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Disorder-to-order conformational transitions in protein structure and its relationship to disease

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Abstract Function in proteins largely depends on the acquisition of specific structures through folding at physiological time scales. Under both equilibrium and non-equilibrium states, proteins develop partially structured molecules that being intermediates in the process, usually resemble the structure of the fully folded protein. These intermediates, known as molten globules, present the faculty of adopting a large variety of conformations mainly supported by changes in their side chains. Taking into account that the mechanism to obtain a fully packed structure is considered more difficult energetically than forming partially "disordered" folding intermediates, evolution might have conferred upon an important number of proteins the capability to first partially fold and—depending on the presence of specific partner ligands—switch on disorder-to-order transitions to adopt a highly ordered well-folded state and reach the lowest energy conformation possible. Disorder in this context can represent segments of proteins or complete proteins that might exist in the native state. Moreover, because this type of disorder-to-order transition in proteins has been found to be reversible, it has been frequently associated with important signaling events in the cell. Due to the central role of this phenomenon in cell biology, protein misfolding and aberrant disorder-to-order transitions have been at present associated with an important number of diseases.

Keywords Protein structure · Protein misfolding · Disorder-to-order transitions · Disease

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Introduction

Although for many years now human disease has been directly related with specific anomalies in protein–protein, protein–DNA and protein–RNA interactions, in the near future such accumulated knowledge will require expansion in order to take the next technological step with the application of many proteomic concepts to patient-oriented therapies [1]. Recently in this regard, an important number of diseases have been associated with problems specifically related with protein folding. The concept of protein folding is directly related with the process of reversible disorder-to-order transitions, by which an unfolded polypeptide chain folds into a specific functional native structure [2, 3]. Although for a long time it was thought to be only a theoretical concept, it was only recently that it became clear that incorrectly folded proteins might be related with the development of disease. From that time, conformational or protein-folding diseases have been divided basically into two groups. The first, includes errors in the genetic blueprint that leads to incomplete or incorrectly folded proteins directly affecting function; classical examples of this group comprise malfunction of p53 as a critical tumor suppressor protein directly related with cancer [4, 5] and specific alterations in diseases such as cystic fibrosis [6] and sickle cell anemia [7]. The second group, which is made up to excessive quantities of incorrectly conformed proteins

causes the formation of multimolecular structures or plaques with the property of altering normal cell function. Such alterations, known as amyloidosis, are found in diseases like Alzheimer disease [8], Creutzfeldt–Jakob disease [9], Parkinson disease [10], and type II non-insulin-dependent diabetes mellitus [11]. Although in all of the previously mentioned diseases, protein aggregates or plaques are known to be constituted of amyloid fibrils polymerized as beta-sheet structures, important factors involved in the process dealing first with formation and propagation, and second with their stability are far from being understood in vivo.

Physicochemical approach

For folding into a native state, unfolded polypeptide chains require the intervention of weak interactions. Driven by hydrophobic interactions, a polypeptide chain begins to fold when placed in an aqueous medium, and rapidly becomes a molten globule followed by an important release of latent heat. Stabilization of the molten globule is achieved mainly through the distribution of hydrophobic residues away from the water matrix. On the other hand, because the polar residues contained in a protein develop hydrogen bonds with the water network as well as with each other, α-helices and β-sheets can be formed when bonds switch between molecules. It has been calculated that such bonds might be in the order of 10^{-12} s, very similar to those we find in water itself. The random equilibrium can be shifted toward one of these conformations by means of two stages: a fast stage, during which the unfolded polypeptide becomes a molten globule; and a slow stage, in which the molten globule slowly transforms into a fully folded form or native state [12]. These two stages in protein folding can be illustrated by a "folding funnel", during which due to a small change in entropy with a large loss of energy, a molten globule evolves into the native state (Fig. 1) [13, 14]. Although the process is extremely efficient, there is always the possibility that this accurate mechanism might fail, and the possibility of finding a protein folded into a non-native state becomes a reality [15]. Proteins that follow this pathway might present transiently stable conformations, promoting their interaction with other molecules and facilitating the fact that they might form amorphous oligomers and end in a state of aggregation. Aggregation does not arise from a random coil state, but rather from a series of intermediates that—based on the type of secondary structure acquired during folding—might or might not resemble the native state (Fig. 2) [14, 16]. It is well known now that primary polypeptide sequences become the key factor during this process, while the environment surrounding the protein is an important

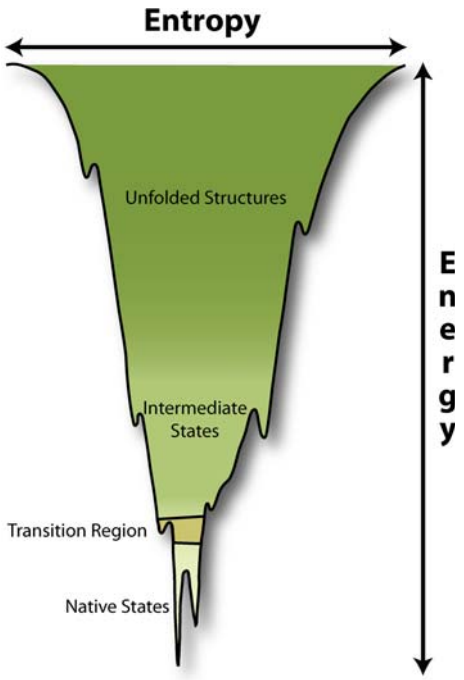

Fig. 1 Folding funnel energy landscape. Globular proteins organize themselves from a random coil to a molten globule during a large loss of entropy and small changes in energy. However, the molten globule becomes transformed to a native state during a low change in entropy at the expense of a large loss of energy. Adapted from references [12–14]

factor for explaining the folding process [17]. On the other hand, natively unfolded proteins, known to lack the presence of permanent secondary and tertiary structures, have been recognized at least in the absence of other proteins, to present the tendency to organize themselves into amyloidogenic structures. This is the case for α-synuclein, an important protein found in Lewy bodies in the brain of patients affected with Parkinson disease [18]. In the case of prion diseases, the P_rP protein has been isolated from amyloid plaques, in which a clear conformational change in secondary structure from α-helix into β-sheet following a templating mechanism has been recognized as the process that causes aggregation [17].

