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2. Neurodegenerative diseases: A protein misfolding consequence

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Abstract. Protein misfolding and aggregation into amyloid-like structures is related with an increasing number of both non-neuropathic (either localized or systemic) and neurodegenerative human disorders. Decrypting the mechanisms and implications underlying amyloid assemblies has become a central issue in biology and medicine. Compelling evidence show that the formation of amyloid aggregates has a negative impact in cell physiology, entailing the cell dysfunction and finally apoptosis and cell death. The aim of the present review is to illustrate the currently status of the most common and/or debilitating conformational diseases, from Alzheimer to prion diseases.

Introduction

Proteins and peptides are the main cellular components allowing organisms to execute the cellular functions required for life through complex and

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usually transient networks of intermolecular interactions [1]. In this complex network the proteins display functions of (1) binding, wherein the specific recognition of other molecules is central to protein function and specific binding is governed by shape complementarity and polar interactions such as hydrogen bonding; (2) catalysis, essentially every chemical reaction in the living cell is catalyzed, and most of the catalysts are protein enzymes; (3) switching, since proteins are flexible molecules and their conformation can change in response to microenvironment changes act controlling cellular processes.

In the cell, the final protein conformational equilibrium is the result of a delicate and multi-step balance regulated by diverse intrinsic and extrinsic factors. It is known that the unfolded polypeptide chain dramatically determines the conformational structure and folding pathways of the proteins [2]. Usually, when the polypeptide chain leave the ribosome a fast conformational process is produced (with nanoseconds or picoseconds rates) favoring that the smallest proteins fold spontaneously on a millisecond or even microsecond time scale that exclude the possibility of a random-search mechanism for protein folding [3]. Since alternative structures, as amyloid-like ones that in addition may represent the primordial ground state of protein folding and assembly reactions, can be a possible alternative (even probable in certain situations) to native and functional protein structure, protein aggregation has now become recognized as an important and generic aspect of protein energy landscapes [4]. Since the biophysical properties that promote folding also tend to favor intermolecular contacts, leading to the formation of β -sheet-enriched insoluble assemblies, protein folding into stable globular conformations is in competition with aggregation into non-functional and usually toxic structures as amyloid-like structures [5].

It is known that the self-assemble potential into β -sheet enriched amyloid-like structures of any protein is embedded in their primary structure [6,7]. However, although all polypeptide chains could theoretically aggregated in amyloid conformations, it has been stated that while the majority of the primary sequence is unable to self-associate *per se*, short sequences in the chain protein, usually named “hot-spots” are the final responsible to trigger the protein aggregation in amyloid conformation [8]. Interestingly, although these short regions, able to form amyloid fibrils by themselves [9], are inherently present in the sequence of globular proteins, evolutionarily it effect have been minimized by the flanking with anti-aggregation sequences named “gatekeepers”, being embedded in the protein core or protected for the quaternary structure. Nevertheless, when these amyloid-like regions are exposed to solvent (*i.e.* in situations of deregulations of the protein synthesis, environmental alterations), the intermolecular contacts leading the formation of β -sheet enriched aggregates could be

drastically favored [10]. Importantly, the presence of these hot-spot regions is usually observed in the proteins involved in conformational diseases.

In the recent years, protein misfolding and aggregation has become a widely active area of research, mainly because of the connection between the formation of insoluble protein deposits in human tissues and the development of dozens of human diseases. The conformational diseases, linked to protein aggregation into amyloid conformations, ranked from neurodegenerative affections such as Alzheimer (AD), Parkinson (PD), Huntington (HD), frontotemporal dementia (FTD), amyotrophic lateral sclerosis (ALS) or human transmissible sporadic encephalopathies (TSEs) commonly known as prion diseases, to non-neurodegenerative systemic and localized amyloidosis as light-chain (AL) amyloidosis or type II diabetes, respectively [11] (see Tables 1a-c).

Table 1a. Human diseases associated with formation of extracellular amyloid deposits or intracellular inclusions with amyloid-like characteristics: Neurodegenerative diseases

Disease	Aggregating protein or peptide
Alzheimer's disease	Amyloid β peptide
Spongiform encephalopathies	Prion protein or fragments thereof
Parkinson's disease	α -Synuclein
Dementia with Lewy bodies	α -Synuclein
Frontotemporal dementia	Tau
Amyotrophic lateral sclerosis	Superoxide dismutase 1
Huntington's disease	Huntingtin with polyQ expansion
Spinocerebellar ataxias	Ataxins with polyQ expansion
Spinocerebellar ataxia	TATA box-binding protein with polyQ expansion
Spinal and bulbar muscular atrophy	Androgen receptor with polyQ expansion
Hereditary dentatorubral-pallidoluysian atrophy	Atrophin-1 with polyQ expansión
Familial British dementia	ABri
Familial Danish dementia	ADan

Extracted from ref. [11].

