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Review

Structural, morphological, and functional diversity of amyloid oligomers

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ABSTRACT

Protein misfolding and aggregation are known to play a crucial role in a number of important human diseases (Alzheimer's, Parkinson's, prion, diabetes, cataracts, etc.) as well as in a multitude of physiological processes. Protein aggregation is a highly complex process resulting in a variety of aggregates with different structures and morphologies. Oligomeric protein aggregates (amyloid oligomers) are formed as both intermediates and final products of the aggregation process. They are believed to play an important role in many protein aggregation-related diseases, and many of them are highly cytotoxic. Due to their instability and structural heterogeneity, information about structure, mechanism of formation, and physiological effects of amyloid oligomers is sparse. This review attempts to summarize the existing information on the major properties of amyloid oligomers.

1. Introduction

Misfolding and aggregation of polypeptides and proteins is a central pathological and biochemical event shared by many neurodegenerative maladies such as Alzheimer's, Parkinson's and Huntington's diseases and prion diseases, as well as other human diseases, such as type II diabetes and systemic amyloidoses [1–3]. In addition, protein aggregates are believed to be involved in several physiological processes such as hormone storage [4] and memory formation [5–7]. Furthermore, many biologically important proteins act in a form of specific homo- or hetero-oligomers. Protein aggregates are usually either classified as amyloid fibrils (structures in which the polypeptides are organized into cross-β sheets), amorphous aggregates, or soluble aggregates often generically described as amyloid oligomers. Amyloid oligomers are defined as soluble non-monomeric structures that appear as intermediates or final products in the process of protein aggregation lacking one or more of the hallmarks of fibrillar structure. Amyloid oligomers have been reported for many disease-related proteins such as amyloid β, huntingtin (Htt), α-synuclein, tau, and the prion protein [3,8–10]. They are highly heterogeneous in size, structure, stability and morphology. Here we will describe amyloid oligomers based on their major properties (Fig. 1) using a variety of aggregation-prone proteins and peptides as examples.

2. Properties of amyloid oligomers

2.1. Secondary and tertiary structure

A number of complications are involved in preparation of even reasonably homogeneous populations of amyloid oligomers. Many amyloid oligomers are unstable and able to convert to more stable oligomers or fibrils over time. For example, Aβ dimers previously believed to be cytotoxic were shown to be inert but capable of converting to larger cytotoxic oligomers [11]. In addition, existing methods of oligomer characterization (e.g. SDS–PAGE, reactivity of conformation-specific antibodies, DLS, various spectroscopic methods) are not always able to distinguish different oligomer populations and sometimes suffer from artefacts [12,13]. Despite these complications, kinetically stable populations of amyloid oligomers have been prepared from a variety of proteins, and the peculiarities of their secondary and sometimes tertiary structures have been analyzed. At the secondary structure level, these oligomers have often been found to incorporate at least some β-sheets, and in many (although not all) cases arrangement of β-strands into β-sheets in oligomers was found to be antiparallel [14–18]. This is distinct from amyloid fibrils where, with a few

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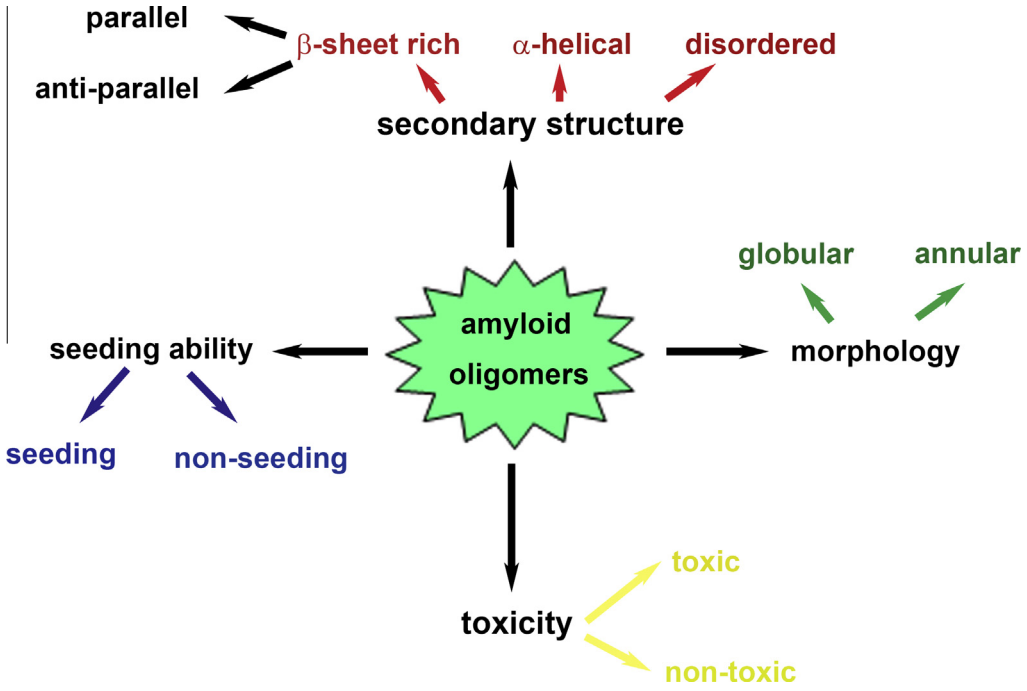

