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Cross-interactions between the Alzheimer Disease Amyloid-β Peptide and Other Amyloid Proteins: A Further Aspect of the Amyloid Cascade Hypothesis*

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Many protein folding diseases are intimately associated with accumulation of amyloid aggregates. The amyloid materials formed by different proteins/peptides share many structural similarities, despite sometimes large amino acid sequence differences. Some amyloid diseases constitute risk factors for others, and the progression of one amyloid disease may affect the progression of another. These connections are arguably related to amyloid aggregates of one protein being able to directly nucleate amyloid formation of another, different protein: the amyloid cross-interaction. Here, we discuss such cross-interactions between the Alzheimer disease amyloid-β (Aβ) peptide and other amyloid proteins in the context of what is known from *in vitro* and *in vivo* experiments, and of what might be learned from clinical studies. The aim is to clarify potential molecular associations between different amyloid diseases. We argue that the amyloid cascade hypothesis in Alzheimer disease should be expanded to include cross-interactions between Aβ and other amyloid proteins.

Alzheimer disease (AD)[3] is the most common form of elderly dementia. Its causes have not yet been clearly elucidated. The two classical AD lesions are depositions of intracellular neurofibrillary tau tangles and extracellular deposits of aggregated amyloid-β (Aβ) peptides in amyloid plaques in the gray matter of the brain, mainly the hippocampus and neocortex. Aβ is a 36–43-residue peptide cleaved from the amyloid-β protein precursor (AβPP) by γ-secretase and β-secretase enzymes. Some AβPP and Aβ mutations increase Aβ production and deposition and/or extend the half-life of Aβ in the brain, but only a fraction (5%) of Alzheimer disease is familial AD (1). Several studies indicate that alterations of the pathologies of other amyloid proteins such as α-synuclein (2) and tau (3) are observed in familial AD.

The amyloid cascade hypothesis suggests that deposition of Aβ aggregates in brain plays a vital role in AD development (4). The amyloid form of Aβ aggregates is generally defined by *in vitro* observations: originally by the so-called cross-β x-ray diffraction pattern or by observation of fibril structures in microscopy (transmission electron microscopy or atomic force microscopy) (5). Molecular probes recognizing the formation of certain ordered molecular structures include Congo red and thioflavin T, which change their optical properties when bound to amyloid material (5). The terms "on-pathway" and "off-pathway" intermediates are used to differentiate between self-aggregated Aβ species that lead to amyloid formation and those that do not. Missense mutations in the AβPP, apoE, PS1, and PS2 genes can increase accumulation and toxicity of Aβ aggregates, and the "on-pathway" intermediate aggregates seem to be the most cell-damaging species (6). This provides strong support for the amyloid cascade hypothesis, which nevertheless remains disputed.

Although two recent reviews (7, 8) respectively reject and support the amyloid cascade hypothesis, they both agree on one point: although AD progression is tightly connected to Aβ aggregation, several other factors likely contribute to the development of AD. Such factors include lysosomal dysfunction, loss of Ca^{2+} homeostasis, neuroinflammation, progressive oxidative damage, and problems in glucose metabolism. The pathological AD characteristics, *i.e.* loss of neurons and formation of Aβ plaques and tau tangles, are complex processes linked by multiple interconnected events that cannot be adequately explained by a single hypothesis.

The aggregates of different amyloid proteins/peptides share many structural similarities. Despite different clinical symptoms, the amyloid-cross-β interaction motif of amyloid proteins appears in several distinct pathologies. The monomers of Aβ and other amyloid proteins have highly flexible and disordered structures, which provide excellent templates for promiscuous interactions with each other *in vivo*. This may explain, in part, why interactions between different amyloid proteins seem to alter the progression of various amyloid diseases. In addition to direct molecular interactions, two amyloid-prone partners may interact with a third entity, thereby interfering with each other's primary effects. This hypothetical third entity could be a membrane receptor, another protein, or even a metal ion. Alternatively, certain amyloid-prone proteins may compete for the same proteolytic systems, or even have them in the proteolytic process, thus enhancing the concentration and amyloid-forming propensity of others (9).