Table 1b. Human diseases associated with formation of extracellular amyloid deposits or intracellular inclusions with amyloid-like characteristics: Neurodegenerative diseases: Non-neuropathic systemic amyloidosis.

Disease	Aggregating protein or peptide
AL amyloidosis	Immunoglobulin light chains fragments
AA amyloidosis	Fragments of serum amyloid A protein
Familial Mediterranean fever	Fragments of serum amyloid A protein
Senile systemic amyloidosis	Wild-type transthyretin
Familial amyloidotic polyneuropathy	Mutants of transthyretin
Hemodialysis-related amyloidosis	β 2-microglobulin
ApoAI amyloidosis	N-terminal fragments of apolipoprotein
ApoAII amyloidosis	AI N-terminal fragment of apolipoprotein
ApoAIV amyloidosis	AII N-terminal fragment of apolipoprotein AIV
Finnish hereditary amyloidosis	Fragments of gelsolin mutants
Lysozyme amyloidosis	Mutants of lysozyme
Fibrinogen amyloidosis	Variants of fibrinogen
Icelandic hereditary cerebral amyloid angiopathy	α -chain Mutant of cystatin C

Extracted from ref. [11].

These protein deposits, constituted mainly by fibrillar structures known as amyloid aggregates, are thread-like protein aggregates with a cross- β structure, which is composed by β -strands stacked perpendicular to the fibril axis [11]. For years the structural characterization of these amyloid-like aggregates were limited due to the lag of crystalline forms and their low resolution by solution nuclear magnetic resonance (NMR). However, these aggregates often display enriched β -sheet structure detectable by X-ray diffraction, Fourier transform infrared spectroscopy (FTIR) and circular dichroism (CD). Like this, they are able to bind amyloid-tropic dyes as Thioflavin-T (fluorescence spectroscopy and optical microscopy) or Congo Red (UV/Vis spectroscopy and birefringence), present proteinase K digestion

resistance and fibrillar structures are detectable by transmission electronic microscopy (TEM) or atomic forces microscopy (AFM). Moreover they show seeding capacity reminiscent of amyloids, form homogeneous aggregates without cross-aggregation, and display aggregation propensities strongly affected by mutations. Importantly, since some of these tests can be non-conclusive, giving false positive and false negative, nowadays the confirmation of amyloid structures is usually based upon the positive in diverse of these amyloid tests [2].

Table 1c. Human diseases associated with formation of extracellular amyloid deposits or intracellular inclusions with amyloid-like characteristics: Neurodegenerative diseases: Non-neuropathic localized amyloidosis

Disease	Aggregating protein or peptide
Type II diabetes	Amylin, also called islet amyloid polypeptide (IAPP)
Medullary carcinoma of the thyroid	Calcitonin
Atrial amyloidosis	Atrial natriuretic factor
Hereditary cerebral haemorrhage with amyloidosis	Mutants of amyloid β peptide
Pituitary prolactinoma	Prolactin
Injection-localized amyloidosis	Insulin
Aortic medial amyloidosis	Medin
Hereditary lattice corneal dystrophy	Mainly C-terminal fragments kerato-epithelin
Corneal amyloidosis associated with trichiasis	Lactoferrin
Cataract	γ -Crystallins
Calcifying epithelial odontogenic tumors	Unknown
Pulmonary alveolar proteinosis	Lung surfactant protein C
Inclusion-body myositis	Amyloid β peptide
Cutaneous lichen amyloidosis	Keratins

Extracted from ref. [11].

Due to the large number of conformational diseases, in this review we tempt to provide readers concise information about the most prevalent conformational diseases as well as the most debilitating ones. In this way we have chosen: Alzheimer's disease (AD), Parkinson's disease (PD), frontotemporal dementia (FTD), Huntington's disease (HD) and amyotrophic lateral sclerosis (ALS) as the most prevalent neurodegenerative diseases. In addition, spongiform encephalopathies including Creutzfeldt-Jakob's disease (CJD), the most prevalent human spongiform encephalopathy, has been added as the most debilitating and transmissible case (see Table 2).