Considering that the native state is located at the lowest minimum of the "folding funnel", it indicates that this region is the most thermodynamically stable configuration of the polypeptide chain under physiological conditions. For proteins, whose functional state is a tightly packed globular fold, a key step in fibril formation related to partial or complete unfolding is less likely to occur and therefore remains protected against aggregation [19]. In this respect, it has been proposed that the more transient structures thus formed in proteins, the better probability for key determinants in amyloid fibril formation to be found [20]. Thus, many of the known forms of amyloid diseases are

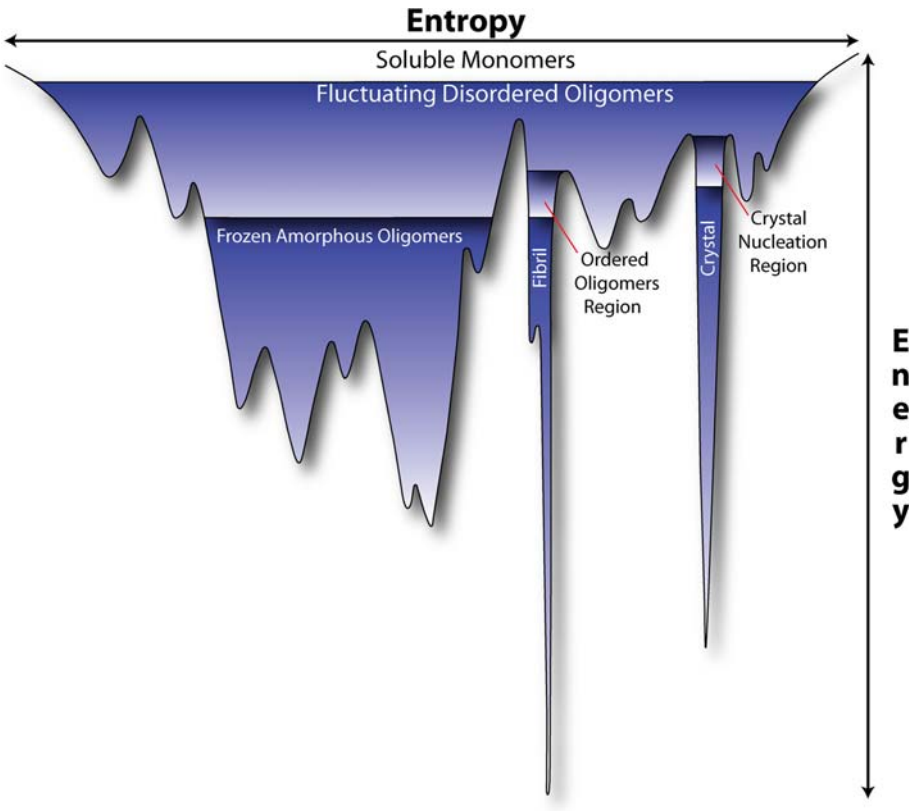

Fig. 2 Protein aggregation energy landscape. Although the funnel shape for protein folding is organized from an active process that results in the selection of forms with favorable native contacts, when a high concentration of polypeptide is present, a large number of interactions appear followed by protein aggregation. Landscape regions characterized by low energy and low entropy are recognized for the appearance of well-ordered species such as fibrils and crystals. Adapted from reference [14]

associated with genetic mutations that decrease protein stability and promote unfolding [20], both related to disorder-to-order conformational transitions.

Chen et al. showed that monomeric polyglutamine in solution represents the nucleus for aggregation and nucleation of a β-sheet aggregate through an initial disorder-to-order transition [21]. Multiple molecular dynamic simulations have provided quantitative characterization of these polyglutamine peptides showing disorder-to-order fluctuations directly related to chain length and average compactness [22]. Here, it was shown that the concentration of side chain primary amides around backbone units and solvation, either by hydrogen bonds or surrounding water molecules, importantly contribute to these average compactness values [22]. In this context, the first experimental evidence about a specific disorder-to-order transition was presented over 30 years ago with the mechanism description for the conversion of trypsinogen to trypsin [23]. This mechanism is characterized by the enzymatic removal of an hexapeptide from the N-terminal region of trypsinogen in order to form trypsin. This basic change promotes the transition from a disordered state of the "specificity pocket" in trypsinogen to an ordered state in trypsin [24].