Here we discuss a series of amyloid proteins as possible modulators of Aβ peptide behavior *in vitro* and *in vivo*, as well as potential clinical consequences (Fig. 1). Table 1 shows how self-

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[3] The abbreviations used are: AD, Alzheimer disease; PD, Parkinson disease; T2D, type 2 diabetes; Aβ, amyloid-β; PrP, prion protein; α-syn, α-synuclein protein; IAPP, islet amyloid polypeptide; TTR, transthyretin; apoA-I, apolipoprotein AI; CysC, cystatin C; SAP, serum amyloid P component; RAGE, receptor for advanced glycation end products; LB, Lewy bodies; CSF, cerebrospinal fluid.

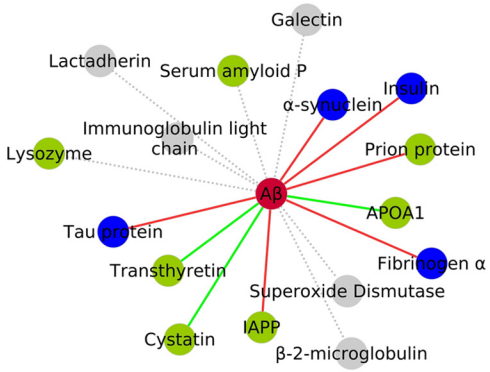

FIGURE 1. **A cross-amyloid network for the Aβ peptide.** *Red lines*: amyloid proteins that enhance the risk of AD in mice models or *in vivo*. *Green lines*: amyloid proteins that decrease the progression of AD in mice models. *Blue circles*: amyloid proteins that promote Aβ fibrillation *in vitro*. *Green circles*: amyloid proteins that suppress Aβ fibrillation *in vitro*. *Gray circles* and *lines*: unknown. The details of the interactions on which the connections are based are discussed in the article for each protein.

aggregation of various proteins has been linked to certain amyloidal diseases. We suggest mutual molecular mechanisms between AD and these other diseases. We argue that the amyloid cascade hypothesis in AD remains valid, but should be expanded to also involve cross-interactions between Aβ and other amyloid proteins.

Amyloid Proteins Displaying Cross-interaction with Aβ

Prion Protein (PrP)

The prion protein (PrP) is 208 residues long and mainly expressed in nerve cells. When misfolded, PrP acts as an infectious agent (prion) inducing transmissible spongiform encephalopathies, such as mad cow disease. Prions also can infect the human brain and induce misfolding of other proteins into the prion form. Accumulation of prion structures leads to fatal disease, such as Creutzfeldt-Jakob disease in humans.

PrP seems to affect the biological activity of Aβ42 through direct interactions, and aggregated forms of human PrP and Aβ42 have been co-purified from AD brain material (10). Cellular PrP has been identified as a high-affinity receptor for Aβ oligomers. Several *in vitro* studies have shown mediation of Aβ-induced synaptic dysfunction via prion proteins. By binding Aβ oligomers to the cell surface, PrP reduces the production of Aβ from AβPP by down-regulating the activity of β-secretase BACE1 (11). PrP recognizes only soluble Aβ oligomers, and the binding depends on the integrity of the lipid rafts and LPR1 (the transmembrane low density lipoprotein receptor-related protein-1) (11). Single-molecule imaging of small oligomeric forms of Aβ42 interacting with cellular PrP on neuronal cell surfaces was recently reported, where soluble PrP suppressed Aβ42 fibrillation and protected cells against Aβ oligomer toxicity (12). The N-terminal PrP domain fragment, with its positively charged residues 23–31 and 95–105, strongly binds Aβ oligomeric intermediates and in cultured murine hippocampal neurons strongly mitigates Aβ toxicity (13).

Conversely, Aβ42 affects PrP biological activity because prion binding and prion-dependent inhibition of long-term potentiation are regulated by the presence of Aβ protofibrils. These aggregates have a linear structure, stronger binding

TABLE 1
Associations between amyloid proteins and certain diseases, according to current understanding
An association is indicated if aggregation of the protein leads to amyloidosis associated with the disease, based on results either *in vivo*, *in vitro*, or in mice as discussed in the article for each protein.

	Aβ	Tau protein	Cystatin	Fibrinogen α	Huntingtin	ApoA-I	β-2-Microglobulin	Immunoglobulin light chain	IAPP	Serum amyloid A	Lysozyme	Insulin	Transthyretin	α-Synuclein	Superoxide dismutase	Lactadherin
Alzheimer	×	×	×			×	×		×	×		×	×	×		
Huntington	×				×											
Aortic medial amyloid																×
Hepatic or renal amyloidosis				×												
Familial amyotrophic lateral sclerosis											×					
Type 2 diabetes		×							×			×				
System amyloidosis			×			×		×							×	
Rheumatoid arthritis										×						
Parkinson		×	×											×		
Injection-localized amyloidosis												×				
Dialysis related amyloidosis							×									
Familial amyloid polyneuropathy													×			

affinity toward PrP, and a stronger inhibitory effect on long-term potentiation than non-fibrillar Aβ oligomers (14).