Table 2. Human diseases associated with formation of extracellular amyloid deposits or intracellular inclusions with amyloid-like characteristics.

Disease	Cases	Cases per 100,000 population*
Alzheimer's disease	4 000 000	1 450
Parkinson's disease	1 000 000	360
Frontotemporal dementia	40 000	14
Huntington's disease	30 000	11
Amyotrophic lateral sclerosis	20 000	7
Progressive supranuclear palsy	15 000	5
Spinocerebellar ataxias	12 000	4
Pick's disease	5 000	2
Prion disease	400	<1

Extracted from ref. [12]. * Data are based on a population of approximately 275 millions in 2000.

1. Alzheimer's disease

Among all dementia types, Alzheimer's disease (AD) represents $\approx 70\%$ of these cases. By 2009, more than 35 million cases of AD were recorded worldwide, with an expectancy of doubling this number in 2050 [1,13]. Two distinctive features characterize the brain physiopathology of AD patients: (1) the apparition of extracellular amyloid plaques formed as a consequence of the accumulation in amyloid form of β -amyloid peptide ($A\beta$) and (2)

neurofibrillary tangles mainly formed by hyperphosphorylated forms of neuronal tau protein associated in microtubules [1,14].

While amyloid plaques are primarily composed of the A β , a host of other compounds such as proteoglycans, inflammatory molecules, serum related molecules, metal ions, amyloidogenic related molecules, protease and clearance related elements, antioxidant defense protein, cholinesterases and up to 26 proteins enrich these amyloid deposits [15,16]. A β , the main component of amyloid plaques, is a hydrophobic 39–43 amino acid peptide resulting from the proteolysis of the trans-membrane amyloid protein precursor (APP) by α - or β -, and γ -secretases [15]. Interestingly, this proteolysis can follow two different pathways with different cleavages: (1) non-amyloidogenic pathway in which the action of the α - and γ -secretases undergo the formation of a soluble and non-amyloid peptide or (2) amyloidogenic pathway wherein the action of the β -secretase in a first step entail the apparition of a A β peptide that can be quickly aggregated in amyloid conformation [15].

Tau protein binds microtubules through some repeated domains (R1–R4) (encoded by exons 9–12) located at the C-terminus of the molecule, however in AD this role is ineffective to keep the cytoskeleton well organized in the axonal process [17]. The conformational changes and misfoldings in the normal structure of tau lead the formation of paired helical filament (PHF), the main component of the neurofibrillary tangles, as result of microtubule-associated protein tau in a hyperphosphorylated state. It is known that the hyperphosphorylation of tau trigger its inability to bind to microtubules that are associated in PHFs [18]. Inasmuch as tau protein stabilize the neural axons, this binding incapacity undergoes the axon disruption, and finally the neuron disfunction and neural cytotoxicity.

The apparition of extracellular amyloid plaques and neurofibrillary tangles lead to nerve cell death and tissue loss throughout the brain. In the Alzheimer's brain the cortex shrivels up, initially damaging areas involved in thinking (primarily in the formation of new memories) and language mainly affecting the Broca's and Wernicke's areas in the hippocampus. Although the disease progression rate varies greatly the average survival is 8 years can reach up to 20 in some cases. In early stages, that may have begun 20 years before diagnosis, extracellular amyloid plaques and neurofibrillary tangles begin to form in brain areas involved in learning and memory, and thinking and planning. In mild to moderate stages, generally last from 2 - 10 years, the evolution of the disease entails a dramatic increment of the presence of plaques and tangles in the memory, thinking and language, entailing clear language and spatial difficulties. Finally, in the severe stages, usually last

from 1 - 5 years, senile plaques and tangles are massively scattered for all cortex region entailing dramatic increment of neuronal death with serious damage and consequences for the patient. In this stage the patient lose the abilities of communicate, recognize, love and self-care.

2. Parkinson's disease

Parkinson's disease (PD), disease associated to motor symptoms such as bradykinesia, tremor, rigidity and impaired postural reflexes, as well as mental disorders like depression or psychosis, is the second most common neurodegenerative illness after AD [19]. The prevalence of PD, affecting approximately 7 million people worldwide, is estimated at 0.3% of the entire population and about 1% in people over 60 years of age [20,21]. The prevalence and incidence of PD increase exponentially with age, and are slightly higher in men than in women. Interestingly, although PD traditionally has been considered a non-genetic disorder, around 15% of individuals with PD have a first-degree relative who has the disease and at least 5% of Parkinson's cases have forms of the disease that occur because of a mutation of one of several specific genes [22].

