Amyloid Proteins a Challenge Leading to the Folding Problem

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In the last decades new categories of diseases arising from abnormal protein folding processes have been described. In particular, a common folding-linked origin has been recognised in a group of diseases, named amyloidoses, where aberrant protein folding is responsible for the formation of aggregates of fibrous nature exhibiting the cross-β structure, a particularly stable generic fold of the polypeptide chain, accessible under specific conditions in vitro and in vivo, in spite of sequence and corresponding native fold diversity [1,2]. Due to this relative independence on the specific sequence, the cross-β structure is considered a generic fold of polypeptides driven by the common main chain interactions, contrary to the native folding that instead is driven by the specific side-chains interactions. In amyloid fibrils the aggregating polypeptide chain can be represented by globular proteins or alternatively by short peptides corresponding to truncated forms of protein precursors. Short peptides should acquire a certain level of secondary structure for the occurrence of an aggregation process. The conversion of globular proteins into insoluble fibrillar aggregates requires instead partial unfolding of the native geometry that entails significant conformational changes such as the partial loss of tertiary and quaternary interactions and/or conversion into β secondary structure. For many of these proteins amyloid fibril formation is facilitated by amino acid mutations that destabilize the native state and confer a structural flexibility to the molecule, but other proteins are amyloidogenic in the the wild-type form [3]. Following the wealth of studies on the fibril formation process, some general guidelines to interpret amyloidogenesis have emerged. It is widely accepted that fibril formation occurs through a nucleated growth mechanism [4-7]. Prefibrillar oligomeric species that can be considered structured protofibrils have been repeatedly observed. The morphology of these oligomers is certainly related to the monomer structure which, in turn, depends on the precursor protein rearrangement, except for the de novo adopted conformations of unstructured amyloidogenic peptides. It is generally accepted that aggregation of globular proteins into oligomeric species occurs via partial unfolding, a rearrangement that may constitute an alternative to proper folding – misfolding – through which partially folded intermediates are driven to an aggregate state with favourable overall free energy [3-8]. The conformational distance of these partially unfolded intermediates from the native state may be not very large. Especially in the initial oligomerization steps, native-like structures should be involved. Over the last years many research efforts have been devoted to the identification and structural definition of the intermediates, along the same general line as the protein folding studies. The structural characterisation of the folding/misfolding intermediates, from which the fibril formation is primed, should give very useful clues to prevent pathological misfolding. The progress in outlining the conformational features of the early oligomers and in identifying the mechanism of their further growth is accompanied by relevant advancements in the interpretation of the whole fibrillogenesis process [9]. To date, some 30 different proteins or fragments have been described to cause amyloidosis such as Alzheimer’s and Parkinson’s diseases, type II diabetes, familial amyloid neuropathies, etc. [3]. Of those proteins, some 15 are responsible for systemic amyloidses in humans, where the pathogen is a plasma protein that is transported as a soluble product and forms fibrils at the deposition sites by partially or totally unclear mechanisms. Several proteins involved in the systemic amyloid diseases belong to the immunoglobulin superfamily. Coping with the complexity of partial unfolding, early oligomerization and subsequent evolution calls for sophisticated analytical tools. From the viewpoint of the biophysical characterization, besides the traditional optical spectroscopies, mass spectrometry and morphological analysis, the advanced approaches of native mass spectrometry, real-time NMR and single-molecule techniques are more and more emerging as necessary to progress further in the comprehension of the problem, which eventually addresses the general issue of the protein folding. The conformational states of a protein are populated according to the Boltzmann distribution, with the native state being generally the most populated in standard conditions, i.e. a Gibbs free energy several kcal/mol lower than all the other states. The definition of the equilibrium unfolding landscape of a protein is of fundamental importance in cases where non-native states play a crucial role in biological function or disease. In cellular compartments, the folded proteins can interact with other proteins, glycosaminoglycans, polysaccharides, lipid membranes or can be affected by molecular crowding thereby modifying their conformational propensities towards local or more extensive unfolded states, or with the onset of aggregation-prone structures. Monitoring structural dynamics of proteins is important not only for misfolding disorders or for their interaction with other types of biopolymers, but also for their role as targets of ligands such as other proteins, hormones, drugs that are capable of affecting their function. Being able to

Cite this article: Esposito G (2013) Amyloid Proteins a Challenge Leading to the Folding Problem. JSM Biochem Mol Biol 1: 1002.
measure the thermodynamics or kinetics of the phenomena involving proteins is a direct way of addressing their function.

REFERENCES


