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Amyloid B-Protein Aggregation at Physiologically Relevant Concentrations. A Critical Role of Membranes

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Hypothesis Paper

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Abstract

Background: The aggregation of amyloid beta (Ab) is a self-assembly process that results in the production of fibrillar structures along with neurotoxic aggregates. However, in the vast majority studies in vitro the required Ab concentrations is several orders higher of the physiological relevant concentrations of Aβ; no aggregation is observed at physiological low nanomolar range of Aβ. This suggests that the assembly of Aβ in aggregates in vivo utilizes pathways different from those used in experiments in vitro.

Results: The spontaneous assembly of Aβ oligomers within the physiologically relevant concentration range can occur, but it is the on-surface aggregation mechanism, in which the surface pays a role of the catalyst of the aggregation process. The model for the on-surface aggregation process suggests that the self-assembly of Aβ oligomers is initiated by the interaction of amyloid proteins with the cellular membrane. The membrane catalyzes amyloid aggregation by stabilizing an aggregation-prone conformation of amyloids. The lipid composition contributes to the membrane-mediated misfolding and aggregation of Aβ monomers.

Conclusion: Membrane-mediated aggregation catalysis explains a number of observations associated with the development of AD. The affinity of Aβ monomers to the membrane surface is the major factor defining the aggregation process rather than Aβ concentration. According to the model, the development of potential preventions for the interaction of monomeric amyloids with membrane can help control the aggregation process. This is a paradigm change for the development of efficient treatments, early diagnostics, and preventions for Alzheimer's disease.

Keywords: Amyloid beta; Membrane composition; Oligomers; Alzheimer's disease

Abbreviations: AD: Alzheimer's disease; Aβ: amyloid b proteon; PD: Parkinson's disease; ACH: amyloid cascade hypothesis.

Introduction

Amyloid Cascade Hypothesis

The involvement of protein aggregates in the development of protein misfolding diseases, including *Alzheimer's disease (AD)* and *Parkinson's disease (PD),* among others, is supported by numerous data and the formation of deposits (plaques) in the brain [1]. Numerous physical, chemical, and structural data reveal a spontaneous assembly of amyloidogenic proteins into aggregates, and the amyloid cascade hypothesis (ACH), proposed more than a quarter-century years ago, and is the major model used to describe the pathology of AD and other neurodegenerative diseases

[2-6]. ACH posits that the onset of diseases involves the spontaneous assembly of an amyloidogenic polypeptide. In turn, accumulation of aggregates defines the disease state. Translational studies in the framework of ACH are focused on decreasing the concentration of amyloid proteins to decelerate the aggregation process [2,3,7]. However, drug development based on decreased Aβ concentration, as well as disaggregating the plaques, has failed [1,8], which challenges the validity of ACH. Indeed, in the monomeric state, all amyloidogenic proteins are functionally important and the findings in Hillen H, et al. [9-11] point to neuroprotective features of monomeric Aβ. Therefore, approaches focused on the decreased concentration of amyloids can impair positive functional roles of amyloid proteins. In fact, there are a number of problems with ACH, and the most challenging is the concentration of Aβ [3]. Specifically, *in vitro* aggregation experiments require Aβ concentrations in the micromolar range, whereas Aβ levels in brain and cerebral spinal fluid (CSF) are frequently in the low nanomolar range [7,12-15]; this value remains in the same range regardless of the disease state [16,17]. No aggregation of Aβ and other amyloidogenic proteins occurs in vitro at such low concentrations. At the same time, plaques are formed *in vivo*, suggesting that Aβ aggregation, regardless of a low concentration, does occur, but the mechanism allowing for the amyloid protein to aggregate is unknown.

Ab Aggregation at Physiologically Relevant Concentrations

It was found recently by the direct observations of the aggregation process with atomic force microscopy (AFM) that a spontaneous assembly of Aβ monomers into aggregates can be observed at physiologically low concentrations if aggregation takes place at surfaces [18]. The process occurs at ambient conditions, physiological pH values, and without agitation, which is often used to stimulate the aggregation. These findings suggest that the surface plays a role of a catalyst and a model for the surface mediated catalysis has been proposed and tested in Pan Y, et al. [19]. According to this model, aggregation starts with protein monomers transiently attaching to the surface due to molecular interactions. This process increases the local concentration of proteins, which in turn increases the probability of oligomerization reactions to occur on the surface. These results are in line with Lindberg DJ, et al. [20] that reported catalytic properties of the zwitterionic lipid vesicles during the formation of Aβ42 fibrils. Note previous publications in which catalytic property of surfaces in amyloid fibrils formation has been discussed [21-24]. The catalytic effect of surfaces in amyloid aggregation explains the experiments on aggregation of Aβ40 at low nanomolar concentrations in cell culture [25]. Local intracellular compartmentalization including the formation of proteinaceous membrane-less organelles is considered as a potential mechanism alleviating the problem with the overall low concentration of amyloids; however, it is considered as a complement to effects of membranes and membrane-encapsulated organelles [26].