PD is a progressive neurodegenerative disease, primarily affecting voluntary and controlled movement, consequence of death of dopamine-generating cells in the *substantia nigra* and loss of dopaminergic terminals in the basal ganglia and with motor impairments [23]. The abnormal accumulations of α -synuclein in Lewy bodies suggest that this protein has a central role in a group of neurodegenerative diseases known as synucleinopathies [23]. α -synuclein is a presynaptic neuronal protein of 140 amino acids encoded by a gene on chromosome 4 with a putative role in synaptic function and neural plasticity [24]. Although α -synuclein is extensively expressed in the central nervous system, neuronal death and Lewy body formation in PD are mostly restricted to the *substantia nigra* [23]. As previously shown in AD, under certain conditions α -synuclein can self-polymerize in amyloid-like conformations. Thus, α -synuclein soluble monomers nucleate becoming oligomers (protofibrils) that can be associated forming fibrils and finally resulting Lewy's body inclusions. While the toxicity of Lewy's bodies is nowadays unclear, it seems clearer the implication of protofibrils in the toxicity *via* formation of circular amyloid pores entailing ion deregulation, membrane disruption and finally apoptosis and cellular death [25].

Despite the amyloid aggregation of α -synuclein is initially localized in the *substantia nigra* in the mesencephalon, during the progression of the disease are increasing protein aggregates that appears in different areas of the brain. The increment of the amount of Lewy's bodies in the brain entails

increment in the severity of the symptomatology and neuronal affectation. Interesting, this pathology appears to spread throughout the brain as the disease progresses. Recent works show that this spreading process could be caused by neuron-to-neuron spread of α -synuclein aggregates and that the anatomical pattern of progression of lesions between axonally connected areas results from the axonal transport of such aggregates [26].

3. Frontotemporal dementia

Frontotemporal dementia is a term grouping diverse uncommon disorders that primarily affect the frontal and temporal lobes of the brain. The degeneration of these FTD lobes is associated with alterations of the personality, behavior and language. As previously observed in AD, the loss of neuronal cells is associated to the misfolding of tau protein. For years this fact has led to diagnostic confusions entailing an infra-diagnosis of FD cases which were erroneously attributed to AD; however, nowadays more accurate evaluation methods allowing more clear differentiation between both disease have shown that the incidence and prevalence of FTD were clearly more elevated than the initial considered.

Although FTD tends to occur at a younger age than does AD, typically between the ages of 40 and 70, but incidence and prevalence is increased for the age and it is more frequent in men. The prevalence estimates in the age categories of 45–64 years old have ranged from 15 to 22 per 100,000 person each year and an estimated incidence from 2.7 to 4.1 per 100,000 person each year [27]. Age-specific prevalence rates is calculated for 1.2 per 100,000 in the 40 to 49 age group; 3.6 per 100,000 in the 50 to 59 age group; 9.4 per 100,000 in the 60 to 69 age group; and 3.8 in the 70 to 79 age group. Thus, the highest prevalence is found at ages 60 to 70, although patients older than 85 years have been reported. Interestingly, about 25% of patients have a hereditary form of FTD with autosomal dominant inheritance. Mutations in the tau gene are present in less than half of familial FTD cases. A mutation in the CHMP2B gene on chromosome 3 is probably even rarer. Therefore, it is very likely that more common disease-causing genes, one of them possibly located on chromosome 17q close to the tau gene, have still to be identified [27,28].

4. Huntington's disease

Polyglutamine (polyQ) Pathies are a particular class of conformational diseases linked to proteins associated to several different types of hereditary neurodegenerative disorders wherein a polyQ extension become thus a

molecular hallmark for fibril propensity, undergoing the protein polymerization in amyloid-like conformations. Now, nine different conformational diseases have been shown to be related to polyQ extensions: Huntington's disease (HD), spinocerebellar ataxia (SCA) types 1, 2, 3, 6, 7, 17, dentatorubral-pallidoluysian atrophy (DRPLA) and bulbar muscular atrophy (SBMA) [1].