The presence of PrP enhances Aβ accumulation, and vice versa (15). Thus, in transgenic mice, the two proteins mutually accelerate the progression of both pathologies (16). In AD transgenic mice, the onset of prion disease symptoms developed at a rate proportional to the Aβ brain levels (16). For humans, significant levels of Aβ deposition, similar to those found in AD patients, were seen in the brains of relatively young individuals who had died from Creutzfeldt-Jakob disease (17). In cellular form, however, PrP may inhibit Aβ production, and one study found 53% reduction of PrP in the hippocampus of aging sporadic AD patients (18), suggesting that PrP reduction may increase AD incidence in older people.

α-Synuclein

Aggregation of the 140-residue neuronal α-synuclein protein (α-syn) into Lewy bodies (LB) induces Parkinson disease (PD). The presence of Lewy bodies also accelerates cognitive dysfunction in AD patients, and up to 50% of AD cases exhibit significant LB pathology in addition to Aβ plaques and tau tangles (19, 20).

Aβ40/42 and α-syn appear to strongly interact and mutually promote each other's oligomerization *in vitro*. The addition of α-syn induces a global structural change in Aβ42/40, whereas α-syn seems to have a specific binding pocket for Aβ interaction (21). Aβ directly interacts with α-syn to form cationic nanopore oligomers embedded in the cell membrane (22). Aβ and α-syn cross-seeding fibrillation effects suggest that the aggregation pathways of both molecules can be significantly stimulated by the presence of fibrils of either molecule. Although non-fibrillar oligomers may also stimulate aggregation, they were less effective (23). Thus, synergistic cross-amyloid interactions of monomeric/oligomeric/fibrillar Aβ and α-syn may promote protein aggregation and contribute to both PD and AD progression.

In transgenic mice, Aβ enhances α-syn accumulation and neuronal damage (24). In DLB (dementia with Lewy bodies)-AD mice, a dramatic increase of amyloidal Aβ42 was observed (19). AD patients with this Lewy body variant have a lower survival rate and more pronounced cognitive dysfunction than pure AD patients (25). For PD patients, accumulation of Aβ aggregates produces aggressive PD with dementia (26). α-syn may also promote Aβ-related tau inclusion in neurons and *in vivo* (27). Aβ and α-syn therefore appear to synergistically accelerate cognitive decline in AD and PD.

Tau

The tau proteins, a family of 352–441-residue microtubule stabilizers, are abundant in the central nervous system. The presence of neurofibrillary tau tangles is a characteristic AD histopathology. Tau and Aβ interactions appear to mutually influence the aggregation and toxicity of both molecules, as well as the progression of synaptic dysfunction in AD. Three mechanisms were proposed (28): Aβ drives tau pathology or tau modulates Aβ toxicity, or synergistic toxicity exists between Aβ and tau.

The Aβ C terminus can bind multiple tau domains and subsequently form soluble Aβ-tau complexes *in vitro* (29). Such intracellular Aβ/tau complexes could conceivably accelerate tau hyperphosphorylation and Aβ nucleation. Extracellular fibrillar and oligomeric Aβ peptides seem to promote tau hyperphosphorylation, thereby inducing loss of tau's microtubule binding activity, leading to neural dysfunction and degeneration (30). Similarly, Aβ aggregation induces tau hyperphosphorylation in AβPP transgenic mice (31). Injection of extracellular Aβ fibrils into tau transgenic mice accelerates the tau tangle pathology (32). However, no aggressive Aβ plaque pathology has been observed either in tau transgenic mice or in cross offspring of tau transgenic mice and AβPP transgenic mice (33). In conclusion, Aβ/tau amyloid cross-interactions likely contribute to the synaptic dysfunction involved in AD.

