Published in final edited form as:

J Mol Biol. 2012 August 10; 421(2-3): 172–184. doi:10.1016/j.jmb.2011.11.023.

Selective molecular recognition in amyloid growth and transmission and cross-species barriers

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Abstract

Mutual conformational selection and population shift followed by minor induced fit optimization is the key mechanism in biomolecular recognition; and monomers and small oligomers binding to amyloid seeds in fibril growth is a molecular recognition event. Here, we describe amyloid aggregation, preferred species, cross-species barriers and transmission within the broad framework of molecular recognition. Cross seeding of amyloid species is governed by conformational selection of compatible (complementary) states. If the dominant conformations of two species are similar, they can cross-seed each other; on the other hand, if they are sufficiently different, they will grow into different fibrils, reflecting species barriers. Such a scenario has recently been observed for the tau protein which has four repeats. While a construct consisting of repeats 1, 3 and 4 can serve as a seed for the entire 4-repeat tau segment, the inverse does not hold. On the other hand, the tau protein repeats with the characteristic U-turn shape can cross-seed Alzheimer's A β , and similarly the Islet Amyloid Polypeptide (IAPP). Within this framework, we suggest that the so-called 'central dogma' of amyloid formation, where aggregation takes place through non-specific backbone hydrogen bonding interactions which are common to all peptides and proteins, is a simple reflection of the heterogeneous, polymorphic free energy landscape of amyloid species. Here, we review available data and make some propositions addressing this key problem. In particular, we argue that recent theoretical and experimental observations support the key role of selective molecular recognition in amyloidosis and in determining cross-species barriers and transmission.

Graphical Abstract

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Keywords

beta-amyloid oligomers; amyloid fibril structures; Alzheimer's disease; prion; conformational selection; nucleation polymerization; energy landscape; conformational diseases

1. Introduction

Conformational diseases, such as Parkinson's and Alzheimer's, are related to proteins that unfold abnormally and form nonnative oligomeric or polymeric aggregates, which largely consist of β -sheet structures. Common characteristics of conformational diseases display late or episodic onset due to gradual accumulation of these aggregates and the acceleration of their formation by stress.¹ However, increasing evidence indicates that soluble oligomers of amyloidogenic proteins are both responsible for amyloidosis^{2; 3} and are the toxic agents.^{4–6} Some data suggest that their final large aggregates can also lead to cytotoxicity.^{7; 8} Thus, a complex picture emerges, where oligomers, fibrils, and fibril fragments/fibrillar oligomers can all be involved in cytotoxicity, albeit through different mechanisms.^{9; 10}

The two most studied amyloidogenic proteins are the prion protein in prion (mad cow) disease and amyloid β peptide in Alzheimer's disease. Prion diseases can cause fatal neurodegenerative infections that affect human and animals. The conformational changes of the prion protein underlie the biology of prion infection and strains. The normal prion protein (PrP^C) itself is not toxic; however, a conformational isoform of the prion protein (PrP^{Sc}) is able to polymerize and is neurotoxic. PrP^C has a partially structured N-terminal segment (1–100) and a well folded C-terminus (121–230) with short antiparallel β -sheets and three longer α -helices. There is no structural information for the isolated PrP^{Sc} protein, but its polymerized form is an amyloid fibril dominated by β -sheet conformation. The infectious prion protein is related to the PrP^{Sc} isoform, and can catalyze the conversion of the normal PrP^C form to the PrP^{Sc} isoform, and the autocatalysis of PrP^C to PrP^{Sc} is the prion replication process. The toxic form of the prion protein derives from either small oligomers, which are formed during the polymerization of the PrP^{Sc} isoform, or from intermediate species produced during the conformation conversion from PrP^C to PrP^{Sc}. Since the kinetics

of the autocatalysis has a long lag time, large scale spread of the PrP^{Sc} isoform in the infected host only occurs years after infection.

