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Kinetic Control of Amyloidogenesis Calls for Unconventional Drugs To Fight Alzheimer's Disease

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ABSTRACT: Computer simulations had predicted that amyloid fibrillogenesis is governed by free energy barriers and kinetic traps (kinetic control), rather than the free energy of the final aggregates. The simulations suggested that the diversity in fibril morphologies can originate from variations in the number of protofilaments which has been confirmed by recent cryo-electron microscopy studies of amyloid-β fibrils derived from brain tissue of Alzheimer's patients. The kinetic control of fibril formation and polymorphism imply that chemical substances with new mechanisms of action are needed to fight Alzheimer's disease.

KEYWORDS: *Amyloidogenesis, Alzheimer's disease, fibrillogenesis, molecular dynamics, coarse-grained simulations*

Alzheimer's disease is an incurable disorder of the brain. Fibrils consisting of the 40-residue and 42-residue peptides called amyloid-β (Aβ) accumulate in the brain very slowly, a multistage process that usually requires decades. Although Alzheimer's disease was diagnosed for the first time more than 100 years ago, the toxic species and their mechanism(s) of formation and neuronal damage are still elusive. For instance, the severity of the pathology does not seem to correlate with the amount of fibrils purified from postmortem brain tissue of Alzheimer's patients. Here, I propose that the development of anti-Alzheimer's drugs should take into account the kinetic control of fibrillogenesis, which was first observed in computer simulations of amyloid aggregation.

A recent cryo-electron microscopy (cryo-EM) study has shown that Aβ amyloid fibrils from Alzheimer's patients are right-hand twisted and polymorphic.[1] The polymorphism originates from variability in the number of intertwined protofilaments while the individual protofilaments have identical structure. The right-hand twist and variable number of protofilaments observed in the recent cryo-EM study[1] are remarkably similar to the fibrillar morphologies predicted a decade ago by molecular dynamics simulations of amyloid self-assembly with a coarse-grained model (see Figure 2 of ref 2). The simulation study revealed that, at conditions of low aggregation propensity, the most frequent fibrillar morphologies are not necessarily the most stable which is in essence a kinetic rather than thermodynamic control. More in detail, the simulation results provided evidence that specific intermediates compete for fast growth, and the population of a given morphology depends more on the production rate of the previous morphology-competent intermediates than the relative free energy of the final aggregates (Figure 1). In other words, amyloid fibril formation is under kinetic control as the free energy barriers and kinetic traps (pronounced local minima) along the self-assembly pathways determine the outcome of the aggregation process.

Concerning the early phase of aggregation, one of the first atomistic simulation studies of a dimeric Aβ peptide system had suggested that kinetic trapping governs dimerization and the formation of early aggregates.[3] Thus, computer simulations have predicted that the early oligomers[3] as well as the fibrillar structures[2] are trapped in local minima and accumulate because they are easy to form. The multimolecular process of amyloid fibrillogenesis and protein folding which involves a single macromolecule are both governed by noncovalent interactions and the hydrophobic effect. On the other hand, the kinetic control of amyloid self-assembly is a substantially different mechanism than the thermodynamic control of protein folding. Most of the individual domains of globular water-soluble proteins populate only two states at equilibrium, the folded structure and the unfolded state. Under physiological conditions the vast majority of globular proteins fold to a single compact (and functional) state which is the lowest minimum of the free energy. Kinetic traps along protein folding have been observed only sporadically as nature has optimized proteins for their function and for efficiently reaching the functional (i.e., folded) state.

The recent cryo-EM study focuses on the products of the self-assembly process, i.e., the structures of the fibrils from Alzheimer's brain tissue and their differences with respect to the fibrils generated in vitro from synthetic or recombinant Aβ peptides.[1] The cryo-EM structures validate the previous computer simulations,[2] and, in turn, the simulation results complement the structural data with a description of the fibrillogenesis pathways and kinetics. More precisely, the kinetic control observed in simulations of amyloid self-assembly[2] that result in similar polymorphism as in the cryo-EM structures[1] suggests that a similar kinetic control determines the distribution of different morphologies of fibrils from Alzheimer's brain tissue.