Lysozyme

Human lysozyme is a 148-residue glycoside hydrolase, functioning as an antibacterial agent mainly in blood (34). Lysozyme is also present in CSF, where substantially increased levels have been reported during various disease conditions, especially inflammation, including the inflammatory reactions triggered in the AD brain. AD patients display increased CSF lysozyme levels, and Aβ-lysozyme complexes have been found in AD plaques (35). Because of its capacity to self-assemble, lysozyme is often used as a model to study protein stability, folding, and aggregation.

We have found that human lysozyme prevents Aβ aggregation at a 1:1 ratio *in vitro*. CD and NMR spectroscopy showed that lysozyme does not affect the random coil structure of monomeric Aβ, whereas theoretical simulations indicated that human lysozyme stabilizes the Aβ N terminus and interacts with the C terminus via a hydrophobic surface (36). As an amyloidal protein, lysozyme can modulate the Aβ conformation and fibrillation, which may in part explain the physiological association between AD and inflammation.

Insulin

Insulin is a 51-residue peptide hormone primarily involved in glucose regulation. It also modulates numerous brain functions. A positive effect of insulin has been found on cognitive performance in AD, although treatment with insulin may increase the risk of AD among diabetes mellitus patients.

In vivo, insulin regulates the activity of hyperphosphorylated tau in the formation of AD neurofibrillary tangles (37). Insulin also affects Aβ production and degradation (37), and increases Aβ extracellular levels via regulation of γ-secretase activity (38) and via release of intra-neuronal β-amyloid (39). Insulin inhibits Aβ degradation by blocking the activity of the insulin-degrading enzyme, which also degrades Aβ in neuronal and microglial cell cultures (40). Insulin has been reported to facilitate hepatic cleavage of plasma Aβ by intracellular translocation of the lipoprotein receptor to the plasma membrane (41).

Conversely, Aβ regulates the function of insulin. Aβ inhibits the effect of insulin on the secretion of AβPP, competes with insulin for binding to the insulin receptor, and induces insulin resistance by regulating the signal transduction of the insulin receptor (42). The underlying interaction mechanisms between

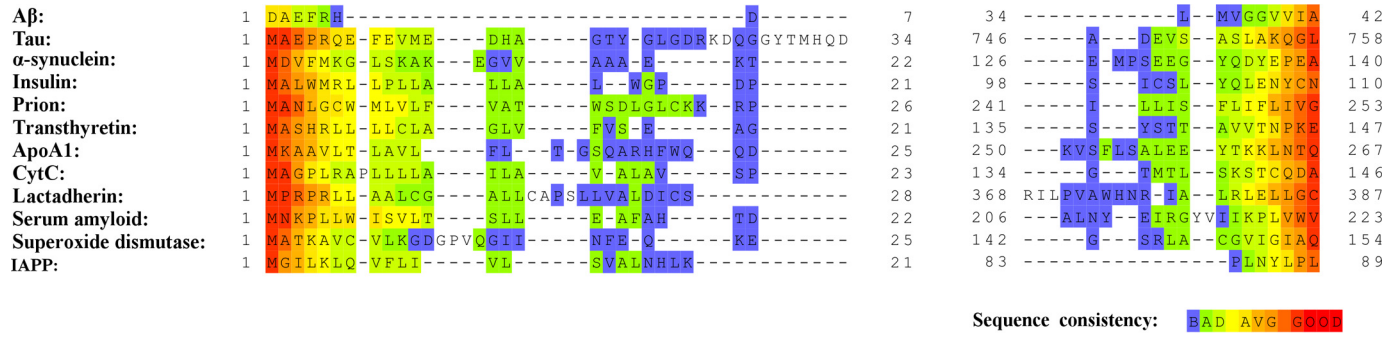

FIGURE 2. **A probabilistic consistency-based multiple alignment of amyloid protein sequences calculated by the T-coffee web server.** Consistencies range from poor (*blue*) to good (*red*). It is clear that both the N termini and the C termini of amyloid proteins display high probabilistic sequence consistency.

insulin and Aβ remain unknown, although we recently showed that monomeric insulin interacts with soluble Aβ *in vitro*, inducing the formation of less toxic Aβ oligomers (43).

