soluble oligomers from several types of amyloid specifically increase lipid bilayer conductance regardless of the sequence, while fibrils and soluble low molecular weight species have no effect. The increase in membrane conductance occurs without any evidence of discrete channel or pore formation or ion selectivity [64]. The results presented in this study indicate that soluble oligomers from many types of amyloidogenic proteins and peptides increase membrane conductance in a conformation-specific fashion and suggest that this may represent the common primary mechanism of pathogenesis in amyloid-related degenerative diseases. The increase in membrane conductivity could lead to depolarization of the plasma membrane, which would be detrimental to the function of cells and especially so for neuronal function. The membrane conductance increase we reported can also account for a wide range of effects, such as defects of cytosolic ion homeostasis and signaling as a direct consequence of the membrane conductance increase [79]. Other experiments suggested that amyloid oligomers break down or reduce the normal dielectric barrier to ion translocation provided by the hydrocarbon region of the lipid bilayer [76]. The authors proposed that $\text{A}\beta$ oligomers increase membrane conductance and permeability to charged species by spreading apart the lipid head groups and consequently thinning the bilayer and lowering the permeability barrier [80, 81]. More recently, Demuro and collaborators were able to image the formation of Ca^{2+} single-channel and pores formed by $\text{A}\beta$ oligomers using total internal reflection fluorescence microscopy [82].

The formation of non-specific $\text{A}\beta$ pores or channels (Fig. 1B) on neuronal membranes in AD brain cause the disruption of calcium and other ion homeostasis may promote numerous degenerative processes, including free radical formation [60] and

phosphorylation of tau [61], thereby accelerating neurodegeneration and cell death. The free radicals also induce membrane disruption, by which unregulated calcium influx is amplified and a vicious circle is initiated lipid oxidation and other modifications [83, 84].

INTRACELLULAR $\text{A}\beta$ OLIGOMER TOXICITY

In addition to extracellular $\text{A}\beta$, there is a large body of evidence to demonstrate that $\text{A}\beta$ accumulates intracellularly [85–87]. Intraneuronal $\text{A}\beta$ accumulation has been identified in AD patients, transgenic mice, and cultured cells [88–94]. Intraneuronal $\text{A}\beta$ accumulation appears prior to extracellular amyloid plaque formation and results in synaptic dysfunction [88, 93, 95–102]. A key question that remains to be addressed is whether the intracellular $\text{A}\beta$ builds up because a portion of the generated $\text{A}\beta$ is not secreted and consequently remains intracellular, or alternatively, whether secreted $\text{A}\beta$ is taken back up by the cell to form these intracellular pools [103–106]. It is well known that is also localized in the trans-Golgi network [107], endoplasmic reticulum, and endosomal, lysosomal [108], and mitochondrial membranes [109]. The liberation of $\text{A}\beta$ could potentially occur wherever $\text{A}\beta\text{PP}$ and the β - and γ -secretases are localized, and it is likely that this occurs in several cellular compartments. In addition to $\text{A}\beta$ being produced intracellularly, previously secreted $\text{A}\beta$ that forms an extracellular $\text{A}\beta$ pool can be taken up by cells and internalized into intracellular pools through various receptors and transporters. A recent study showed that, in mice with a toxin-induced compromise of the blood-brain barrier, fluorescently labeled $\text{A}\beta$ that is injected into the tail vein can accumulate intracellularly in pyramidal neurons in the cerebral cortex [110]. The results presented by the authors provide direct evidence that neurons can take up extracellular $\text{A}\beta$, one of mechanisms that has been proposed is the endocytosis of $\text{A}\beta$ oligomers [111].

It is well known that $\text{A}\beta$ binds to the $\alpha 7$ nicotinic acetylcholine receptor ($\alpha 7\text{nAChR}$) with high affinity, and that this binding results in receptor internalization and accumulation of $\text{A}\beta$ intracellularly [112, 113]. These findings were recently confirmed in a study using the mouse model 3xTg-AD, where the authors show a loss of the $\alpha 7\text{nAChRs}$ restricted to brain regions that accumulate intraneuronal $\text{A}\beta$ [114]. Recently, the analyses of a novel animal model A7KO- $\text{A}\beta\text{PP}$, revealed the significance of $\alpha 7\text{nAChR}$ in AD and its protective role for $\text{A}\beta$ oligomers toxicity in early

stage AD. Analysis in early stage pre-plaque cognitive decline revealed neurodegeneration in A7KO-A β PP hippocampus. These changes occurred concomitant with the appearance of a dodecameric oligomer of A β that was absent from all other genotypic groups [115].