Fig. 1. Schematic representation of properties of amyloid oligomers.

exceptions, β-sheet arrangement was found to be parallel [19–21]. Examples of amyloid oligomer structures found in different proteins are discussed below.

2.1.1. Amyloid β oligomers

Small Aβ oligomers (dimers to tetramers) have been isolated from in vivo sources and prepared in vitro. Their secondary structure was shown to be primarily disordered [22–25], and their β-sheet content increased with increasing oligomer size [26]. $A\beta_{40}$ oligomers prepared in the physiologic-like conditions were shown to have high β-sheet content, and molecular modeling predicted tertiary/quarternary structure of the oligomers to be similar to that of fibrils with some disruptions in the β-sheet stacking [27,28]. Another population of Aβ oligomers prepared under the similar conditions had a more disordered secondary structure. Crystallographic studies suggest that these oligomers may have an antiparallel β-barrel like structure [15]. In the presence of lipid bilayers, these oligomers could be converted to annular protofibrils also shown to be β-sheet rich [29,30].

Aβ oligomers formed in the presence of EGCG appeared disordered upon initial examination [31]. Subsequent NMR analysis determined that in this oligomer population, C-terminal β-sheet (residues 22–39) was included into the secondary structure formation, whereas the N-terminal half of the peptide was unstructured due to the EGCG binding [32]. In $A\beta_{42}$ oligomers formed in the presence of SDS, residues 25–40 were found to form β-strands that were arranged in the antiparallel fashion, whereas the structure of the N-terminal half of the peptide was unclear [14,18]. An EPR investigation of oligomers prepared under the similar conditions indicated gradual increase in the structural order towards the C-terminus of the peptide and antiparallel arrangement of β-strands [18]. NMR analysis of yet another population of $A\beta_{42}$ oligomers ('globulomers') also formed in the presence of SDS suggested the presence of a dimeric structural unit consisting of a pair of in-register parallel β-strands formed by residues 34–40 extending from a β-hairpin formed by antiparallel arrangement of two additional β-strand regions (18–23 and 28–33) [33] (Fig. 2A). Overall, we can see that the Aβ peptides form a wide variety of primarily β-sheet-rich oligomeric aggregates.

2.1.2. α-Synuclein oligomers

Oligomers of α-synuclein, similar to those of many other amyloidogenic proteins, are highly structurally diverse. Three broad classes of α-synuclein oligomers have been identified: β-sheet-rich, primarily disordered and primarily α-helical.

Structural features of the β-sheet-rich oligomers (degree of disorder, surface exposure of hydrophobic residues, extent of the β-structure, mechanical properties) were shown to be intermediate between monomers and fibrils [34–39]. Force spectroscopy [40] and other methods [39] showed that α-synuclein oligomer stability, β-sheet content, and size of the solvent-exposed hydrophobic surfaces increased with the oligomer size. Analytical ultracentrifugation (AUC) measurements combined with the H/D exchange [41,42] and fluorescence analyses [43] have shown that amyloid core (residues 40–80) is consistently protected from the solvent in oligomers, and in some oligomer preparations this protection is extended on all N-terminal half of the protein (residues 1–90) [41]. Oligomers with smaller solvent-protected core were shown to be not on the pathway to fibril formation, whereas the oligomers with larger protected core were easily converted to fibrils [41,44]. β-Sheet-rich α-synuclein oligomers were stable towards thermal and urea denaturation and could be specifically detected with the 9-(2,2-dicyanovinyl)julolidine fluorescent dye [45]. Arrangement of β-strands in some of these oligomers was shown to be antiparallel judging from FTIR spectra [17,38,43]. Another population of oligomers was shown to possess a β-sheet rich hollow cylindrical architecture similar to that of fibrils albeit with higher degree of disorder [39]. Lorenzen and colleagues described a globular ellipsoid oligomer containing 30 ± 6 α-synuclein monomers with a compact interior of antiparallel β-strands and a surrounding shell of disordered peptides [38].

Lipid-derived aldehydes such as HNE reacted with α-synuclein to form lysine adducts and promoted formation of either β-sheet-rich [46–48] or primarily disordered [49] oligomers,

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