IAPP

The islet amyloid polypeptide (IAPP), a 37-amino acid peptide hormone, is cleaved from the pro-islet amyloid polypeptide and secreted with insulin by pancreatic β-cells into the circulation (44). IAPP has 38% sequence similarity with Aβ (Fig. 2). Both peptides can regulate the homeostasis of free Ca^{2+} to control cell death (45). IAPP amyloidosis is a characteristic feature of type 2 diabetes (T2D) (46). IAPP in T2D and Aβ in AD adopt antiparallel β-sheet secondary structures and associate with the same cellular components, such as apolipoprotein E (apoE) and heparin sulfate proteoglycan (47). T2D patients are 1.5 times more likely to develop AD than control individuals (48). In diabetic SAMP8 mice, cerebral Aβ is increased, tau phosphorylation is interrupted, and memory deficiencies are observed, indicating AD-like changes (48).

In vitro results show that IAPP fibrils are poor seeds for Aβ aggregation (49). However, IAPP binds to prefibrillar Aβ40 and blocks the cytotoxicity of Aβ aggregates. Conversely, Aβ binds prefibrillar IAPP, and Aβ and IAPP aggregates reciprocally regulate each other's cytotoxicity (50). IAPP inhibits the cytotoxicity of Aβ aggregates at nanomolar concentrations and inhibits Aβ fibrillation at stoichiometric ratios (51). Several small Aβ fragments bind to full-length IAPP, some with nanomolar affinity (52). These results agree with the hypothesis that amyloidal peptides can dissolve amyloid material containing similar sequence motifs (53).

Thus, although IAPP suppresses Aβ fibrillation and toxicity *in vitro*, there seem to be aggressive effects of IAPP *in vivo*, particularly as the molecule induces cleavage of Aβ from AβPP.

Transthyretin

Transthyretin (TTR) is a 55-kDa protein, secreted by the liver into the bloodstream and functioning as a serum and CSF carrier of thyroxine (T4) and the retinol-binding protein. Aggregation of wild-type TTR causes a sporadic, non-genetic disease, whereas aggregation of a mutated TTR leads to familial amyloid cardiomyopathy (54). As for Aβ, production and deposition of TTR amyloid are age- and mutation-dependent. TTR is deposited in peripheral nerves and in the heart, but is also present in the eyes, choroid plexus, and kidney (55).

Expression of TTR in brain regions such as the hippocampus and cortex has been observed in both wild-type animals and AD rodent models. During aging, a TTR-null mouse suffers reference memory deficits, but no other impairments (56). TTR promotes Aβ clearance, decreases its deposition, and suppresses cognitive deficits in AD mouse models (57). TTR has therefore been suggested to generally slow AD progression. TTR appears to be a major Aβ-sequestering protein in human CSF, inhibiting and even reverting the formation of amyloid fibrils, as well as reducing their toxicity *in vitro* (58, 59). TTR forms a complex with Aβ monomers/dimers, with stronger binding affinity observed for the more structurally flexible S85A TTR mutant (60), reinforcing the idea that less structured forms of amyloid proteins may be more likely to engage in cross-amyloid interactions.

Apolipoprotein AI

Apolipoprotein AI (apoA-I) is the 396-residue main member of human high-density lipoproteins, which play an important role in lipid metabolism. It is present in human CSF and can also be detected in senile AD plaques (61). ApoA-I can self-assemble into amyloid fibrils and generate atherosclerotic plaques (61). ApoA-I directly interacts with AβPP (62), and has a nanomolar affinity for Aβ. Upon binding to apoA-I, Aβ fibril formation is inhibited and the toxicity of Aβ aggregates is attenuated (62). Polymorphisms of the promoter region of apoA-I are associated with increased AD risk (63). In an AD mouse model, overexpression of apoA-I impaired learning and caused memory deficits (64).

Cystatin C

Cystatin C (CysC) is a 13.3-kDa basic protein abundantly located and expressed in brain tissue (65). CysC plays a role in different diseases, from cancer to neurodegenerative disorders (66). Mutations of CysC can lead to fatal hereditary cystatin C amyloid angiopathy. CysC counteracts the formation of Aβ oligomers and protofibrils (67) and thereby reduces Aβ neurotoxicity (68). A specific high-affinity Aβ-CysC binding has been observed *in vitro* (69), whereas *in vivo* Aβ/CysC complexes have been detected in the human central nervous system (70). CysC may function as an endogenous inhibitor of cysteine proteases such as cathepsin B (71), which can degrade Aβ and thereby lower Aβ levels *in vivo* (72). CysC is thus likely indirectly involved in Aβ regulation. Epidemiologically, a polymor-

phism in the CysC gene (*CST3*) has been linked to enhanced risk for AD (66), and CysC modulates cerebral β-amyloidosis in AβPP transgenic mice (71).