Ab Misfolding and Interaction with Membranes

Recent time-lapse AFM experiments provided direct evidence for the Aβ catalysis by phospholipid bilayers, which are models for cell membranes [27-30]. Importantly, the computer modeling revealed that at the bilayer surface Aβ dramatically changes conformation. As is illustrated in Figure 1, overall unstructured Aβ42 monomer (Figure 1a) adopts conformations with extended β-sheet segments (yellow arrows in Figure 1b). The β-sheets are characteristic features for Aβ42 fibrils, suggesting that the membrane-bound Aβ42 monomer adopts the aggregation prone, misfolded conformation. Indeed, the simulations in Banerjee S, et al. [28] showed that dimerization on the bilayer surface was rapid, although the dimer interacts with the lipid surfaces transiently. This finding is in line with the experiments according to which the aggregates assembled on the surface can dissociate into the bulk solution [27-30]. These features are not limited to Aβ interaction with the bilayers. Similar results were obtained with β-syn [27-30]. Combined experimental and computer modeling studies led to the hypothesis that the on-surface amyloid misfolding is the mechanism by which the disease-related aggregation nuclei are formed, providing the seeds for aggregation [27,28]. Inside the brain, the surface-assembled oligomers can induce neurotoxic effects induced by binding to specific receptors and phosphorylation of the tau protein to initiate its misfolding and aggregation, among other problems [15]. According to the AFM observations, the vast majority of cases, the aggregates formed on the surface are oligomers, which are considered to be the most neurotoxic amyloid aggregates [3,4,15,31]. Thus, these observations suggest that interaction of amyloid proteins with cellular membrane can be the mechanism by which amyloid aggregation can be initiated *in vivo* at the physiological concentration range. According to the model proposed in Banerjee S, et al. [28], the aggregation of Ab is a stepwise process, which starts with the conformation change of the monomer upon interaction with the membrane. Therefore, another monomer, after the induced conformational change, assembles with the first into a dimer followed by the growth of the oligomer. The aggregate can dissociate from the surface and initiate neurotoxic effects via different pathways [3,32-40]. This model is supported by a very recent publication [41] in which accelerated aggregation of Aβ42 on membranes of

neuroblastoma cell was visualized.

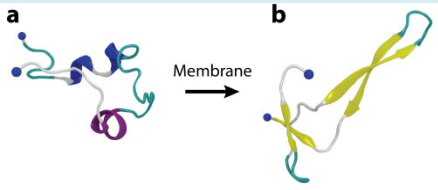

Figure 1: Conformational change of Aβ42 following interactions with lipid membranes. Snapshots show the dramatic change of Aβ42 conformation and secondary structure before, a, and after, b, interacting with a POPC bilayer. Protein is depicted as cartoon following VMD coloring scheme (yellow β-strand and purple β-helix), N- and C-terminal Cβ are presented as large and small blue spheres, respectively.

Membrane Composition and the Ab Self-Assembly Process

Cell membranes consist of a large number of lipids suggesting that the lipid composition can be a factor contributing to the on-membrane aggregation of amyloids. Indeed, recent publications revealed the role of such lipids as cholesterol, sphingomyelins and gangliosides on the formation of Aβ fibrils on membrane surfaces [42-44]. Time lapse AFM studies demonstrated that even the ratio between phospholipids changes the aggregation propensity of supported bilayers for Aβ42 and more strongly for a-synuclein [27,29]. Very recent publication [45] demonstrated that cholesterol in the lipid bilayer significantly enhances the aggregation process of Aβ42 at nanomolar monomer concentration. Importantly, computer modeling showed that Aβ42 has an elevated affinity to cholesterol-containing membranes adopting a set of aggregation-prone conformations.

Membrane Catalysis of Amyloid Aggregation and Early Stages of the Disease Development

Recent studies with the physiologically relevant concentrations of Aβ proteins lead to a concept on a critical role of membranes in triggering the aggregation process and hence, the disease state. Within this concept, the membrane composition is a factor controlling the aggregation process, so the change in membrane composition can shift the ratio between monomeric and aggregated states of Aβ towards aggregated ones, which define the disease state. The findings on contribution of cholesterol, sphingomielins and gangliosides to neurotoxic effects of Aβ aggregates [15,46,47] makes these lipids as prime candidates, suggesting that their content in cell membranes can be the disease defining parameter.

A number of observations can be explained in the framework of the membrane composition concept. Note the role of cholesterol in AD pathogenesis and specifically hypercholesterolemia as a risk factor in AD [48-50]. Catalysis of the aggregation process by cholesterol explains these observations. Additionally, the role of diet in controlling the AD development is widely discussed [51-54]. Note a recent article [54] in which the link between the AD biomarkers and a protective dietary pattern (Mediterranean-style low fat diet) is reviewed. Contributions of the low-lipid diet to the lipid composition of membranes can explain this effect.

In concussion, a novel concept explains the self-assembly of amyloid proteins in the disease- prone aggregates at physiologically relevant concentrations. It also explains a number of observations associated with the development of AD. The affinity of Aβ monomers to the membrane surface is the major factor defining the aggregation process rather than Aβ concentration. Therefore, development of therapeutics need not focus on the change of concentration of Aβ monomers. This is another important feature of the membrane aggregation concept as the change of the monomers concentrations can impair their functional roles. It is very likely that the membrane aggregation concept can be extended to other neurodegenerative diseases.

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Authors Contribution

YLL designed and supervised the research and wrote the manuscript.

Competing Interests

The author has no competing interests.

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