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Review article

Structure of amyloid oligomers and their mechanisms of toxicities: Targeting amyloid oligomers using novel therapeutic approaches

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ABSTRACT

Protein misfolding is one of the leading causes of amyloidoses. Protein misfolding occurs from changes in environmental conditions and host of other factors, including errors in post-translational modifications, increase in the rate of degradation, error in trafficking, loss of binding partners and oxidative damage. Misfolding gives rise to the formation of partially unfolded or misfolded intermediates, which have exposed hydrophobic residues and interact with complementary intermediates to form oligomers and consequently protofibrils and fibrils. The amyloid fibrils accumulate as amyloid deposits in the brain and central nervous system in Alzheimer's disease (AD), Prion disease and Parkinson's disease (PD). Initial studies have shown that amyloid fibrils were the main culprit behind toxicity that cause neurodegenerative diseases. However, attention shifted to the cytotoxicity of amyloid fibril precursors, notably amyloid oligomers, which are the major cause of toxicity. The mechanism of toxicity triggered by amyloid oligomers remains elusive. In this review, we have focused on the current knowledge of the structures of different aggregated states, including amyloid fibril, protofibrils, annular aggregates and oligomers. Based on the studies on the mechanism of toxicities, we hypothesize two major possible mechanisms of toxicities instigated by oligomers of Aβ (amyloid beta), PrP (prion protein) (106–126), and α-Syn (alpha-synuclein) including direct formation of ion channels and neuron membrane disruption by the increase in membrane conductance or leakage in the presence of small globulomers to large prefibrillar assemblies. Finally, we have discussed various novel innovative approaches that target amyloid oligomers in Alzheimer's diseases, Prion disease and Parkinson's disease.

1. Introduction

Protein folding is a complex process that progresses through a series of intermediates which undergo further folding to give rise the native functional structure. If proteins misfold, specialized proteins called molecular chaperones assist in their refolding. Despite of cellular protein quality control, proteins often misfold in the cell. This occurs primarily because of mutations, from changes in environmental conditions (pH temperature, protein concentration), errors in post-translational modifications, increase in the rate of degradation, error in trafficking, loss of binding partners and oxidative damage. All of these factors can act either independently of each other or simultaneously [1]. Protein misfolding occurs through the formation of partially unfolded or misfolded intermediates, which have exposed hydrophobic residues and interact with complementary intermediates to form oligomers and consequently, protofibrils and fibrils. These amyloid fibrils accumulate in the brain and central nervous system thereby trigger brain diseases including Alzheimer's disease, Prion disease and Parkinson's disease. The pathway of fibril formation is depicted in Fig. 1. Now a group of roughly 20 protein deposition diseases usually referred as amyloidoses are known. These amyloidoses contain specific peptide or protein that differs in the extent of disease manifestation [2]. In spite of the fact that the misfolded proteins are either evolutionarily or structurally not related, the structural characteristics of the misfolded proteins are highly similar in that

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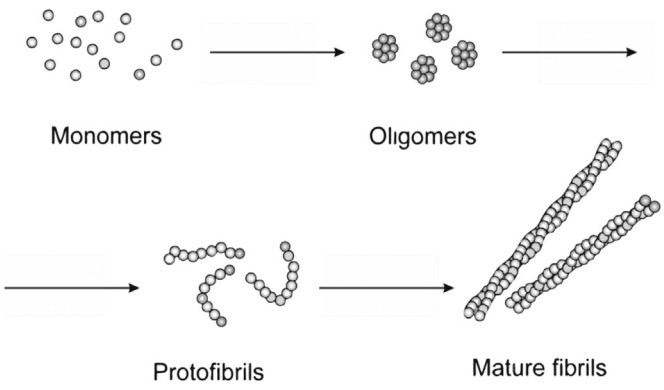

Fig. 1. The pathway of fibril formation.

they show an increasing order of β-sheet contents in oligomers, and fibrils [3–5]. These fibrillar aggregates bind dyes including Congo red (CR) and Thioflavin-T(Th-T) and result in birefringence and fluorescence, respectively.

In the early 1990 s studies have shown that the amyloid fibrils were the main toxic species present in the amyloid plaques of AD patients. These findings were not confirmed till then. However, at the end of the 1990 s attention shifted to the cytotoxicity of amyloid fibril precursor: amyloid oligomers [6]. This was further supported by the severity of cognitive impairment in Alzheimer's disease which appears to better correlate with the levels of oligomeric species of Aβ rather than with the amount of fibrillar deposits [7]. Therefore, amyloid oligomers are now considered as important key players in instigating cytotoxicity. This finding was further confirmed when more amyloid oligomers were discovered which were also implicated in other neurodegenerative diseases [8]. These amyloid oligomers are highly diverse in structure, morphology and function [9].

There are several major possible mechanisms of toxicities instigated by oligomers, including neuron membrane disruption by increase in membrane conductance or leakage in the presence of small globulomers to large prefibrillar assemblies, direct formation of ion channels, binding to different cell-surface receptors and oxidative stress.