Serum Amyloid P Component and Fibrinogen

Blood proteins such as serum amyloid P component (SAP) and fibrinogen are found in human amyloid deposits. SAP is a 25-kDa pentameric plasma glycoprotein that generally binds to amyloid fibrils, including those formed from aggregated Aβ. Recent studies show that SAP accelerates the formation and enhances the proteolytic stability of Aβ42 fibrils (73). *In vivo*, human amyloid deposits often contain SAP together with a primary amyloid component such as Aβ (74). SAP may be removed from blood and/or CSF by pharmaceutical intervention. It has been suggested that such removal might be beneficial to AD patients (75).

The 340-kDa clotting precursor fibrinogen is present only in blood plasma but not in serum. Fibrinogen-Aβ interactions have been shown to induce oligomerization of fibrinogen and fibrillation of the Aβ peptide (76). Abnormal depositions of fibrinogen have been found in AD patients. Similar to SAP, fibrinogen modulates Aβ deposition and fibrillation, and also further affects neurodegeneration (76).

Other Amyloid Proteins

For several other amyloid proteins associated with Aβ, the types of interaction and their effects are less known. The levels of galectin-3, associated with idiopathic pulmonary fibrosis, are increased in the serum of AD patients. I*n vitro* galectin-3 has been found to reduce the neurotoxicity of Aβ42 (76). The levels of lactadherin, playing a vital role in phagocytosis, are decreased in AD patients (77). Lactadherin amyloid, a deposit known as medin that is localized in aortic medium, occurs in virtually all individuals older than 60 years. The huntingtin-associated protein 1 modulates the AβPP subcellular trafficking pathway, thus negatively regulating Aβ production in neurons (78). Loss of superoxide dismutase (SOD) increases production of Aβ in neurons and SHSY5Y cells, an effect caused by enhanced AβPP processing by the β-site AβPP-cleaving enzyme (79), whereas earlier studies have shown that overexpression of superoxide dismutase reduces Aβ neurotoxicity (80). Another question is whether non-toxic aggregating proteins such as β-lactoglobulin in milk could interact with and promote toxic amyloid formation.

The Co-factors and Loci of Cross-amyloid Interaction

Various metal ions are known to bind Aβ and interfere with its aggregation process (15, 81). Recent work has shown that multiple amyloid protein molecules may share coordination of a single metal ion, promoting protein aggregation and possibly also cross-interactions (82). Cross-amyloid interactions may also be modulated by other clusters involving, for example, small charged molecules. Polyamines modulate the conformation, fibrillation, and toxicity of Aβ, α-syn, and IAPP *in vitro* (83, 84).

We recently found that certain non-chaperone proteins such as lysozyme and catalase prevent Aβ fibrillation and toxicity (36, 85). These enzymes could act according to the model of molecular crowding *in vivo* to regulate cross-amyloid effects (86). Proteostasis capacities (referring to protein quality control *in vivo*) are decreased in neurodegenerative amyloidoses (87). Increased Aβ production could overload the proteostasis system, leading to aggregation of various other amyloid proteins. These entirely indirect effects of cross-amyloid interactions may explain, at least in part, the association of different amyloidoses. We propose that the direct and indirect effects discussed here are likely to be complementary to each other in cross-amyloid interactions.

Cell membranes are obvious location candidates for cross-amyloid interactions, given their hydrophobic interiors and the large proportion of hydrophobic residues in amyloid protein sequences. Most amyloid proteins travel between different cellular compartments and tissues, and the membrane boundaries would be natural places for these proteins to accumulate and/or interact. Lipid membranes are known to influence the structure, aggregation, cell permeability, and toxicity of amyloid proteins. Aβ, IAPP, and α-syn all adopt more well defined structures in lipid membranes. Cell membrane damage has been proposed as a disease mechanism in amyloidosis, and damage could result from uptake of lipids into amyloid aggregates formed on or in lipid membranes (88). Amyloid proteins may also form harmful nanopores in lipid membranes (89). Although α-syn and tau predominantly appear as intracellular proteins, and Aβ and IAPP mainly function as extracellular peptides, all of them can appear intracellularly as well as extracellularly. Both intracellular and extracellular amyloid proteins are associated with the progression of amyloid diseases (90–92).

