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Strain phenomenon in protein aggregation

Interplay between sequence and conformation

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Studies of yeast and mammalian prions introduced the idea that the protein aggregates can exist in multiple stable conformations that can be propagated by seeding. These conformational states (aka strains) were shown to have distinct physical (secondary structure, stability) and biological (cytotoxicity, infectivity) properties. For mammalian prions they were also tied to differences in disease pathology and incubation time. It was later shown that this phenomenon is not limited to prion proteins, and distinct conformational states of amyloid fibrils and oligomers derived from a variety of proteins can be propagated both in vitro and in vivo. Moreover, in some cases these conformations were preserved even when propagated into a protein with a different sequence. There is now an increasing body of evidence that strain phenomenon is a generic feature of protein aggregation, and characteristic features of amyloid strains can be transmitted between unrelated sequences.

Keywords: prion, amyloid, strains, protein aggregation, seeding

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For decades our understanding of protein structure has been driven by Anfinsen's dogma: a protein possesses a single native structure that is determined only by its amino acid sequence.[1] Discovery that proteins can be infectious,[2-4] and that this infectivity is due to an autocatalytic conversion of a protein into a different, misfolded conformation,[5,6] represented a significant milestone in biology. Together with the concept of intrinsic disorder[7,8] this discovery showed that protein conformation can be plastic and malleable.

Initially autocatalytic conversion of proteins into misfolded, β-sheet rich conformation was proposed in order to explain the unusual properties of transmissible spongiform encephalopathies (TSEs) where prion protein (PrP) serves as an infectious agent.[2-4] These diseases are caused by misfolding and aggregation of prion protein (PrP^{C}) into fibrillar aggregates (PrP^{Sc}).[9] PrP^{Sc} fibrils can be transmitted between individuals and propagate themselves by seeding. Seeding process involves binding of a PrP monomer to a PrP^{Sc} fibril followed by conversion of this monomer to a conformation closely resembling that of an initial aggregate.[10] This mechanism of propagation is common for all amyloids. However, not all of them are infectious in vivo. Other factors such as the ability of protein aggregates to fragment and self-propagate in physiological conditions and their resistance to clearance are necessary to make the amyloid infectious.[11,12]

An important feature of TSEs is the presence of multiple disease strains. Strains have been initially defined as the isolates of infectious prions characterized by the specific incubation time of the disease, characteristic neuropathological lesions, and in some cases certain patterns in animal behavior that are faithfully recapitulated upon serial passage.[13,14] For example, Hyper and Drowsy TSE strains lead to, respectively, increased and decreased activity of infected animals.[15] It has been shown that different disease strains correspond to distinct conformations of PrP fibrils as they can be differentiated by the protease cleavage pattern,[16] antibody

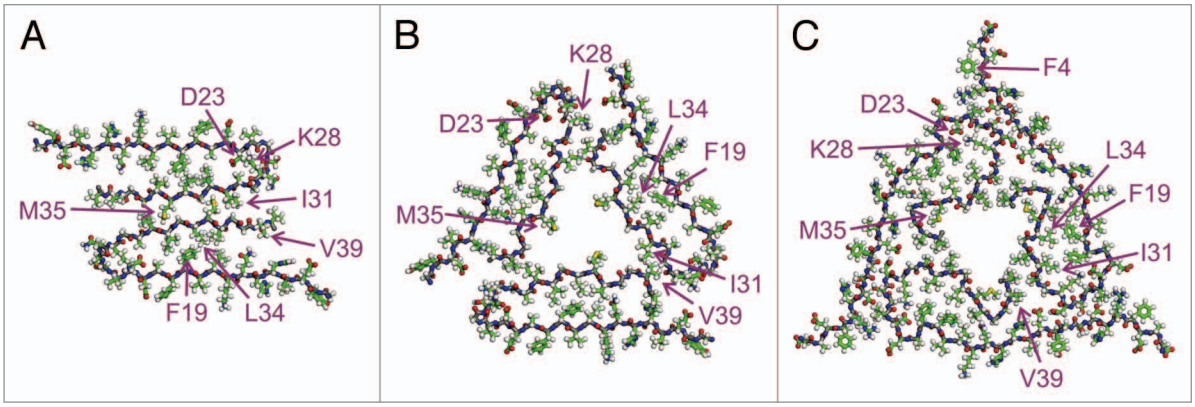

Figure 1. Molecular structures of Aβ40 fibrils. (**A**) Aβ40 fibrils prepared with shaking. (**B**) Aβ40 fibrils prepared in quiescent conditions. (**C**) Aβ40 fibrils isolated from the AD patient. Adapted with permission from ref. 29