Since it is known that several amino acids that make up a protein strongly favor a disordered state, at present this "new view" of folding is beginning to be further studied, in which the influence of external or environmental conditions sustains well-tested transitions between disordered and ordered states [25–27]. Specific polypeptide chains contained in proteins or complete proteins lacking defined tertiary structures are known to have the capacity to undergo disorder-to-order transitions upon binding to specific [28] or multiple partners [29]. It is precisely this ability that allows the concept of "protein disorder" to be proposed as an important feature in the capability of proteins to present regions with switching properties [30–32]. Dunker and Obradovic [26] and later Uversky [27] designed a protein/function paradigm extended from the classic form of thought in which ordered 3D structures are indispensable for function due to the fact that the function might arise from ordered structures as efficiently as from disordered functions, namely pre-molten globules and random coils (Fig. 3). An example of the latter would be α-synuclein, shown to be partially folded in the presence of di- and trivalent metal ions, in which in response to cation-binding intrinsic coils change into a pre-molten globular conformation [33]. On the other hand, structural arrangements that take place from a random coil to a molten globule-like conformation have been observed with the myelin basic protein upon binding to lipids [34]. From an evolutionary point of view, it appears that intrinsic disorder in proteins might have been the driving force behind many of the adaptability processes found in proteins [15, 35].

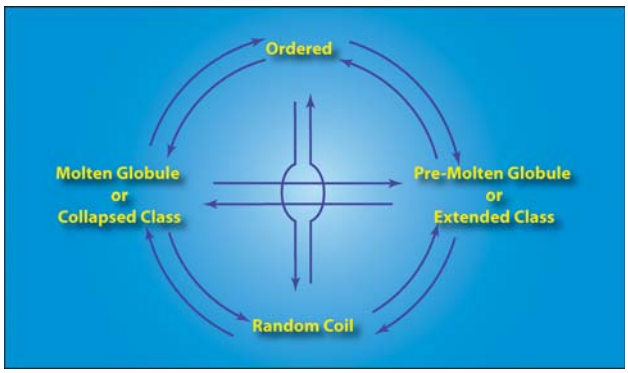

Fig. 3 Protein quartet model for protein structure transitions. Adapted from references [26, 27]

Taking into account that the number of proteins presenting disordered regions directly related with function and therefore with disease is increasingly growing, an interest to also generate accessible data banks for improving information management has increased. Therefore, the database of disordered proteins (DisProt) was created and released in August 2006 by the group of Dunker [36] with extremely good results at present [37]. Since then, other systems for studying disorder in proteins have been released, such as the Integrated Protein Disorder Analyzer, which aims at identifying and predicting disordered region in proteins [38], or algorithms for predicting and evaluating aggregation "hot spots" (AGGRESCAN) [39]. According to Dunker's group and as predicted by PONDR^{r} [40], a large percentage of all proteins involved with some sort of a disease have been identified as directly related with disordered regions in proteins closely associated with signaling.

Protein conformational diseases

From a general point of view, disordered regions in proteins have been divided into the following two classes: the class in which proteins retain a low percentage of secondary structure together with unstable tertiary structures during a molten globule state, recognized as the collapsed class; and second, the class in which proteins with a highly extended backbone resemble a β-sheet conformation related with the extended class [25, 41]. In general, proteins containing disordered regions have been recognized as associated with several human diseases, including cardiovascular disease, cancer, degenerative diseases, and diabetes. Interestingly, because in many of these cases cell signaling function has been involved, there is a strong possibility that disorder-to-order transitions in proteins playing normal switching roles in the cell might become distorted and therefore abolish or transform the normal protein–protein language into an aberrant one. Therefore, the basic properties of a switching mechanism must be based on the equilibrium between high specificity and weak affinities accompanied by a large conformational entropy decrease. This phenomenon is based principally on the fact that upon binding, disorder-to-order transitions can overcome steric restrictions and thereby enable larger interaction surfaces in protein–protein complexes than those that could be obtained for rigid partners [42]. Despite the extraordinary importance of this type of transition, we continue to lack detailed biophysical studies that might demonstrate a close relationship between this type of disorder-to-order organization and protein function.

During the last few years and mainly employing powerful bioinformatics and data mining, many proteins showing intrinsic disorder have been studied in relationship with the disease [43, 44]. A good number of these proteins can be considered as potential candidates in the understanding and treatment of the disease when specific group domains undergoing abnormal disorder-to-order transitions are recognized [42, 45]. An example of this possibility is the lymphoid enhancer-binding factor 1 (LEF-1), which corresponds to a sequence-specific and cell type-specific transcription factor playing a key role in T-cell receptor (TCR)-α gene-enhancer modulation [46]. Based on circular dichroism studies, helix I adopts a helical structure and becomes fully stabilized, reaching a well-folded state in the presence of DNA [47].

Another example corresponds to the p53 tumor-suppressor protein as one of the most studied proteins in history. It is known that p53 activates a large number of genes, with its main function being the arrest of the cell cycle in G1 and G2, allowing the activation of DNA repair mechanisms and therefore the development of its cancer-inhibiting properties. Persons inheriting only one functional copy of the p53 gene are predisposed to develop several tumor types. This condition has been found in the Li-Fraumeni syndrome (LFS), in which individuals are predisposed to develop sarcomas, leukemias, adrenocortical carcinomas, and breast cancer at early ages [48, 49]. More than 50% of human cancers have been associated with mutations in p53, and according to systematic analysis of a large number of mutations, it has been revealed that 304 of the 882 mutations studied affecting the structure of the p53 core domain can be explained by their effects on protein folding [50]. Although reversible aggregation appears to play an important role in p53 core-domain folding [51], it remains to be studied whether a percentage of the structural changes found with this important protein might be associated with localized disorder-to-order transitions, which in turn could modulate—and therefore affect, for example—protein–DNA interactions.

