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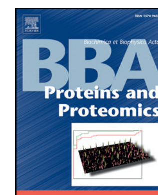

Review

Antibodies and protein misfolding: From structural research tools to therapeutic strategies ☆

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ABSTRACT

Protein misfolding disorders, including the neurodegenerative conditions Alzheimer's disease (AD) and Parkinson's disease (PD) represent one of the major medical challenges or our time. The underlying molecular mechanisms that govern protein misfolding and its links with disease are very complex processes, involving the formation of transiently populated but highly toxic molecular species within the crowded environment of the cell and tissue. Nevertheless, much progress has been made in understanding these events in recent years through innovative experiments and therapeutic strategies, and in this review we present an overview of the key roles of antibodies and antibody fragments in these endeavors. We discuss in particular how these species are being used in combination with a variety of powerful biochemical and biophysical methodologies, including a range of spectroscopic and microscopic techniques applied not just *in vitro* but also *in situ* and *in vivo*, both to gain a better understanding of the mechanistic nature of protein misfolding and aggregation and also to design novel therapeutic strategies to combat the family of diseases with which they are associated. This article is part of a Special Issue entitled: Recent advances in molecular engineering of antibody.

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1. Protein misfolding, amyloid deposition and disease

A wide range of human pathologies, including Alzheimer's disease (AD), Parkinson's disease (PD), Huntington's disease (HD), Creutzfeld Jacob disease (CJD), type II diabetes, amytrophic lateral sclerosis (ALS) and a variety of systemic amyloidoses are linked to the conversion of disease-specific proteins from their soluble state into highly ordered β-sheet rich fibrillar amyloid structures [1–6]. These disorders, known variously as protein misfolding aggregation, conformational or deposition diseases, have major human and economic costs to society.

All these diseases are characterized by the conversion of a normally soluble and functional protein into insoluble and pathogenic protein deposits in a variety of organs or tissues. When these disorders were originally investigated, the observation that affected tissue could be stained with iodine, led to the misconception that the deposits were rich in starch, leading to their common name as amyloid (starch-like) deposits [7]. Amyloid deposits are, however, largely composed of protein molecules that have aggregated into fibrillar species rich in ordered β-sheet structure. Each disease is associated with one or more specific proteins, *e.g.*, Amyloid-β (Aβ) peptide or tau protein in Alzheimer's disease (AD), mutant forms of huntingtin (mHTT) in Huntington's disease (HD), α-synuclein (aSyn) in Parkinson's disease (PD), β2-microglobulin (β2m) in dialysis-related amyloidosis (DRA) and the human prion protein (hPrP) in Creutzfeld–Jacob Disease (CJD) [4].

1.1. Mechanism of the formation of protein amyloid fibrils

It is now well established that the ability to form amyloid structures is not limited to the small subset of proteins or peptides that are involved in disease, but that any protein can in principal adopt this structural state [8–11]. The relative propensity of different proteins to convert into the amyloid state vary significantly, however, and depends on the overall thermodynamic stability of the native state of the protein as well as on the kinetic accessibility of partially folded intermediates that initiate the amyloid formation cascade [11,12]. The latter factor determines the frequency at which such conformations are sampled by a protein and thus the rate at which the protein is able to form fibrils under given conditions. Changes in the stability of specific proteins by the addition of certain co-solvents, denaturants, or as a result of the

Abbreviations: AD, Alzheimer's disease; PD, Parkinson's disease; HD, Huntington's disease; CJD, Creutzfeld–Jacob disease; mAb, monoclonal antibody; scFv, single-chain Fv; VH, variable domain of the heavy chain; VL, variable domain of the light chain; VHH, variable domain of a camelid heavy-chain antibody; Nb, nanobody; WT, wild-type; HuL, human lysozyme; aSyn, α-synuclein; aβ, amyloid-beta; HuPrP, human prion protein; β2m, β2-microglobulin; ROS, reactive oxygen species; HTT, huntingtin; mHTT, mutant huntingtin; NAC, non amyloid component; BBB, blood–brain barrier

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presence of destabilizing mutations, may allow amyloidogenic species to be sampled more frequently, thereby initiating the amyloid fibril formation process more readily [11,12].

The molecular mechanisms of the amyloid formation cascade and its associated toxicity have been extensively investigated *in vitro* and *in vivo* for a number of different proteins [13–20]. These studies have led to the realization that the ready formation of the amyloid form of proteins involves several key steps. Initially, a protein species with a high propensity for self-association needs to be formed, for example as a result of the exposure of hydrophobic residues; such species can be partially unfolded intermediates populated on the folding or unfolding pathways of globular proteins, or partially folded aggregation-prone members of the ensemble of structures in intrinsically disordered proteins [20]. In subsequent steps, these aggregation-prone species self-assemble into a variety of oligomeric species that convert into highly organized mature fibrils through a series of complex steps, typically involving primary nucleation, conformational rearrangement, aggregate growth and fragmentation, and secondary nucleation through surface mediated catalysis [11]. The kinetics of such underlying microscopic process of protein amyloid formation can now be analyzed and dissected using well-defined simple reaction schemes, such as those outlined in Fig. 1 [21–23]. These models allow accurate determination of the microscopic rate constants of the various primary and secondary processes involved in a given aggregation reaction from appropriate experimental measurements, and in addition provide the opportunity for the design and screenings of potential drugs that can perturb the specific microscopic events [3].