reactivity,[17-19] resistance to denaturation,[20] and FTIR spectra.[21] Stability of PrP fibrils was shown to be inversely proportional to the incubation time for the prion disease in vivo,[20] and replication rates of prion strains were shown to be inversely proportional to their conformational stability.[22,23] Later the strain phenomenon was discovered for other amyloidogenic proteins, and the inverse relationship between rate of propagation and stability was found to hold for other proteins as well.[24,25]

Conformational polymorphism of amyloid fibrils is based on their common structure. The atomic architecture of most amyloid fibrils consists of 2 fundamental units: 1) a cross-β spine composed of in-register, parallel, intermolecularly stacked β-sheets running perpendicular to the fibril axis,[26-28] and 2) a motif formed between tightly interdigitated side chains interface between β-sheets known as steric zipper.[26] Structural polymorphisms such as the variations in the folding patterns of the β-sheets,[28,29] length of the amyloid core,[25] and interface between the β-sheets[10] can be propagated from the initial fibrils onto the daughter fibrils by seeding. Since the aggregates are stabilized by intermolecular interactions of β-sheets, even relatively small differences in protein conformation between the aggregates can give rise to distinct protein conformations can become kinetically trapped in local minima on the potential energy surface.

Aggregation of the Aβ40 peptide can serve as a good example of structural polymorphism of amyloids. Incubation of this peptide in buffer with shaking results in formation of fibrils consisting of 2 stacked cross-β strands with parallel in-register alignment (**Fig. 1A**).[30] Fibrils formed by the same peptide in quiescent conditions have twisted morphology and consist of 3 cross-β strands with the same parallel alignment (**Fig. 1B**).[28] Aβ40 fibrils isolated from the Alzheimer disease patients are also composed of 3 cross-β strands, but there are subtle structural differences between them and the fibrils prepared in vitro.[29] For example, fibrils isolated from an AD patient have several kinks and bends in their structure (**Fig. 1C**)[29] that are missing in the fibrils prepared in vitro (**Fig. 1B**). Moreover, similar subtle differences were observed between the fibrils isolated from different patients.[29] All of these fibril strains can be propagated by seeding preserving their unique structural features.

When stable strains of amyloid fibrils are propagated in the conditions different from those used in their preparation (e.g., transition from in vitro to in vivo or a change in pH), they may adapt to the altered environment by changing their structure. This phenomenon (dubbed "deformed templating") has been especially well described for mammalian prions (**Fig. 2**),[31] although it has been observed for other proteins as well.[32] When new mammalian prion strains were created by infecting the animals with the amyloid fibrils prepared from recombinant PrP, animals often failed to show clinical signs of disease and if they did, the incubation time was very long.[5,33] However, after multiple serial passages the incubation time shortened and the clinical signs of disease appeared.[33,34] This process was accompanied by the decrease in conformational stability of the amyloid[5,20] and by the dramatic change in the protein folding pattern within the fibrils.[35] Since a protein has to unfold before incorporation into an amyloid fibril,[36,37] it may refold into a slightly different conformation upon incorporation into a fibril if a new conformation is more thermodynamically stable and kinetically accessible.

Similar sequences containing complementary in shape residues may form mixed steric zippers. These sequences may be derived from different parts of the same protein or from different proteins. Co-aggregation of different proteins into mixed sequence steric zippers can lead to cross-seeding of these proteins when the fibrils of one protein initiate the aggregation of another. For example, in case of curli proteins involved in bacterial biofilm formation an outer membrane protein CsgA serves as a fibril seed while the biofilm-forming fibers themselves are primarily composed from a related protein CsgB. Both CsgA and CsgB subunits can seed aggregation of CsgA proteins from other bacteria despite significant sequence differences.[38] Moreover, curli proteins can promote aggregation of other, unrelated proteins such as fragments of prostatic acid phosphatase.[39] Cross-seeding has been observed for a variety of proteins both in vitro and in vivo. In vivo cross-seeding has been observed for tau and α-synuclein,[40,41] amyloid β and prion protein,[42] and for serum amyloid A and lactadhedrin.[43]