Moreover, with regard to RNA function, several RNA chaperones with key participation in cellular RNA metabolism have been described as organizing several networks of RNA–RNA, RNA–protein, and protein–protein interactions

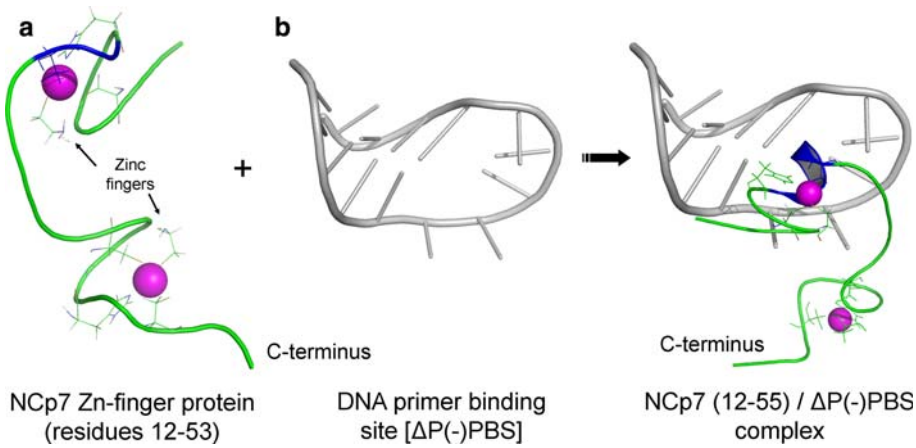

Fig. 4 Structural conformations for the NCp7 (Zn-finger) protein. **a** Relatively unstructured NCp7 (residues 12–53) showing coordination with zinc atoms in purple around a poorly structured section. **b** In the presence of DNA (HIV-1 primer binding site) a change in secondary structure (α-helix, *blue*) is observed, when a complex is formed around the HIV-primer binding site of DNA and the N-terminal region of NCp7 (Zn-finger). Structures were obtained from PDB access code: 1esk and 2jzw. Images visualized employing the Pymol program [212]

[52]. Here, these chaperone proteins presenting an important intrinsic disorder assist RNA function by successive disorder-to-order and order-to-disorder transition cycles to aid RNA in acquiring the most stable conformation required for optimal function [53]. One classical example is NCp7, a nucleocapsid protein from the HIV type 1 virus. NCp7 is a 55 amino-acid nucleic-acid-binding protein that represents an important structural segment of the HIV type 1 virus nucleocapsid. It is characterized by two zinc fingers [54, 55] and participates in several key functions during the HIV-1 viral life cycle [56–58]. The two main activities of NCp7 are destabilization of nucleic acid loop structures [59–61] and nucleic acid aggregation–condensation [62–64]. NCp7 has been mainly studied through its interaction with four contiguous stem-loop structures, where SL1–SL4 of the HIV-1 ψ recognition site [65–67] shows a high degree of disorder [53] and therefore excellent adaptation properties for a wide range of RNA and DNA molecules (Fig. 4) [66–70].

Lipid transfer protein structure and disease

In an attempt to define the possibility that folding key features in proteins could provide us with the manner in which to explain basic issues such as receptor recognition, lipid transfer activity, and self-exchangeability carried out by several lipid transfer proteins including apolipoproteins, our group has attempted to address these points by directly measuring molecular conformational changes of apolipoproteins at air/water and lipid/water interfaces, in order to approach the possible mechanisms that might explain these phenomena [71]. This has been achieved employing Langmuir monolayers in conjunction with Brewster angle microscopy (BAM), atomic force microscopy (AFM) of LB films of protein [72–75], grazing incidence X-ray diffraction on protein monolayers [76], and surface force measurements (SFA) [77]. Because at that time, we were unable to define whether the secondary structure of specific segments of apoCI and -AII remained stable independently of their position at air/water and lipid/water interfaces, more recently we have addressed the possibility that these segments responding to specific environmental changes and following disorder-to-order transitions might function as molecular switches that trigger function [78, 79].

ApoCI is synthesized with a 26-residue signal peptide that is cleaved co-translationally in the rough endoplasmic reticulum which inhibits both phospholipase A2 [80, 81] and hepatic lipase [82] and activates the lecithin-cholesterol acyltransferase (LCAT) [83]. Also, it has been reported that the C-terminal fragment of human apoCI acts as an inhibitor in vitro of the cholesterol ester transfer protein (CETP) [84, 85]. On the other hand, the discovery that apoE-enriched β-migrating very-low-density lipoprotein (β-VLDL) binds to the lipoprotein receptor-related protein (LRP) [86], the effect of apoCI content upon this binding has been studied [87]. When individual members of the C apolipoprotein family were examined, it was found that apoCI is the most potent inhibitor of apoE-mediated β-VLDL binding to the lipoprotein-related protein (LRP) [88]. It has been suggested that in addition to displacement of apoE from the particle, apoCI binding might exert its effect by inducing a change in resident apoE conformation, which in turn abolishes its ability to interact with LRP. Apolipoprotein E is a 299-residue protein that exists as three allelic variants, denominated apo E2, -3, and -4. In Alzheimer disease, the apo E4 allele is a risk factor associated with an earlier age of onset for sporadic cases [89, 90].