Amyloid β peptide (A β peptide) has been a paradigm for studies of amyloid formation and conformations. The full-length A β peptide has 40–42 residues when cut from its precursor protein. A β aggregates are observed in brain tissues of Alzheimer's patients,¹¹ and it is generally believed that A β peptide oligomerization is the major mechanism leading to neuron-cell death.⁷ In addition to the full-length A β peptides, a number of *in vitro*-generated β -amyloid fragments were also observed to form amyloid fibrils. The sequences cover all A β peptide regions: the N-terminus, middle, and C-terminus. Together, the full-length β -amyloid and its fragments constitute a warehouse of sequences prone to amyloid formation with a gigantic polymorphic range.¹² Experimentally, different full-length A β fibril conformations are preferred under different incubation conditions. A broad range of soluble A β forms have also been observed in AD and Lewy body (DLB) brains, and mouse models. For example, the amyloid β -Derived Diffusible Ligands (ADDLs) were proposed to have different morphologies and to exert their toxicity through different mechanisms.¹³ The molecular weight of globular amyloid β -peptide 'globulomer'¹⁴ is about 60 kDa. Another smaller soluble form, A β *56 causes memory deficiency in middle-aged mice.¹⁵ Finally, 'amylospheroids' (ASPDs), which are larger soluble oligomers^{16; 17} with higher mass (more than 100 kDa) were reported to have sizes ~10–15 nm.

Amyloids fold through diverse mechanisms which involve competing folding and binding events.¹⁸ Formation of oligomers and aggregates of amyloidogenic peptides make it difficult to predict and control their polymorphic range, preferred aggregate states, pathways leading to these, timescales, and the subsequent mechanisms of toxicity. Here, we view amyloid formation as a molecular recognition event. Within this broad framework, we discuss the conformational changes involved in amyloid growth within the same or across species and their recognition scenarios and consequences. The underlying mechanism of molecular recognition is (mutual) conformation selection with subsequent optimization, whether side chains and minor backbone movements in proteins; or bases and backbones in RNA/DNA; or in membrane lipid heads and tails. Below, we first describe the mechanism in the healthy functional state in general terms with some examples. We follow with amyloid polymerization. Overall, because of the clear relevance to disease, we expect research in the coming years to increasingly focus on transmission (self-replication) and cross-species barriers.

2. Conformational selection in functional proteins

Stable, folded proteins in crystal structures have well defined three-dimensional structures, which are not as dynamic as those in solution. In solution, proteins exist as conformational ensembles and their populations follow thermodynamic distributions.^{19–21} Local energy fluctuations in water range between 10 to 20 kcal/mol (16.8 to 33.6 kT at 300K),²² which is enough to perturb a well folded protein to a vast number of states. The conformational differences can be small or large; and some conformations are more populated than others (Figure 1A). The more flexible are the proteins the larger the number of their populated states.

The distribution of protein conformations derives from their polymeric nature; however, it is optimized by evolution to fit their functions. Proteins function through their interaction with other molecules. The traditional 'lock and key' mechanism states that a protein has to have an exact match with its ligand to form a functional complex. The 'induced fit' hypothesis²³ argues that the fact that protein complexes often have different conformations from those of their unbound protein constituents, suggests that the bound conformation is 'induced' by the binding partner. The 'conformational selection and population shift' model^{24–27} provides a more detailed description of the real molecular mechanism which prevails in cellular life. The conformational selection concept recognizes that both binding partners are flexible and have conformational distributions. During binding, higher energy (lower population) conformers which are most complementary to some pre-existing ligand conformations can be selected and the equilibrium shifts toward these conformers (Figure 1B).^{24–27} Increasing experimental evidence obtained from single molecule, NMR, and other techniques has validated the conformational selection mechanism.^{28–31}

Nature has used and optimized conformational selection to facilitate normal functions, for example, in enzyme catalysis with step-wise conformational selection^{32; 33} and in transcription factor binding^{34–36} to help recognition of specific DNA regulatory elements; it has used it for functions of folded proteins as well as functions of the disordered states.^{37; 38} For the natively disordered states, the highly flexible protein conformations similarly have preferred conformational ensembles.³⁹ As shown in Figure 1B, the conformation that fits some pre-existing receptor conformation will be selected, get stabilized, with a subsequent equilibrium shift toward this conformation. As described in the next section, such mechanism also applies to mis-folded, denatured (or disordered) states and can lead to amyloid formation.