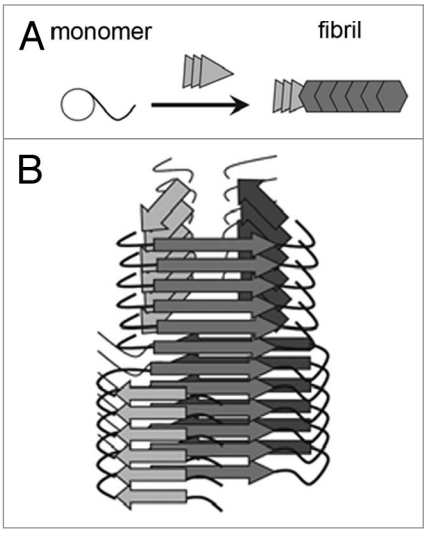

Figure 2. Deformed templating is a change in the β-sheet folding pattern of amyloid fibrils in the course of seeded aggregation. (**A**) Schematic representation of the mechanism. (**B**) Representation of deformed templating within an individual fibril. Adapted with permission from ref. 31

However, the ability to cross-seed aggregation depends on both the sequences of the proteins involved and the structure of the initial aggregate. High sequence similarity is usually required for effective cross-seeding[44,45] although there are exceptions (e.g., α-synuclein and tau or Aβ40).[40,44,46,47] In some cases (e.g., Aβ40 and Aβ42) cross-seeding is unidirectional with Aβ40 fibrils able to seed the aggregation of Aβ42 but not the other way around.[48] Amyloid oligomers are also capable of cross-seeding and may even be more efficient at it than fibrils. For example, Aβ oligomers could seed oligomer formation from tau[49] and α-synuclein.[50]

Protein conformation also plays an important role in the ability of fibrils to cross-seed their aggregation. For example, Guo et al.[40] have recently shown that ability of α-synuclein fibrils to seed tau aggregation in vivo depends on their conformation. While newly formed α-synuclein fibrils could seed the aggregation of endogenous α-synuclein, they could not cross-seed tau aggregation. However, when α-synuclein fibrils were propagated in vitro for several generations, their conformation was altered as indicated by their proteinase K digestion pattern and they gained the ability to seed tau aggregation.

Can the strain identity be preserved upon cross-seeding to a different sequence? Initial evidence of propagation of different fibril strains across multiple sequences came from mammalian prions. The phenomenon of "species barrier" in prion propagation occurs when a prion strain is seeded into a different host species.[51,52] Sequence differences between prion proteins from different species are not particularly large but key amino acids in the regions important for fibril formation are often affected. Some prion strains are unable to cross the species barrier and seed aggregation of proteins with different sequences while others do it efficiently.[51] vCJD strains responsible for "mad cow disease" are good examples of the latter.[53] In some cases seeding across the species barrier will still trigger the disease but strain-specific features will be lost and the disease strain more typical for the host species will appear instead.[32,52,54] It has been proposed that the protein sequences that can adopt a wider range of conformations are capable of supporting a wider variety of prion strains.[55] Similar phenomena are observed for other amyloidogenic proteins. In some cases yeast prions can seed formation of each other while preserving strain identity.[56,57] But for sequences with lower degree of similarity loss of strain identity is a more typical outcome.[58] The outcome can also be strain-dependent as was shown for hamster PrP fibrils[59] where one strain preserved its conformation after cross-seeding into mouse PrP while another lost it.

Given the presence of multiple aggregation-prone proteins in human proteome, the possibility of their cross-seeding or co-aggregation is very important. In general, cross-seeding by amyloid fibrils is subject to several conditions that need to be met simultaneously[44] and thus relatively rare. However, many disease-associated amyloidogenic proteins (tau, amyloid β, α-synuclein, IAPP) are capable of cross-seeding. Since these proteins tend to be foldable IDPs, disorder may allow for higher structural flexibility necessary to accommodate diverse conformations required for effective cross-seeding.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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