Although function that depends specifically on 100% disordered proteins represents the extreme case, the concept of having disordered segments in proteins that only respond and acquire a well-defined secondary structure associated with the binding of specific ligands, might be more common than we thought. We have postulated that changes in lipid composition of HDL particles might promote an alteration in normal disorder-to-order transitions found in apoCI, changing its switching properties, and therefore predisposing the onset of diseases related with LCAT activation and CETP function [79]. Acquisition of a very rapid lipid-specific α-helical conformation following a disorder-to-order transition in the C-terminal peptide of apoCI has provided new insights into how this protein might modulate function [77, 79]. Moreover, following the same approach with specific peptides synthesized from the reported structure of apolipoprotein A1, when left in water at 4°C, a very slow disorder-to-order transition develops over the course of weeks, from a fully disordered state to a well-developed β-sheet secondary structure (Mas-Oliva J, personal communication). This behavior further supports the fact that the physicochemical characteristics of the environment must be considered as a key factor in the equilibrium displacement within the secondary structure of a protein or specific segments toward α-helices or β-sheets [91]. Here, the result that specific segments of apolipoprotein AI slowly develop fibril-like structures indicates the possibility that pathological processes such as atherogenesis might be also considered as an amyloidotic-related process (Fig. 5) [92].

Amyloid-related diseases

At present, an important number of human diseases affecting several tissues and producing a series of common symptoms find their origin in the assembly of proteins into insoluble deposits [93, 94]. Although absolute establishment of this connection is lacking to date, there is solid evidence indicating a strong correlation between the formation of amyloid fibrils and their toxicity upon cells in vitro [95–97]. The missing point continues to reside in basic understanding of the characteristics of the so-called amyloidogenic proteins that define their capacity to organize themselves into a β-structure conformation. This capacity has been, on the one hand, related to a hereditary component with several dominant autosomic diseases [98], and on the other, with a "sporadic" form of the disease [98, 99]. Here, independently of whether the precursor protein is being synthesized as a normal protein, secondary external factors mainly related with the protein environment during synthesis or during transit to its target pathway, define their potential amyloidotic pathway. Because not every protein that aggregates forms amyloid deposits, the study—and eventually the understanding—of the mechanisms that govern, first, protein folding and second, aggregation-related phenomena, include possible implications for disorder-to-order transitions. Again, the potential implications of having disordered segments in these proteins that might present conformational transitions to ordered states still remains to be fully evaluated.

Amyloid-related diseases are in direct association to a failure of the regulatory mechanisms that normally ensure that proteins remain in their correctly folded functional states [13]. Such mechanisms and quality control systems include the action of folding catalysts, molecular chaperones, degrading enzymes, and endoplasmic reticulum-associated degradation, that normally detect misfolded or damaged proteins and either rescue or destroy them [19, 100]. If the function of these protective mechanisms is diminished, the probability of pathogenesis increases [101, 102].

On the other hand, several studies have shown that a certain number of polypeptides not directly related to amyloid disease might be also capable of forming amyloid fibrils under destabilized conditions [103–108]. This shows that amyloid deposition may be a common property of proteins, and not only to the ones associated with disease [109]. In fact, the difference between "functional" amyloids and the ones associated to disease might be explained in terms of evolutionary regulating mechanisms. These mechanisms might have evolved functional amyloids where cellular toxicity associated to their formation might have been quenched by other proteins [110] as in the case of protein Pmel17 [111, 112]. Pmel17 corresponds to a transmembrane protein located in the plasma membrane of melanocytes [113]. This protein is of central importance in the way melanin is polymerized in melanocytes since Mα, a proteolytic fragment of Pmel17 structured as amyloid fibrils

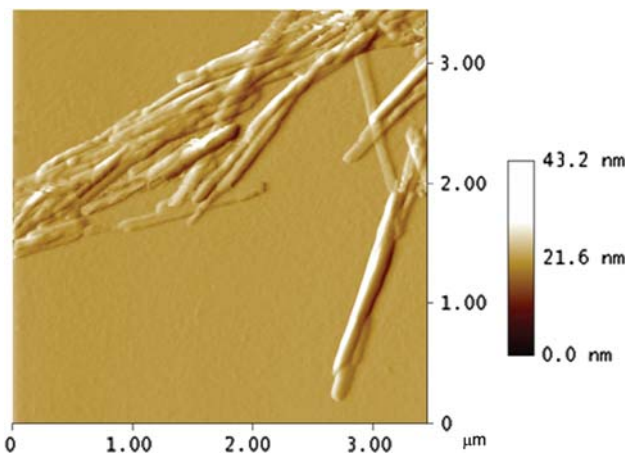

Fig. 5 Atomic force microscopy image of apolipoprotein AI-peptide DRV (amino acids 9–24) (Mas-Oliva J, personal communication). Fibrils show an average length of 300 nm and 25 nm in height

functions as a key support in the polymerization of melanin [111]. Since it has been shown that amyloidogenesis of Mα is four orders of magnitude faster that Aβ and α-synuclein, we can consider this optimized process of fibrillogenesis as an evolutionary way to avoid intrinsic toxicity mostly associated to fibril polymerization [112].

Amyloids are basically classified according to the process-specific protein rather than their clinical manifestations. One of the most important models for studying amyloidogenesis has been the one that occurs during inflammation [114, 115]. This model has been useful in the study of the common characteristics among amyloids, in which an acute phase related with protein synthesis in liver has been described. Because many amyloid peptides/proteins correspond to a fragment of larger precursor molecules, it has been observed that usually a 1,000-fold increase in the plasma concentration of these precursors is needed in order to start the deposition of amyloid. Proteolytic processing of these precursors associated with an altered expression of a series of sorting and trafficking factors appears to be a pathogenic factor in the formation of amyloid deposits [116].