The kinetic control of dimerization[3] and fibrillogenesis[2] calls for new types of self-assembly modulator that interferes with the kinetics of Aβ peptide aggregation rather than the end products of self-assembly. Such modulators (small molecules or antibodies) should provide structural stabilization to the fibrillar states that are not toxic. This strategy is rather

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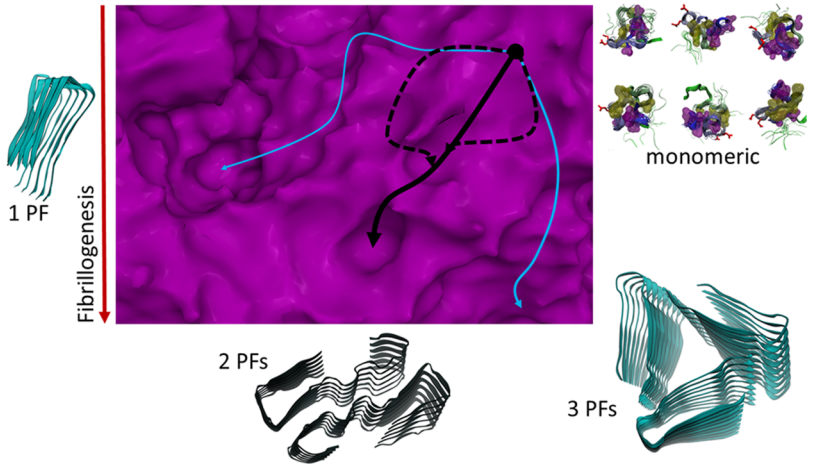

Figure 1. Multiple pathways of fibrillogenesis and kinetic control. Simplified picture of the free energy landscape (magenta) of amyloid fibril formation which shows multiple pathways (cyan and black lines) and multiple minima of the free energy (illustrated by cavities). The vertical dimension reflects the degree of polymerization from the monomeric state (black circle, top right) to fibrils consisting of multiple protofilaments (PFs). The horizontal dimension approximates the number of protofilaments (increasing from left to right). The most probable pathway (black) does not lead to the global minimum but rather to a local minimum, which is the essence of kinetic control of fibrillogenesis.[2,3] This local minimum is a long-lived state, or kinetic trap, because large barriers separate it from other minima. The kinetic trap is reached frequently as multiple pathways (black solid and dashed lines) lead to a metastable state kinetically close to it. Different fibrillar morphologies can arise from different structures and variable arrangements of the peptides in the fibril (cyan vs black) or from a variable number of protofilaments (cyan) as observed in cryo-EM structures[1] and simulation studies.[2]

unconventional because of the rich literature of compounds that have been developed to hinder overall fibrillar growth. Clearly, the main difficulty arises from the lack of knowledge of the toxicity of individual fibrillar morphologies. The limited knowledge on toxic species implies that further studies of fibrils from postmortem brain tissue of Alzheimer's patients, as in the recent cryo-EM analysis,[1] are urgently required. The identification of compounds that interfere with individual phases and intermediate states of the aggregation process is a very promising strategy.[4]

A small molecule that stabilizes fibrillar aggregates should reduce fibrillar fragility and breakage which can promote the formation of toxic species because of the increased amount of nucleation seeds. One successful example of this strategy has emerged from a combined simulation and experimental work on prions which cause transmissible spongiform encephalopathies. A series of polythiophene derivatives functionalized with negatively charged carboxyl groups was designed by molecular dynamics simulations as stabilizers of fibrils of the prion protein.[5] A good correlation was observed between the calculated free energy of binding (to a simplified model of a prion fibril) of the polythiopene-based compounds and their efficacy in vivo. The latter was tested by direct administration of the polythiophene derivatives in the brain of prion-infected mice.[5] Some of the designed compounds showed significant prophylactic and therapeutic potency in mice. This study indicates that molecular dynamics simulations of small molecules that stabilize amyloid fibrils are useful. They should be carried out for identifying small molecules that modulate the self-assembly process of other amyloidogenic peptides, e.g., the Alzheimer's Aβ peptide.

Age is the main cause of Alzheimer's disease. As the world population grows older, the number of patients will increase steadily. The multiple failures of potential therapies based on conventional agents is a consequence, at least in part, of the lack of knowledge of the toxic species and the kinetics of their formation. As an example, antibodies and small molecules developed to block oligomeric states that lead to nontoxic aggregates might even promote the kinetic control of formation of toxic species. Thus, additional knowledge of the kinetics of oligomerization and fibrillogenesis, and new chemical substances inspired by novel modes of action are needed to fight Alzheimer's disease.

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Notes

The author declares no competing financial interest.

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