A recent example illustrates conformational selection in a multi-domain protein, with a hinge in its linker^{40; 41} which can present large scale conformational changes over high barriers. The tandem RNA recognition motif domains of U2AF65 are efficiently recruited to the intron during spliceosome assembly, and have two different domain arrangements in the absence and presence of a high affinity ligand. Conformational selection and population shift between the closed and open conformations of U2AF65 account for recognition of sequence variation,⁴² and the equilibrium between the two conformations quantitatively correlates with the natural variability in the polypyrimidine tract. The Suc1 protein is an example of conformational selection and population shift for two native states, a monomer and a domain-swapped dimer. Single point mutations shift the equilibrium between the states which lead to altered ligand binding preferences.⁴³ Another example, which like amyloids also presents a broad heterogeneous landscape, relates to DNA sequence recognition by a transcription factor (TF). The DNA contains a very large number of response elements (REs) which can be recognized by a TF, with each relating to regulation of a *specific* gene. How does the TF know which to bind?⁴⁴ The affinity (conformational compatibility) appears to play a key role: if the concentration of the TF is low, it will bind only to high affinity REs. On the other hand, if the TF concentration is high, it will bind all its respective REs so long as they are exposed (not covered by nucleosomes in the compact, folded chromatin).³⁴ Current data suggest that TF concentration in the nucleus is high, and all exposed REs are bound to their corresponding TFs. In amyloids, the concentration is expected to always be

very high, which suggests that all polymorphic seeds will be populated and grow, although as we discuss below, at different time scales which depend on the distribution of the populations. In regulation, subsequent events will differ: Because the REs have slightly different sequences, the bound TF will (allosterically) display a slightly different surface, which will be recognized by another protein cofactor. Selective molecular recognition has a physical basis similar to that taking place in crystallization processes.

3. Nucleated polymerization and conformational selection in homo-molecular amyloid formation

Conformational diseases start with perturbation of normal folded proteins, which lead to some conformational changes. Following cleavage from the APP precursor protein and getting away from the membrane environment, the A β peptide is mostly disordered. Polyglutamine in Huntington disease is also a natively disordered protein. However, not all amyloidogenic proteins are completely unfolded. β_2 -microglobulin is a good example of a protein which forms amyloids either from the completely denatured state under highly acidic conditions or through less disrupted states.⁴⁵ The long and straight amyloid (LS) fibril forms through a nucleation-dependent mechanism, leading to parallel, in-register β -sheet.⁴⁶ In less acidic conditions and high ionic strength, β_2 -microglobulin spontaneously forms worm-like (WL) fibril via a non-nucleated pathway.⁴⁷

In general, proteins in disordered states are more like synthetic organic polymers, which typically follow nucleation-dependent pathways, with long time scales for accumulation of aggregates and absence of lag times in the presence of 'seeds'. Protein aggregation from highly disordered states can be viewed as analogous to aggregation of colloidal particles, with certain unique polymer dynamics.⁴⁸ The aggregation of the A β peptide is surprisingly similar to the self-assembly of block copolymers into nanofiber micelles.⁴⁹ Depending on the solvent properties, the phase diagrams of block copolymers can present nano-structures with chain-like, spheres, and vesicles morphologies, which are comparable to the linear fibrils, nanospheres, and ring-like structures observed for A β peptides. In a certain sense, the sequence of full length A β peptide resembles a block copolymer with a highly polar and charged N-terminal and a non-polar C-terminal segment. Some studies indicate that the neurotoxicity of A β 42 is mediated by a nucleated polymerization process rather than by discrete A β 42 species.⁵⁰

Unlike the synthetic block polymer, the protein backbone atoms are able to form hydrogen bonds; thus, the nucleation of amyloidogenic proteins is not a simply random micelle aggregation. Secondary structure features can be expected to accompany initial nucleation processes; and to be stabilized, pre-nucleation intermediates need to sample intramolecular β -sheets.⁵¹ At the pentamer level, TEM (transmission electron microscopy) and AFM (atomic force microscopy) images indicate that A β 42 pentamers are round disk-like particles.⁵² However, the loosely packed pentamer is unlikely to be stable.⁵³ H/D exchange protection experiments indicated that there are turns in the His13-Gln15, Gly25-Gly29, and Gly37-Gly38 regions,⁵² which suggest an intra-chain β -hairpin structure for the pentamer. Mixtures of intra-chain β -hairpin turns and α -helical regions can account for most of the