To date, many proteins have been proposed as presenting amyloidogenic properties. Interestingly, on examining their shared characteristics from the perspective of primary structure, no common features are found among them. Therefore, their amyloidogenic properties must rely on the secondary and tertiary levels. Kinetic data are consistent with the possibility that "intermediate" or "molten globule-like" conformational states are in equilibrium, and that the process of fibril formation takes place only by shifting this equilibrium [117]. Since amyloidogenesis corresponds to a two-step reaction with a slow lag period related with the formation of a nucleation center and as a secondary stage its propagation, this process has been compared with protein crystallization [118]. The presence of metal ions and the association with accessory proteins such as apolipoproteins and sulfated proteoglycans has shown the property to modulate amyloidogenesis [119–121]. Therefore, the sometimes denominated *pathological chaperones* have also been shown to contribute to amyloid toxicity [122].

Amyloid-associated proteoglycans

Perhaps the most common amyloid-associated molecules are proteoglycans, which contain a large number of sulfate glycosaminoglycan (GAG) chains linked to large molecular-weight protein cores [123, 124]. The possibility that GAG interaction contributes as a driving force in fibril assembly and amyloid plaque formation has been suggested [125]. In this context, sulfated proteoglycans are ubiquitously expressed on various cell membranes and they are common to all type of amyloids studied to date. They have been also suggested as key factors in the formation of mature plaques serving as scaffolds and protecting against proteolysis [126–128]. Several subtypes have been associated with Aβ plaques, including heparin, dermatan, keratin, and chondroitin sulfate proteoglycans [129, 130].

It seems that the most common amyloid-associated proteoglycan is perlecan [130, 131] that constitutes the major component of the basement membrane/extracellular matrix proteoglycan of the cell [127, 132, 133]. Perlecan has been associated to virtually all human amyloid diseases including Alzheimer's disease, familial amyloidosis, and type 2 diabetes [128, 134–137]. Although several in vitro studies have shown that sulfated GAG chains can induce extensive Aβ aggregation via electrostatic interactions [138] and have been found to increase the β-sheet content of several amyloidogenic proteins such as serum amyloid A protein (SAA) [139], sulfated GAG chains also seem to reduce amyloid fibril degradation [140]. The SAA [139] has been reported to contain specific binding sites for heparin and heparan sulfate, associated to phylogenetically conserved basic residues. The occupation of these sites is likely to increase the amyloid conformation of SAA [141].

β amyloid precursor protein (AβPP) and β amyloid (Aβ)

Together with its precursor protein, the amyloid peptide is considered a normal molecule found in plasma, cerebrospinal fluid, and the extracellular space. AβPP corresponds to a transmembrane protein with a low amyloidogenesis potential in vitro. This is in contrast with the high tendency of Aβ to form fibril aggregates [142]. Three AβPP isoforms are shown to date (751, 770, and 695 amino-acids) [143] and all of them, followed by the action of an α-secretase, form a soluble ectodomain with the retention in the membrane of the carboxy end fragment [144]. Secondary to the action of β and γ secretases, Aβ is liberated generating diverse forms of the β amyloid peptides ranging in size from 39 to 43 residues, being $A\beta_{42}$, the one with the highest fibrillogenic potential (Fig. 6) [145]. Several years ago, we found that upon activation platelets secrete a 120 kDa proteoglycan that presents the ability to inhibit acetylated-low-density-lipoprotein internalization through binding to the scavenger receptor class A (SR-A) in macrophages [124]. This proteoglycan was identified as an α-secretase product of AβPP [146]. This finding supports the possibility that SR-A might participate in the clearance of several forms of AβPP from atherosclerotic lesions, thus contributing to the reduction of foam cell formation. Moreover, competition of AβPP for β-amyloid uptake by microglial cells through the SR-A, might contribute to β-amyloid accumulation in the brain's extracellular space. Although changes in secondary structure of AβPP related to a disorder-to-order transition has not been addressed, at

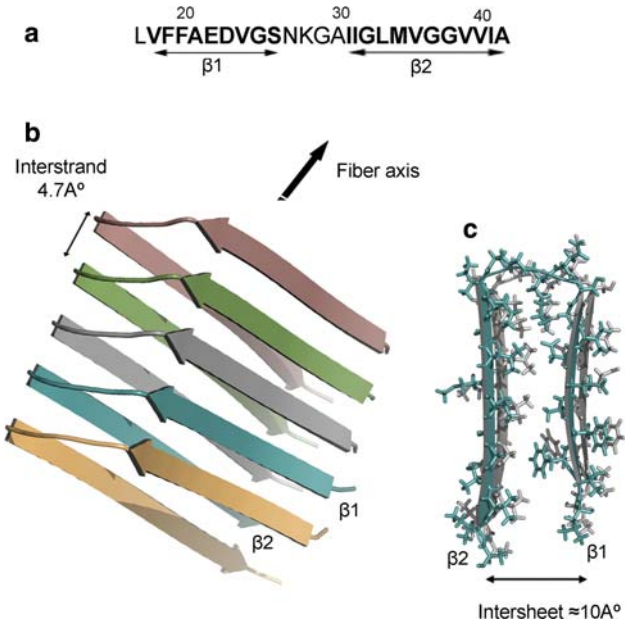

Fig. 6 Structural representation of Aβ peptides. **a** Primary sequence of Aβ fragment 17–42 showing segments that correspond to β1 (18–26) and β2 (31–42) connected through a poorly structured region (residues 27–30). **b** Fibrilar structure of Aβ (17–42) obtained with NMR and mutagenesis complementation methodologies. The structure shows a pentamer with interchain distances of approximately 4.7 Å. **c** Lateral view through the axis of a Aβ fiber showing the lateral amino-acid residues of both β-sheets separated by a 10 Å gap. PDB access code: 2beg. Images visualized employing the Pymol program [212]

this stage this possibility can not be discarded. β-amyloid has been also shown to promote an important cellular oxidative state [147] and further promote, for example, the development of Alzheimer disease, the most common amyloidosis and leading cause of dementia among the elderly.