The resulting fibrillar structures have "generic" features, such as a characteristic "cross-β" structure, which can be readily established through X-ray fiber diffraction studies, and the ability to bind dyes such as Congo Red or Thioflavin T [24]. The basis for these generic features of amyloid fibrils can be found in the fact that the atomic interactions that stabilize the β-sheet structures of fibrils are primarily mediated through backbone atoms of polypeptide chains [11]. In contrast, the structures of the native states of globular proteins are determined by specific side-chain interactions that are characteristic of their unique individual sequences [25,26]. Indeed, as mentioned above, the amyloid structure can be considered to be a generic fold, which is accessible in principle under appropriate conditions by all proteins regardless of their sequences, although the propensity to convert into this state can vary widely [26].

The toxic nature of the different misfolded species populated during fibril formation is still a matter of intense discussion. In some situations, for example, in the case of misfolding of lysozyme, which underlies a type of familial systemic amyloidosis [27], the fibril deposits themselves are likely to be the direct cause of the disease by inflicting physical damage to vital organs; a similar situation occurs with liver damage caused by deposition of α1-antitrypsin although in this case the deposits are not specifically amyloid like in nature [28].

In a large number of studies, however, it is the smaller, more mobile oligomeric species with high surface-to-volume ratios and high hydrophobicities that have been identified as the direct mediators of cell damage and cell death [17,29]. Although these small oligomeric structures might be the most direct toxic agents, however, the presence of larger fibrils can contribute significantly to the toxicity, as these structures can, in at least some cases, enhance dramatically the generation of toxic oligomers through surface catalyzed secondary nucleation (Fig. 1). Such secondary processes may be of great importance in the progression and spreading of Alzheimer's disease [3,23] and Parkinson's disease [30], and their existence further underscores the importance of designing therapeutic strategies that suppress the occurrence of specific microscopic steps in the overall aggregation process [11].

1.2. Disease pathology: the mechanisms of cytotoxicity

As mentioned above, it is generally believed that the precursors of fibrillar deposits, particularly small oligomeric species, are important causative agents for cellular toxicity in protein deposition diseases. The high surface-to-volume ratios and presence of exposed hydrophobic residues [31] in such pre-fibrillar species are very likely to trigger aberrant behavior as a result of inappropriate interactions with cellular components, such as transcription factors, receptors or membranes, which can lead to high oxidative stress, or stimulate apoptosis or other forms of cell death. The high propensity of oligomeric species to bind to membranes, attributable to their flexible, dynamic and unstable nature, has received a great deal of attention in the literature [32–35], and could lead to pore formation and membrane permeability, which can in turn might lead to loss of protein homeostasis and the appropriate regulation of signaling pathways.

These oligomeric species have also been found to interact inappropriately with a number of cell surface receptors. In the context of AD, for example oligomeric species of the Aβ-peptide have been reported to interact strongly with the prion protein (PrP) [36,37], with NMDA [38,39] receptors and the associated tyrosine kinase EphB2 [39] receptor, and a variety of other cell-surface receptors (reviewed in [40]). Such interactions could possibly lead to aberrant

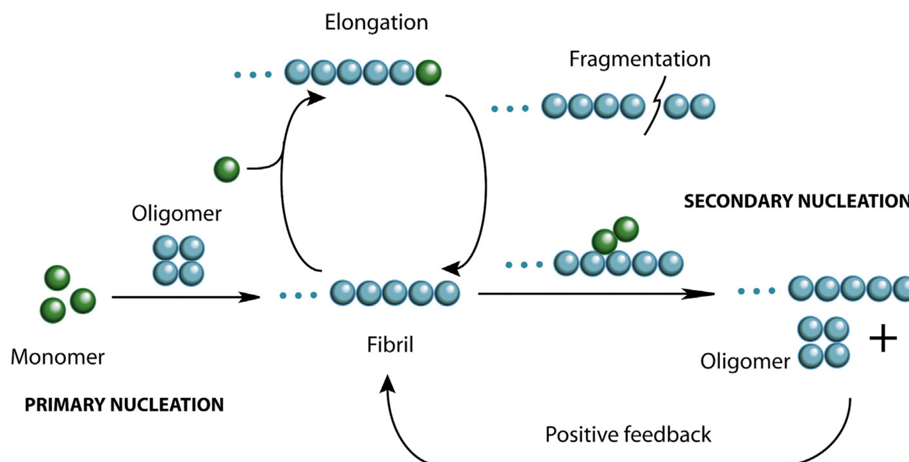

Fig. 1. A kinetic model of fibril formation including primary and secondary processes. Soluble monomeric forms of proteins undergo primary nucleation to generate oligomeric species that have the potential to convert into fibrils. The formation of fibrils is significantly enhanced by secondary processes that result in the proliferation of aggregates able to grow by the further addition of soluble protein molecules. The latter processes include fragmentation, which generates new fibril ends at which growth occurs and surface catalyzed nucleation, in which fibril surface functions as a template for the generation of new oligomeric species.
(Figure adapted from [22] and [23]).

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