experimental H/D exchange protection data.⁵³ Consistently, several kinetic models considered the nucleation of nanosized amyloid fibrils to be composed of successively layered β -sheets at the molecular level, which make it possible for (β -strand) segments to directly interact with, and extend the β -sheets.^{54; 55} Nucleation and oligomer formation at this stage may resemble a 'molten globule',⁵⁶ which has native-like secondary structures; but without a tightly packed protein interior, whose formation may follow via conformational selection.³¹ Nucleation polymerization can be viewed as multiple such molecular recognition processes which allow fast seed growth (Figure 2, top panel).⁵⁷ In the prion protein, localized small sequence segments were observed to be able to initiate distinct intermolecular recognition events that drive the formation of different amyloid assemblies. These segments control the nucleation and templating of soluble protein structures, catalyzing their transformation into prion amyloid strains.⁵⁸ Further, templating can take place even in the earliest events of aggregate nucleation.⁵⁶

Some amyloidogenic proteins form amyloids near their native states.^{59; 60} *S. solfataricus* acylphosphatase remains in a native-like conformation which persists even when the protein forms the initial aggregates.⁶⁰ The spontaneous formation of worm-like (WL) β_2 -microglobulin fibrils via non-nucleated pathways⁴⁷ can provide an example of conformational selection in the early amyloid formation stage. A (relatively minor) perturbation of a folded β_2 -microglobulin can generate certain conformations that can act as templates. Deletion of the first six residues of β_2 -microglobulin can shift the equilibrium toward amyloidogenic conformations, which can serve as templates to select (catalyze) amyloid formation by wild-type β_2 -microglobulin.⁶¹ Proline cis-trans isomerization may also accelerate conformational changes of β_2 -microglobulin.⁶² It is possible that highly amyloidogenic conformations relate to domain swapping. Single domain antibody can trap a domain swapped dimer of N6 β_2 -microglobulin.⁶³ Domain opening of β_2 -microglobulin was observed in early molecular dynamics simulations, even when the disulfide bond was left intact.⁶⁴ When the disulfide bond is rearranged, swapping leads to β_2 -microglobulin fibrillation.⁶⁵ Domain swapping has been proposed to be one of the general mechanisms for amyloid formation.^{66; 67} Other amyloidogenic proteins, like p13suc1,⁶⁸ human stefins,⁶⁹ and human cystatin C⁷⁰ were proposed to form amyloids via domain swapping. A recent MD simulation suggested that the aggregation of γ -crystallins associated with human cataracts may also follow a domain swapping mechanism.⁷¹

Figure 2 summarizes the initial nucleation processes. The top yellow box highlights the initial perturbation or unfolding of the native protein structure which leads to the formation of small oligomers; the blue box in the middle panels illustrates the nucleation polymerization pathway and the green box symbolizes molecular recognition. Even though two pathways (nucleation polymerization and molecular recognition) are depicted, they are not necessarily entirely distinct. In the middle panel, we also highlight the formation of spherical oligomers. Stable spherical oligomers may not convert to amyloids directly. Some oligomers can have homogenous distributions. For example, it has been estimated that the A β 42 globulomer has exactly 12 monomers.¹⁴ Even though their formation may be under kinetic control and depend on solution conditions;^{72; 73} spherical oligomers may need to be thermodynamically stable and are unable to grow through conformational selection. Molecular dynamics simulations suggested that the A β 42 dodecamer globulomer may have

orthogonal β -sheets,⁷⁴ although under different environment, other globulomer forms are possible.⁷⁵

Figure 3 illustrates two A β 42 globulomer models (GO1 and GO3). The correlation of the NH solvation factors of the GO3 model with experimental H/D exchange protection ratio for the A β 42 fibril may suggest that the globulomer model has a biological role.^{53; 74} As shown in the figure, GO1 could be the most stable conformer for A β 42 dodecamers, satisfying the thermodynamic stability condition. In both GO1 and GO3 the edge β -strands are blocked, indicating that further growth of the globulomer beyond dodecamer is unlikely. Molecular recognition may play a role in the initial globulomer formation, because the A β 42 globulomers can be promoted by fatty acids.¹⁴ The orthogonal β -sheets conformation in globulomer models (GO1 and GO3) resemble the fatty acids proteins binding motif (Figure 4III), and it is possible that binding between fatty acids and the A β 42 globulomer selectively favors orthogonal β -sheet conformations.