The amyloid-enhancing factor (AEF) is defined as a factor that dramatically shortens the induction time for amyloid development during inflammatory processes (from 36 h to 2–3 weeks). This characteristic is consistent with amyloidogenesis requiring a nucleating event that shortens initiation of the process. Likewise, many AEF characteristics are related with experiments in which exogenously delivered prions have been injected, and apparently served as templates for endogenously synthesized prions transformed into pathologically active agents [148, 149]. However, different from prions, AEF generates amyloidosis only in the presence of an inflammatory event, reason why instead of being an infective agent it is considered a potentiator of the disease [150].

Prion disease

Prion diseases are chronic neurodegenerative disorders associated with the accumulation of abnormal isoforms of PrP protein in the brain. Among these diseases, we recognize at present scrapie (in sheep and goat), spongiform encephalopathy (in cattle) [151, 152], and in the human, Kuru [153], Creutzfeldt–Jakob disease (CJD) [154], fatal familial insomnia (FFI), Gerstmann–Sträusler–Scheiker disease (GSS), and PrP-cerebral amyloid angiopathy (PrP-CAA) [155–157]. The cellular prion protein (PrP^c) corresponds to a single gene-encoded 35 kDa sialoglycoprotein [158]. The translated protein contains 253 amino acids with glycine/proline-rich octopeptide repeats spanning residues 51–91. It is polymorphic at residue 129 with methionine/valine and at residue 219 with glutamic acid/lysine, and is glycosylated at residues 181 and 197 [159]. Circular dichroism has shown that PrP^c presents a high content of α-helical secondary structure and shows no β-sheet conformation [160]. It is transported in secretory vesicles while anchored to these structures through a GPI moiety [161]. Although the normal function for PrP^c remains unknown, it has been suggested that it might play a role in synaptic function [162]. Because PrP knockout mice have shown to be resistant to development of scrapie, it has been postulated that synthesis of the normal form of PrP^c is an absolute pre-requisite in this protein's abnormal form (PrP^{sc}), which involves a conformational change from an

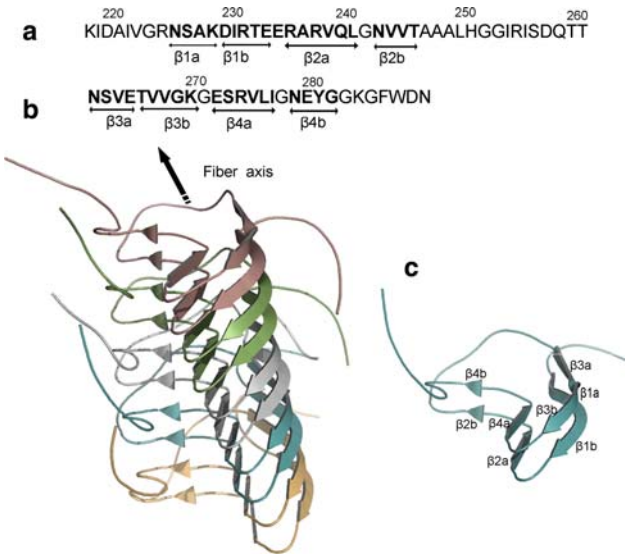

Fig. 7 Structure of the prion like domain of HET-s (218–289). **a** Primary sequence of HET-s fragment 218–289 showing segments that correspond to β-strands β1a (226–229), β1b (230–234), β2a (236–241), β2b (243–246) and β3a (262–265), β3b (266–270), β4a (272–277) and β4b (279–282) separated by a poorly structured region (residues 247–261). **b** Side view of five domains of HET-s (218–289) calculated from solid state NMR with a tridimensional structure in the form of a left-handed-β-solenoid. Each color represents a single domain. **c** Side view of a single domain showing β-structured regions as marked in (**a**). PDB access code: 2rnm. Images visualized employing the Pymol program [212]

α-helix-based structure into β-sheets [163]. Prion rods possess the same tinctorial properties of amyloid fibers (binding the amyloidophilic fluorophores thioflavin and Congo red) [164] and resemble amyloid fibrils found in vivo (Fig. 7) [165, 166].

Peripheral nerve amyloidosis and transthyretin (TTR)

Peripheral nerve amyloidosis is common in familial amyloid polyneuropathy (FAP) [167] and can be a key feature in primary light chain amyloidosis and β2-microglobulin-related amyloidosis. FAPs are a heterogenous group of autosomal dominant disorders characterized by deposition of a fibrillar protein associated to transthyretin (TTR) in the form of amyloid [168, 169]. TTR composed of four identical 127 residue subunits is the plasma protein responsible for transport of thyroxin and vitamin A [170, 171]. Although several mutations in TTR causing extracellular tissue-selective deposition have been described [172], the clinical basis for the predominant manifestation of each mutation has not been established yet [173]. Nevertheless, pathogenesis has been associated with dissociation of the native tetramer molecule into partially unfolded species, which can subsequently self-assemble in the form of amyloid fibrils (Fig. 8) [174–177].