Since amyloid oligomers are now considered as the most toxic entities than mature fibrils. Therefore, novel strategy would be to design the drugs that aim at oligomeric species for preventing AD, prion disease and PD. Currently, several therapeutic approaches that target amyloid oligomers are under development, which among others include inhibition of oligomerization using small molecule inhibitors [10–25], neutralization of oligomeric species by immunotherapy [26–37], overexpression of amyloid-beta-degrading enzymes involved in degradation of amyloid oligomers [38–65], catalytic amyloid beta antibodies that hydrolyze specific aggregate [66,67], β-sheet breakers [68–71] that break existing beta sheet structure and amyloid β-blockers [72–92] that block amyloid channel. Furthermore, peptide fragments have also been used for modulating aggregation reaction [93,94].

Keeping the above views in mind, here we present state of the art review that focuses on the current knowledge of the structures of different aggregated states, including amyloid fibril, protofibrils, annular aggregates and oligomers. Furthermore, we will describe possible mechanisms of toxicities caused by oligomers of Aβ and PrP (106–126) and α-synuclein. We also argue how molecular chaperones rescue neurons from the toxic effects produced by accumulated amyloid oligomers. Lastly, we shall discuss various novel therapeutic approaches that target amyloid oligomers in these neurodegenerative diseases.

2. Structure of mature amyloid fibrils

The full-length Aβ fibrils poses parallel β-sheet structure. The core structure of the fibrils seems to be stabilized mainly by the hydrogen bonds involving the polypeptide main chain. Because the main chain is common to all polypeptides, this observation explains why fibrils formed from different polypeptides showed significant similarities in their backbone structure [95,96]. The structure of fibrils has been observed by transmission electron microscopy (TEM) or atomic force microscopy (AFM). These microscopic studies have shown that fibrils consist of a number of (2–6) protofilaments, where each protofilament is about 2–5 nm in diameter, which is often twisted around each other, to form supercoiled rope-like structure, that is 7–13 nm wide [95,97]. The protofilaments may also associate at laterally to form long ribbons, which are 2–5 nm thick and up to 30 nm wide [98,99]. Circular dichroism, Fourier transform infra-red spectroscopy, solid-state NMR (nuclear magnetic resonance) (Fig. 2) [100] and X-ray fiber diffraction data have shown that each protofilament is arranged such that β-strands stack in register and run perpendicular to the long axis of the fibril and generate a structure which is known as cross-β structure [95]. Each strand in β-sheet is in register with neighboring strand and forms hydrogen bonds with the strands above and below the fibril. Most recent data have shown that each antiparallel pair of strand is out of register with neighboring pairs by six residues, leaving the hydrogen bonds dangling [101]. These out-of-register β-sheets (amyloid fibril) assume cylindrin structure which may be cytotoxic in nature [101].

In general, the core of most amyloid fibrils structure is dehydrated. This results from packing of hydrophobic residues inside of amyloid fibrils that give rise to one of the 8 possible steric zipper arrangements [102]. These arrangements occur mainly because there are 2 possible types of β-sheet including parallel or antiparallel, 2 types of stacking possibilities parallel or anti-parallel and 2 surfaces for inter-sheet packing (face-to-face or face-to-back) (Fig. 3) [103].

Additional complexities in the fibril structure may also arise from quaternary interactions in which protofilaments containing a

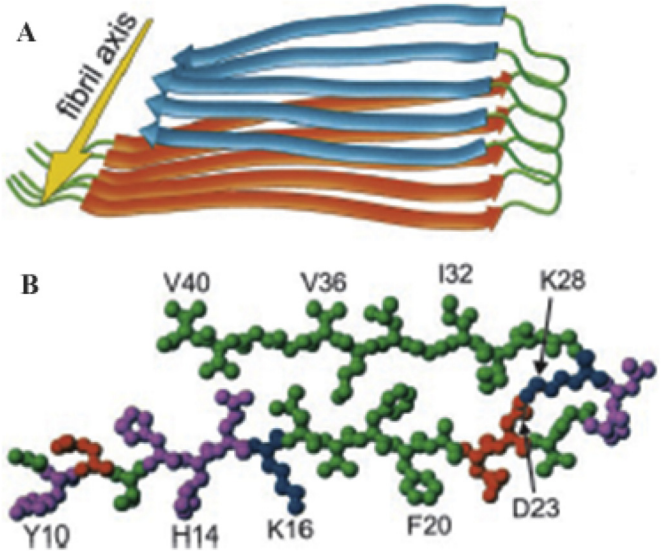

Fig. 2. Structural model for $A\beta_{1-40}$ fibrils, consistent with solid state NMR.(A) Schematic representation of a single molecular layer, or cross-β unit.(B) Central $A\beta_{1-40}$ molecule from the energy-minimized, five-chain system, viewed down the long axis of the fibril. Reprinted with permission from Petkova et al., 2002. Copyright 2002 PNAS USA.