Following the lag period, amyloid growth is likely to be dominated by molecular recognition (pink box, Fig 2). For A β 42, because the C-terminal β -sheet in proto-oligomers is largely curved, which impedes fast growth along the fibril axis, the conformation of the seed may consist of two stacked U-shaped proto-oligomer β -sheets.^{74; 76} In Figure 3, we illustrate two fibril seed conformers of A β 42, one with ‘traditional’ double- β -sheet conformation;^{7; 52; 77; 78} the other with the recently proposed triple- β -sheet conformation, which may be favored for the E22Q Dutch mutant in Alzheimer’s Disease.⁵³ The edge β -strands in the seed would select an approaching A β 42 peptide with similar conformation, which would catalyze fibril formation. This conformation selection mechanism was termed a ‘dock and lock’ mechanism for the deposition of soluble monomers onto a growing amyloid.⁷⁹ The ‘dock and lock’ mechanism is mediated by two distinct kinetic processes: in the first ‘dock’ (conformational selection) phase, the addition of A β to amyloid seeds can be reversible, while in the second ‘lock’ (minor induced fit optimization) phase, the deposited peptide becomes irreversibly associated with the template in a time-dependent manner.⁸⁰ Thus, conformational selection is consistent with the energy landscape description that Massi and Straub used to explain A β amyloid growth by a ‘dock-lock’ mechanism⁷⁹. The monomer does not necessarily have a stable β -sheet conformation; however, the selected conformation can react and reorganize at the growing fiber tip.⁸¹ Conformational selection of fibril morphology through multiple rounds of seeding is also commonly used to generate samples for structural studies and may also be important in biological processes.

4. Molecular recognition in hetero-molecular and cross-species amyloid formation

Prion strain-specific properties create prion transmission species barriers. Prions isolated from one species are often less infectious to others (i.e., incurring longer incubation time and reduced attack rates). The explanation relates to the differences in the amino acid sequence which delay the initial conversion process from the PrP^C form (species A) to the PrP^{Sc} isoform (species B). Different strains may co-exist; however, with different tendencies to induce toxic effects in different organs. Prion strains have been one of the most puzzling

phenomena.⁸² Even though it has been suggested that prion strains derive from different PrP^{Sc} isoform conformations, their structural basis has been elusive. To have specific replication properties, the conformation must be sufficiently stable and this is only possible with the oligomerized PrP^{Sc} isoforms. The compatibility between conformations of two co-existing sequences in the ensemble decides the cross-species transmission. Recent studies indicated that the stability of amyloid oligomer correlates with the conformational stability of the prion strain.^{83; 84} Sequence differences alone cannot selectively account for species barriers if the seeds are prepared following identical procedure,⁸⁵ which can lead to amyloids with similar structures. For example, two HET-s prions with only 38% sequence identity may have highly similar structures, and consequently can efficiently cross-seed each other.⁸⁶

The structural basis of prion strain variants was proposed to relate to different amyloid cores formed from different amino acid recognition segments.⁸³ Atomic level evidence has also emerged. Three X-ray structures were solved for the same segment from human, mouse, and hamster PrP. This segment is critical for forming amyloid and confers species specificity in PrP seeding experiments. The structures reveal that as expected, sequence differences can accompany structural variability, which gives rise to transmission barriers, such as those that protect humans from acquiring bovine spongiform encephalopathy (BSE) and chronic wasting disease (CWD).⁸⁷ This supports the mechanistic role of conformational selection in transmission barriers, where the barriers relate to overlap of the populations of the species (Figure 4I).⁸⁸

Structural similarities can lead to amyloids composed of different sequences. The U-shaped β -sheet, which was initially found for A β peptides, has been observed to constitute a common amyloid structural motif, and consequently, A β peptides may interact with other molecules in amyloid formation. Experimentally, such cross-sequence interaction between A β 40 and IAPP peptides has been observed, leading to amyloid hetero-assembly.⁸⁹ This cross interaction may provide the molecular explanation for the apparent link between AD and type II diabetes.⁹⁰ A β 42 also interacts with prion proteins in the Alzheimer brain,⁹¹ and with tau protein, to form soluble complexes that may promote self-aggregation, in both cases into the insoluble forms observed in Alzheimer's.⁹² A computational study indicated that A β 42 may interact with three domains in the tau protein, the R2, R3, and R4 repeats; all with high β -structure propensity. Among these, A β 42 oligomers are likely to interact with the R2 domain to form a stable complex with better alignment in the turn region and the β -structure domain⁹³. Further, it is known that there is synergistic fibrillation between tau and the α -synuclein protein.⁹⁴ However, it still remains to be seen if A β 42 or A β 40 can trigger amyloid formation of α -synuclein. The high potential of the A β 42 peptide to induce other proteins to form amyloids makes us echo the question 'is Alzheimer's disease infectious?'⁹⁵