Implications of Aβ Cross-amyloid Interactions

Although the sequences of amyloid proteins vary in length, all amyloid proteins discussed above can form highly similar β-cross-amyloid fibrils. In non-aggregated states, most amyloid proteins exist as random coil structures prone to conformational changes. Surprisingly, the N- and C-terminal sequences of amyloid proteins show a high probabilistic consistency (Fig. 2). This is in agreement with, for example, the observed interaction between Aβ oligomers and the PrP N terminus (13). We here propose that the N and C termini of many amyloid proteins can initialize cross-amyloid interactions.

Cross-amyloid interactions could be driven by hydrophobic associations, as the presence of hydrophobic amino acids is known to yield higher amyloidal propensity (93). Most amyloid proteins display an abundance of hydrophobic residues, which could facilitate hydrophobic associations between, for example, misfolded amyloid proteins and other amyloid proteins with different sequences. Such associations might interfere with, for example, the Aβ self-fibrillation pathway. Our observation of Aβ peptides adsorbing on the surfaces of hydrophobic carbon nanotubes appears to support this hypothesis (94). For Aβ, the hydrophobic regions around residues 16–21 and 29–35 form the two legs of the Aβ hairpin, which is considered to be the basic unit for Aβ self-aggregation and co-aggregation with other molecules (5).

Most amyloid proteins adopt a variable and heterogeneous conformation in solution, often displaying an extremely flexible loop structure that allows amyloid proteins to act as promiscuous binding partners for other molecules. For instance, the Aβ

N terminus (residues 1–15) interacts with many different small charged molecules (15, 84). Interaction between two heterogeneous amyloid proteins may prevent fibrillation of one of them, but may also be the precursor of a cross-amyloid interaction. Initial cross-amyloid protein interactions are most likely limited by the flexibility/heterogeneity of the proteins involved. The subsequent rate of co-aggregation may then be governed by their initial interactions and by hydrophobic associations.

As shown in Fig. 1 and Table 1, the effects of cross-amyloid interactions between different amyloid proteins may vary substantially. TTR (59), CysC (67), and apoA-I (62) all suppress Aβ fibrillation and delay AD progression in mice (57, 64). In contrast, α-syn (23), tau (28), and fibrinogen-α (95) promote Aβ toxicity and/or fibrillation and increase the risk of AD in mice (32) and/or patients (25, 76). IAPP prevents Aβ fibrillation *in vitro* (50), yet IAPP-associated T2D may promote AD progression *in vivo*. The different ways amyloid proteins modulate Aβ fibrillation may depend on their varying structures and stabilities. Most proteins preventing Aβ amyloid fibrillation have a well folded or partially folded monomeric structure (*e.g.* lysozyme), whereas amyloid proteins with random or disordered structures are prone to promote Aβ fibrillation. Many amyloidal proteins have been reported to protect cells against the toxicity of Aβ aggregates. The different roles of the amyloid proteins affecting fibrillation and toxicity of the Aβ peptide could also be regulated by other *in vivo* factors, such as protein homeostasis.

Interactions between Aβ and the RAGE receptor have been proposed to induce cellular perturbations via oxidative stress and synaptic dysfunction. Some Aβ-binding amyloid proteins have been reported to compete for the RAGE receptor and inhibit its interaction with Aβ (96). Interruption of the Aβ-RAGE receptor interaction by other amyloid proteins could affect the cell toxicity of Aβ and its aggregates.

Other questions concern how, where, and whether cross-amyloid interactions should be inhibited. Although molecules such as β-sheet breakers (97) and cyclic peptides (98, 99) have been devised to prevent amyloid aggregation, traditional antibodies have so far provided the best preliminary treatment results, at least for AD (100). It is unclear to what extent current amyloid inhibitors will block the formation of amyloid co-aggregates. As for location, it might turn out to be important to prevent cross-amyloid interactions in or on lipid membranes A drastic yet simple way to prevent cross-amyloid interactions is of course to remove one of the components — *cf.* the pharmacological removal of SAP discussed above.

Cross-interactions between various amyloid proteins concern not only potentially therapeutic interventions against amyloidosis, but also point at molecular associations between different diseases. As shown in Table 1, Aβ can interact with at least 10 other amyloidal disease proteins. In our opinion, this supports and expands the amyloid cascade hypothesis as an underlying cause for AD: cross-amyloid interactions between Aβ and other amyloidal proteins may play a critical role in AD progression, and cross-amyloid interactions might also modulate amyloidosis in other diseases.

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