Several studies have shown that apolipoprotein E (APOE) receptors, which are members of the low-density lipoprotein receptor family, modulate A β production and cellular uptake [116]. LDL receptor-related protein, which is another member of this family of receptors, binds to A β directly, or through ligands such as APOE, and undergoes rapid endocytosis, facilitating A β uptake [116]. It is well known that APOE ϵ 4 is the major genetic risk factor for AD, and it is remarkable that one of its functions appears to be to directly mediate the accumulation of intracellular A β . It has been reported that A β is internalized through the scavenger receptor for advanced glycation end products (RAGE), in neurons and microglia [117–119]. The binding of A β to RAGE in neurons initiated a cascade of events that produces oxidative stress and nuclear factor- κ B (NF- κ B) activation, which induce the production of macrophage colony-stimulating factor [120] and an enhanced microglial response. Additionally, it has been shown that RAGE-A β complexes are internalized and that they co-localize with the lysosomal pathway in astrocytes in AD patients [119].

The toxicity mechanism of intracellular A β oligomers remains unclear. Almeida et al. demonstrated that in A β PP mutant transgenic mice and in human AD brain, progressive intraneuronal accumulation of A β occurs, especially in multivesicular bodies (MVBs) [121]. The authors provided evidence that A β accumulation in neurons inhibits the activities of the proteasome and deubiquitinating enzymes. These data suggest a mechanism whereby A β accumulation in neurons impairs the MVB sorting pathway via the ubiquitin-proteasome system (UPS) in AD. Indeed, the authors hypothesize that the inhibition of the UPS by A β impairs the endocytic trafficking of neuronal receptors and thereby may be the cause of synaptic dysfunction in AD. Furthermore, several other studies suggest that an inhibition of the proteasome leads to an increase of A β levels [122, 123]. Recent studies by LaFerla's group have shown proteasome inhibition in the 3xTg-AD mice at ages at which oligomeric A β accumulation is seen within neuronal cell bodies [123, 124]. These findings show that oligomeric A β accumulation within neuronal cell bodies has pathological consequences, as proteasome impairment led to the build-up of tau protein. Another study, by Mousnier and colleagues,

reported a possible prefolding-mediated proteasomal protein-degradation pathway [125]. This suggests that A β oligomers-prefolding complex could cause proteasome dysfunction and subsequent cell death.

Accumulation of A β has also been observed in mitochondria [126]. Progressive accumulation of intracellular A β in mitochondria is related to diminished enzymatic activity of respiratory chain complexes III and IV, and a reduced rate of oxygen consumption [127]. These observations correlated with the multiple mitochondrial defects reported in AD and mouse models of the disease [128]. A marked disturbance of autophagy has recently been appreciated in AD [129, 130], adding to evidence for extensive dysfunction of the lysosomal system in this disease [131]. A β can accumulate in lysosomes in the AD brain. A β within the lysosomal compartment destabilizes its membrane [132], which will lead to the release of A β in the cytosolic compartment.

The studies described in this section suggested that the toxicity mechanism of intracellular oligomers could be different from the one produced by extracellular oligomers (Fig. 1C). However, further studies are necessary to determine the exact mechanism of toxicity produced by A β oligomers in AD.

CONCLUSIONS

Based on the studies discussed here and the countless targets associated with toxicity of A β oligomers, it is conceivable that oligomers are not specific and interact with many targets, or it is possible that the toxicity is associated with the formation process rather than a specific oligomeric species, this (kinetic model of toxicity) model [133, 134] demonstrates that A β aggregation and the formation of the fibrils causes toxicity at low concentrations. Alternatively, we propose that A β oligomers possess a large number of exchangeable, still distinct conformational polymorphisms [135], similar to the structural polymorphisms described for A β fibrils [136–139], and that different subgroups of A β oligomers and fibrils induce neurotoxicity and may contribute to AD pathology via different mechanisms [15, 25, 140, 141]. The unique combination of size, hydrophobicity, and conformation of each oligomeric species determines both its toxicity and the final aggregation state (Fig. 2). The existence of polymorphisms in what are now known as oligomers may be analogous to the polymorphisms that exist within yeast prions [142, 143]. Identifying these subtle differences between oligomers both *in vitro* and *in vivo* represents