It is interesting that cross amyloid seeding may be a 'one way street' in some cases. The tau protein exists in two major isoforms: one with four microtubule binding repeats; the other without the second repeat. A peptide construct with all four repeats is called K18 peptide, and the construct with three repeats (R1, R3 and R4) is called K19. K18 and K19 can mix and co-assemble into heterogeneous filaments.⁹⁶ However, when mixing preformed seeds from individual solutions of K18 or K19, the K19 seeds can recruit both K19 and K18 to

form amyloids, while K18 seeds can only recruit K18, but not K19.⁹⁷ The asymmetric barrier between K18 and K19 indicates a population-dependent⁸⁸ cross-species transmission of amyloid structure. As shown in Figure 4II, if the polymorphic amyloid population of species C has some forms which are similar to the seeds from species D, then seeds from species D can recruit and catalyze amyloid formation of species C. However, because the major amyloid form of species C does not have corresponding polymorphic population in species D, the seeds from species C cannot recruit species D to form amyloids. The K18 and K19 tau isoforms might be exactly such a case, which indicates that a sequence and structural compatibility with an amyloid structure with higher population will eventually control the transmission rate. This suggests that it could be more relevant to study an ensemble of amyloid motifs rather than focus on one specific structure.

Conclusions

The ‘central dogma’ of amyloid formation has long held that aggregation takes place through non-specific backbone hydrogen bonding interactions which are common to all peptides and proteins. However, when we consider that the β -pleated sheet structure, which is the building block of amyloid fibers, is the thermodynamically most stable supramolecular arrangement of all the possible peptide dimers and oligomers,⁹⁸ and the broadly heterogeneous, polymorphic free energy landscape of amyloid species, these nonspecific hydrogen bonds may well be an integrated reflection across all such β -sheet containing species. These generic interactions do not explain the species barriers. It is challenging to figure out the key interactions and their organization which would allow seeding and cross-seeding (Figure 4), and currently it is still unclear whether a quantum mechanical treatment⁹⁸ would be needed, or a classical molecular dynamics approach^{99; 100} would already be able to obtain coherent clues. Protein conformational dynamics and transformation into amyloid species are built into the amino acid sequences. The high energy fluctuations in water make the protein exist as an ensemble of states. A change in the solvation environment, mutational events, binding of small molecules,¹⁰¹ or a shift in the biological balance in the human body can lead to nonnative, populated protein conformations. These conformations may be selected to form polymeric aggregates which underlie the molecular mechanisms for many conformational diseases.

Selective macromolecular recognition governs biological processes; and conformational selection and population shift with subsequent, minor, optimization is the key recognition mechanism.¹⁰² The fundamental role played by molecular recognition of amyloid surfaces¹⁰³ was recently highlighted in the case of a B10 antibody fragment, which displays conformation-specific binding to amyloid fibrils. Remarkably, among the highly variable amyloid surfaces present in the ensemble, B10 binds amyloid fibrils from D- or L-amino acid peptides and non-proteinaceous biopolymers which present highly regular and anionic surface properties, thus illustrating discrimination of distinct fibril populations. These data establish that B10 binding does not depend on an amyloid-specific or protein-specific backbone structure. Instead, it involves the recognition of a highly regular and anionic surface pattern.¹⁰⁴ Even though it was suggested that conformational selection could be a mechanism for prion infection, the molecular and atomic underpinnings for this earlier proposal were missing. In this review, we address molecular recognition events in key stages