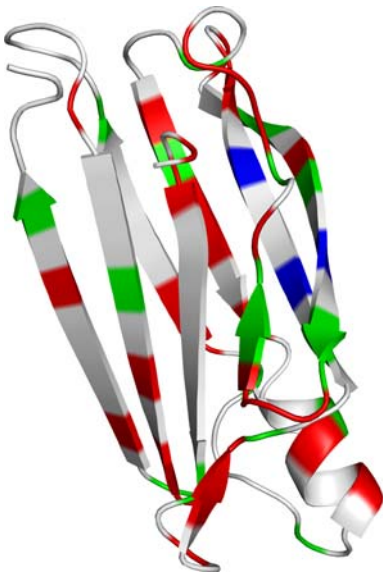

Fig. 8 Three-dimensional structure of the transthyretin monomer obtained from X-ray diffraction. *Arrows* represent β-sheet secondary structure showing in color the position of regions with the most common amyloidogenic mutations. *White color* represents regions with no incidence of mutation, *red* one mutation, *green* two-three mutations, and *blue* four or more mutations. Citation for each mutation can be found at the TTR database of mutations maintained by C. E. Costello at Boston University School of Medicine (http://www.bumc.bu.edu/msr/ttr-database/). PDB access code: 1rlb. Image visualized employing the Pymol program [212]

FAP can also occur secondary to apolipoprotein A-I [178] and gelsolin deposition [179], where two mutations described in the gelsolin gene have been directly associated to this type of disease [180, 181]. In this respect, it has been also shown that serum apo A-II concentrations are much higher in patients with FAP than in normal controls or asymptomatic carriers, suggesting that apo A-II may play a role in amyloid formation in these patients [182]. Moreover, the disease known as familial amyloidosis of Finnish type (FAF) related to gelsolin deposition is characterized by progressive cranial neuropathy, corneal dystrophy, and skin elasticity complications [183, 184]. The first step in FAF is determined by an aberrant proteolysis carried out by furin [185] followed by the proteolytic cut of a MT1-matrix metalloprotease generating amyloidogenic peptides of 5 or 8 kDa [186].

Islet amyloid polypeptide (IAPP) and Beta 2 microglobulin (β2m)

IAAP or amylin synthesized in pancreatic islet β-cells suffers a series of post-translational modifications to yield a mature 37-amino acid peptide (Fig. 9) [187, 188]. IAPP is a molecule involved in the modulation of glucose metabolism [189, 190] as well as in calcium metabolism [191]. IAPP aggregates are the primary component of amyloid deposits found in the pancreatic β-cells of patients with type 2 diabetes mellitus [192]. Prefibrillar oligomeric IAAP has been shown the property to permeabilize membranes through a pore-like mechanism, suggesting that this process might be related to the pathogenic mechanism involved in the genesis of non-insulin-dependent (type II) diabetes mellitus (NIDDM) and other amyloid-related diseases [193]. In adult diabetes (type II), it has been

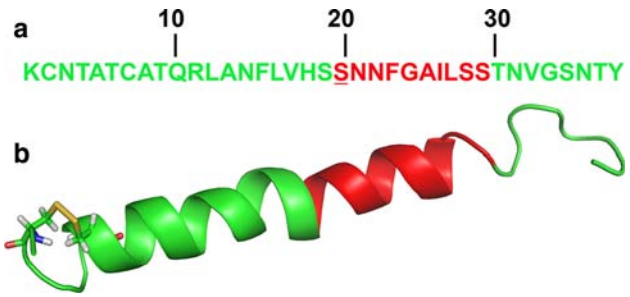

Fig. 9 Three-dimensional structure of human amylin. **a** Primary amino-acid sequence of the entire amylin molecule (1–37) showing in red the amyloidogenic region in between S20 and S29. A mutation that changes S20 for G20 has been directly related to the most severe cases of non insulin dependent diabetes mellitus (NIDDM). **b** Secondary structure of amylin determined by NMR using SDS micelles. The amyloidogenic region of amylin is shown in *red* as in (**a**). PDB access code: 2kb8. Image visualized employing the Pymol program [212]

observed that 90% or more of patients with this disorder present amyloid deposits in the islets of Langerhans [194].

β2m is a protein found in a noncovalently association with the heavy chain of major histocompatibility class I complex (MHCI). Due to the natural turnover of β2m, it is normally found in plasma and therefore carried to the kidneys where it is degraded and excreted [195]. Due to renal disfunction, the concentration of β2m in plasma can increase up to 60-fold, where it accumulates as a filamentous structure in connective tissues and leads to dialysis-related amyloidosis [196–198]. Although it is known that dissociation from MHCI predisposes the amyloid-transition of β2m [199], the mechanism underlying β2m fibrillogenesis in vivo is still largely unknown [200, 201].

Concluding remarks

According to scientists working in different fields of knowledge, nature appears to have employed disorder to create high levels of organization. Moreover, in some cases nature seems to have created disorder, when there is, in the first place a lack of it [202]. This latter situation extrapolated to medicine has shown that many diseases find their origin in the way proteins carry out many structural changes employing finely tuned disorder-to-order and order-to-disorder transitions.

Taking into account that several amyloid-functional-structures have been characterized in bacteria [203, 204], fungi [205–207], insects [208, 209], and mammals [111, 210], there is consensus that the formation of amyloid fibrils represents a well conserved evolutive pathway in protein structure [110, 211]. Therefore, differences between "functional" and "pathological" amyloids might simply reside in the modulatory pathways involved along their synthesis. As professor Christopher M. Dobson has stated, "One can therefore think of the amyloid diseases as resulting from the reversion of the highly evolved biologically functional forms of peptides and proteins into an alternative and unwelcome structural state that exists as a result of the inherent physicochemical nature of polypeptide chains" [19]. Without a doubt we can state that in the near future, many diseases with still unknown origins will find their explanation in the way this class of phenomenon is regulated.

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