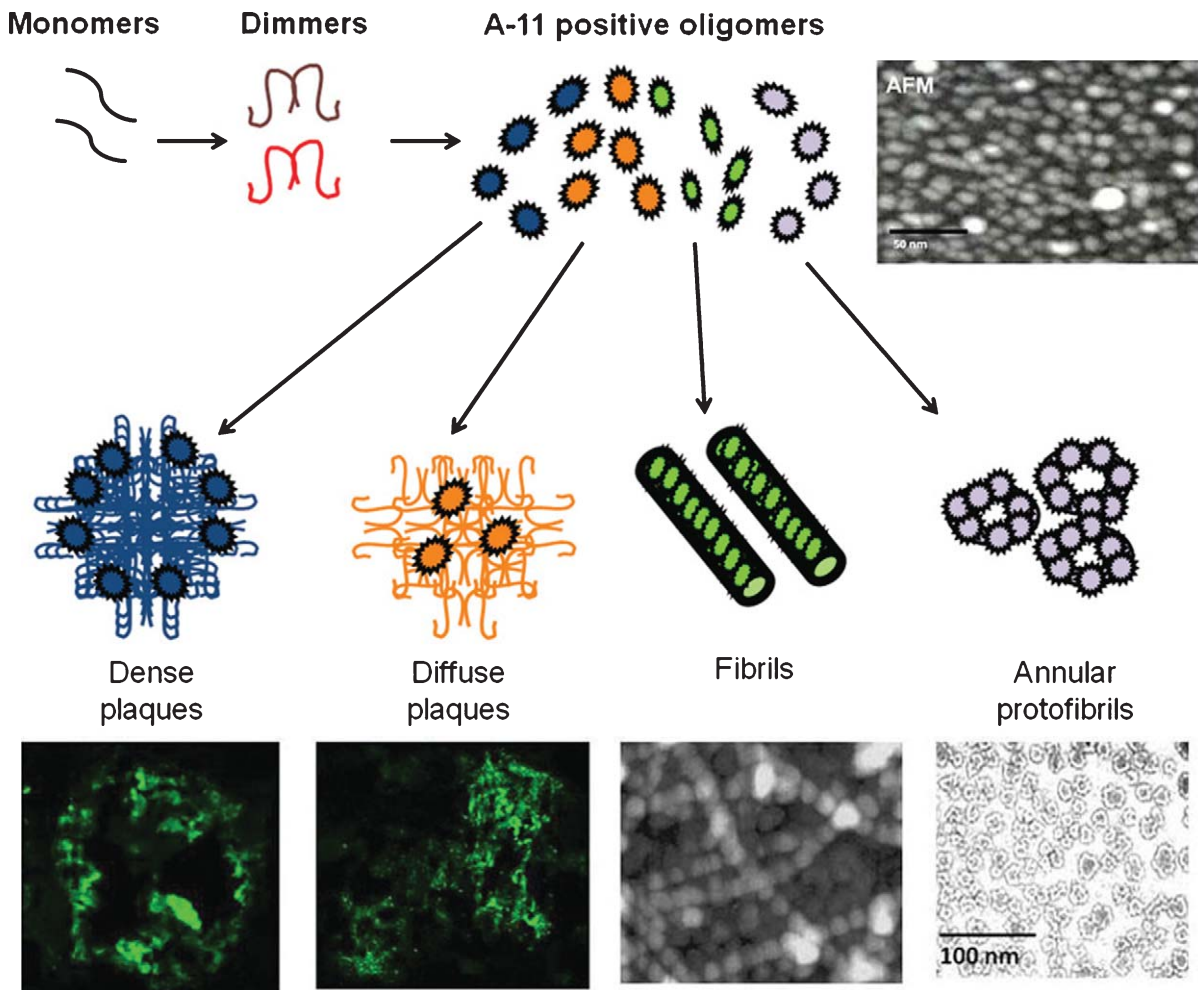


Fig. 2. Amyloid oligomers have different sizes and possess different conformations, and the structural diversity of A β oligomers shape the aggregation pathway of each species and determine their toxicity. This may explain the large number of toxic events associated with A β oligomers.

the next challenge facing the amyloid field and requires novel methods and reagents.

DISCLOSURE STATEMENT

Authors' disclosures available online (<http://www.j-alz.com/disclosures/view.php?id=1246>).

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