in amyloid formation: nucleation polymerization and seeded growth. We further relate these events to prion strain variance, infectivity and cross-species transmission. We suggest that prion behavior is not unique in this sense, as recently shown by cross-seeding of tau protein repeats isoforms by Margittai and his colleagues.⁹⁷ The asymmetric cross-seeding observed for the tau repeats constructs underscores the generality of this concept. Cross seeding of amyloids is controlled by selective recognition, where higher population will eventually govern the transmission rate. Even though two species may present similar amyloid organization, the differences in their dominant and most populated conformers may be responsible for the asymmetric transmission barrier. The challenge is to figure out the recognition sequences and motifs; the prevailing populations; and the range of their conformational states. The potential occurrence of cross seeding in disease, in addition to prion and tau proteins, as also for example for A β and IAPP,⁹⁰ and albumin,¹⁰⁵ if the species populate the same organs or environment, emphasizes these problems. The highly complex free energy landscapes of amyloids, the enormously heterogeneous population which can easily shift in experiment and under different simulation protocols, make these studies difficult. Further, subtle differences in the conformations and their compatibility can lead to different outcomes. The sequence and structural basis of molecular recognition mechanisms in amyloid formation and propagation follow the principles of functional processes in the cell. It has been suggested that within a set of select proteins, prion-like transmission of biological information can arise spontaneously; yet specifically. These metastable proteins can be intricately linked to stress-response pathways.¹⁰⁶ Together, these critical aspects of amyloid behavior challenge our imagination.

Acknowledgements

This project has been funded in whole or in part with federal funds from the National Cancer Institute, National Institutes of Health, under contract number HHSN261200800001E. The content of this publication does not necessarily reflect the views or policies of the Department of Health and Human Services, nor does mention of trade names, commercial products, or organizations imply endorsement by the U.S. Government. This research was supported (in part) by the Intramural Research Program of the NIH, National Cancer Institute, Center for Cancer Research.

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Highlight:

- Conformational selection is the key mechanism in biomolecular recognition.
- Mayloid seed formation may be classified by the type of association events that take place: random nucleation coupled with molecular recognition followed by rearrangement; and directly via conformational selection without nucleation.
- Amyloid growth is similarly a molecular recognition event. Cross seeding of amyloid species is also governed by conformational selection of compatible (complementary) states.

Figure 1.

An illustration of conformational selection and population shift in protein recognition. Top: four protein conformations with different populations are shown as A, B, C, and D. The ligand may have conformation α , β , γ and δ . The mutual conformational selection between protein and ligands may generate five (roughly typical of real scenario's) leading conformers: A α , B β , C γ , D γ , and D δ . The B β conformer has the highest population in final complex.

Figure 2.

Conformational selection mechanism may operate in the early and late stages of amyloid polymerization. The top yellow box highlights that the initial perturbation or unfolding of the native protein structure can lead to the formation of small oligomers (top yellow box); the formation of nucleation site for further polymerization may take long time for total disordered monomers, with many rounds of association-disassociation events. Partially unfolded proteins, as in the case of domain swapping, may accelerate the formation through direct molecular recognition. The middle panels relate to the formation of larger oligomers. The blue box is the nucleation polymerization pathway and the green box depicts molecular recognition. The middle panel also highlights the formation of spherical particles. In the bottom panel, molecular recognition dominates fibril growth, with possibly leading to polymorphic amyloid states. Molecular recognition takes place via mutual conformation selection and population shift.

Figure 3.

Unlike amyloid seed oligomer, globulomers cannot recruit additional monomers to extend their size through conformation selection. (I) A β 42 globulomer model with parallel β -sheets (GO1 model). (II) A β 42 globulomer model with antiparallel β -sheets (GO3 model). The interlocking of two hexamer β -sheets makes the globulomer unable to bind incoming β -strands. (III) The orthogonal β -sheets conformation of the globulomer models is similar to the motif of 'classical' fatty acids binding proteins (pdb code: 1eal). (IV). Structure of a traditional amyloid motif with double β -sheets conformation. (V) Structure of a traditional amyloid motif with a triple β -sheets conformation, which may explain E22Q Dutch mutation in Alzheimer's Disease⁵³.

Figure 4.

Amyloid cross-seed growth is decided by the overlap in the populations of polymorphic amyloid structures. (I) This is the case where both species A and B share a similar structure with high population. The amyloid formation should be transmittable freely between species A and B. (II) If species C has some polymorphic population of an amyloid form which is similar to the seeds from species D, then seeds from species D can recruit and catalyze the amyloid formation of species C. (III) However, because the major amyloid form of species C does not have corresponding polymorphic population in species D, the seeds from species C recruit species D to form amyloid.