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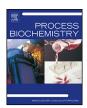
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#### Review

## Protein misfolding and aggregation: Mechanism, factors and detection

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#### ABSTRACT

Amyloidogenic diseases are characterised by the formation of amyloid aggregates inside or outside the cell. Amyloid-associated human diseases include Alzheimer's disease, Parkinson's disease, prion diseases and type II diabetes. Currently, these diseases are incurable; thus, detailed insight into the mechanism of amyloid formation, deposition and inhibition is required to develop treatment strategies. Herein, we have described the mechanism of amyloidogenesis in detail highlighting the major events including the association of native monomers into higher-ordered fibrillar structures. A review of the modern technologies that aid characterisation of amyloid aggregates is also discussed. Further, we have described the factors influencing the microenvironment of protein, which in turn promotes amyloidosis.

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#### 1. Introduction

Proteins perform several different biological functions with high fidelity ascribed to their specific three-dimensional (3D) structures. Generally, misfolded or partially folded proteins are degraded by cellular quality control systems such as proteasome and autophagy, but failure of this system or overloading results in protein aggregation, in turn leading to protein-misfolding disorders [1]. Amyloidogenesis is a process wherein peptide or protein molecules self-associate to form dimers and oligomers, subsequently transforming into mature fibrillar amyloid aggregates. In contrast to amorphous protein aggregates, amyloids have a quasi-crystalline structure and possess characteristic properties [2]. During amyloidogenesis, misfolded monomers give rise to toxic protein fibrils whose deposition in tissue or cells leads to various serious pathological consequences. The term 'amyloidosis' is widely used to denote the lethal consequences of amyloid deposition [3]. Particularly, its deposition in neuronal cells leads to neuron degeneration (neurodegenerative diseases), which manifests symptoms such as memory loss and dementia. Some of the prevalent neurodegenerative diseases include Alzheimer's disease and Parkinson's disease, which remain incurable. The lack of detailed elucidation of self-assembly mechanisms is one of the possible reasons for the failure of therapies.

#### 1.1. Protein misfolding and aggregation

Living systems are composed of four key macromolecules: proteins, carbohydrates, nucleic acids and lipids. Proteins perform a wide array of functions within living organisms. The life of every living organism depends on chemical reactions controlled by about 100,000 types of protein. Each protein can be distinguished from the other based on its constituent polymeric sequence of amino acids [5]. Proteins are synthesised on ribosomes within the cell [6]. In some cases, protein folding starts immediately, while the nascent polypeptide chain is still attached to the ribosomes in a cotranslational manner. Other proteins follow a folding pathway in the endoplasmic reticulum after the translation process. Organisms have evolved various methods of controlling the folding process of proteins such as the use of folding catalysts and chaperones [7]. In adverse environments such as stress condition, mutation and ageing, proteins may lose their ability to fold properly and start to misfold (Fig. 1). Generally, misfolded proteins trigger a complicated biological response such as unfolding of protein and heat shock, which help in protein folding and protein degradation [8]. Incorrect folding of proteins may lead to their degradation by the proteasome machinery of the cell or aggregation, thus leading to various pathogenic conditions. Fig. 1 shows a schematic diagram of misfolding and the aggregation process. The various intermediate steps involved in the aggregation process are shown in Fig. 2AII.

Failure of any of these processes may lead to the loss of particular protein function, overabundance or aggregation of misfolded proteins, subsequently leading to pathogenic conditions [4]. The factors underlying protein misfolding include loss of cellular protein quality control system, inability of the ubiquitin–proteasome complex to degrade and eliminate misfolded aggregation-prone molecules, inefficient functioning of the molecular chaperone

machinery, obstruction of normal cellular transport of protein, production of amyloidogenic fragments of protein due to inappropriate protease activity, destabilising mutations, etc. [9–18]. The protein aggregates may be deposited both intracellularly and extracellularly. Deposition of ordered structures also known as 'amyloids' results in >20 diseases in humans such as Alzheimer's disease, Parkinson's disease, type II diabetes and systemic amyloidosis (Table 1). Proteins that are not associated with any pathological conditions may also form amyloids under in vitro conditions. This indicates that amyloid formation is not restricted to any specific protein, but the propensity to form amyloids is modulated by the amino acid sequence of polypeptides [19]. The fibrils are usually toxic to cells possibly giving rise to some of the most debilitating pathological conditions [20]. The amorphous aggregates and the related cytotoxicity are discussed in Supplementary section S1.

#### 1.2. Classification of protein aggregates

Various groups have classified protein aggregates in different ways, as no precise definition exists. Two broad categories of protein aggregates include in vivo versus in vitro and fibrillar versus amorphous. For example, amyloid fibrils are fibrillar or ordered aggregates that are observed both in vivo and in vitro, whereas inclusion bodies are amorphous or disordered aggregates that are formed in vivo [21]. Similarly, in vitro aggregates formed during refolding at high protein concentration are disordered aggregates. Other classifications have also been proposed such as physical (or non-covalent) versus chemical (or covalent) aggregates, reversible versus irreversible aggregates and soluble oligomers (dimer to decamer) versus insoluble particles.

#### 1.3. Structure and morphology

The morphology of protein aggregates is independent of the protein sequence; it is determined primarily by the solution conditions. This is because the same protein can form both fibrillar and amorphous types of aggregates based on the environmental conditions. pH has been found to play a key role in determining the aggregate morphology as it affects the charge distribution and the degree of structural perturbation to the protein as well. Krebs et al. [22] in a study on seven vastly different proteins, revealed that a pH that provides a high net charge to the protein favours the formation of fibrillar aggregates, whereas a low net charge on protein is likely to yield aggregates with amorphous morphology [23].

Although it is difficult to study the pathogenic amyloid fibrils because of their large size, poor solubility and non-crystalline structure, the structure of aggregates has been extensively studied at the molecular level. Much of the advancement in the knowledge of fibril structures is facilitated by solid-state nuclear magnetic resonance (NMR), electron microscopy (EM) and X-ray diffraction [24].

The amyloid fibrils formed from different unrelated peptides and proteins are characterised as having well-ordered, elongated and relatively straight fibrillar structures. EM and atomic force microscopy (AFM) revealed that fibrils are composed of substructures called 'protofilaments'. A single protofilament is either straight or curved with a diameter of 2–5 nm. About two to six of such protofilaments join by either twisting together like a rope or

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