Huntington's disease (HD), also known as Huntington's chorea, is a rare, adult-onset, autosomal dominant linked to mutation in Huntingtin (*HTT*) gene, and progressive neurodegenerative disease. *HTT* was the first disease-associated gene to be molecularly mapped to a human chromosome. The mutation turns out that the *HTT* gene contains a region where the triplet nucleotide CAG is repeated several times. The number of CAG repeats present in the *HTT* gene determines whether an individual will have HD. Thus, while from 6 to 26, normal allele, and 27-35, intermediate allele (IA) also termed large normal allele, CAG repeats do not entail misfolding protein and aggregation; 36-39 repeats, incomplete or reduced penetrance allele (RPA), will be at increased risk for HD; and 40 or more CAG repeats, full penetrance allele (FPA), will definitely manifest disease phenotypes undergoing amyloid-like aggregation [29]. Importantly, recent works show that the length of polyQ extension is directly related with the protein destabilization, and consequently the formation of amyloid aggregates [30]. This fact is in correlation with the previously shown; the number of repeats determines the probability an individual will have HD because an increased number of repeats triggers the amyloid conversion of the protein.

The worldwide prevalence of HD, similar for men and women, is 5-10 cases per 100,000 persons. HD symptoms, which typically manifest between 35 and 55 years of age, ranked from behavioral changes, psychiatric, movement, feeding, communication and sexual problems in a progressive manner. In early stage the usual symptoms are personality changes, mood swings and unusual behavior as consequence of the initial affectation of basal ganglia called the *neostriatum*, which is composed of the caudate nucleus and putamen, as well as the *substantia nigra*, layers 3, 5 and 6 of the cerebral cortex, the hippocampus, *purkinje* cells in the cerebellum, lateral tuberal nuclei of the hypothalamus and parts of the thalamus [31].

5. Amyotrophic lateral sclerosis

Amyotrophic lateral sclerosis (ALS), also known as Lou Gehrig's disease and motor neuron disease, encompasses a group of genetic neurodegenerative disorders characterized by progressive and lethal muscle weakness caused by

loss of both upper and lower motor neurons of central and peripheral motor neurons [32-34]. The hallmark of this disease is the selective death of motor neurons in the brain and spinal cord, leading to paralysis of voluntary muscles. The paralysis begins focally and disseminates in a pattern that suggests that degeneration is spreading among contiguous pools of motor neurons [35]. This progressive degeneration of the motor neurons in ALS eventually leads to their death. When the motor neurons die, the ability of the brain to initiate and control muscle movement is lost. With voluntary muscle action progressively affected, patients in the later stages of the disease may become totally paralyzed. Symptoms typically have a localized limb or bulbar onset and progress to other muscle groups of the body. The degeneration of motor neurons, that can no longer send impulses to the muscle fibers altering the muscle movement, also entail denervation of respiratory muscles leading dysarthria from early phases of the illness and finally respiratory complications that are the most common causes of death. In addition, the dysphagia is a characteristic symptom that appears in the disease evolution dramatically difficulty the deglutition and the alimentation of the patients. Thus, ALS is characterized by 3- to -5-yr median survival post-diagnosis [36].

The incidence and prevalence of ALS are 1–2 and 4–6 per 100,000 each year, respectively [35]. Although most cases are classed as sporadic ALS (sALS), 10% of cases are inherited known as familial ALS (fALS). Interesting, ALS most commonly occurs in people between the ages of 40 and 60, and is slightly more men than women [37]. Five Mendelian gene defects were initially reported to cause ALS. The protein products of these mutated genes are cytosolic Cu/Zn superoxide dismutase (SOD1), alsin, senataxin (SETX), synaptobrevin/ VAMP (vesicle-associated membrane protein)-associated protein B (VAPB) and dynactin [35]. However, fALS have been attributed to mutations in 12 different genes, the most common being SOD1, FUS and TARDBP—mutations in the other genes are rare [38]. The SOD1 misfolding and precipitation in amyloid-like aggregates is considered one of the main causes of ALS. SOD1 is a ubiquitous, predominantly cytosolic protein consisting of 153 amino acids that acts as a homodimer. Each subunit of SOD1 binds one zinc and one copper atom, and through cyclical reduction and oxidation (dismutation) of copper, SOD1 converts superoxide radicals, a by-product of oxidative phosphorylation, to hydrogen peroxide and molecular oxygen. The exact mechanism by which SOD1 mutations lead to ALS pathology is unknown although several toxic properties of mutant SOD1 such as aberrant oxidative stress, protein instability, and mitochondrial damage have been proposed to be causative [35]. Interestingly, the presence of mutant SOD1 in non-neuronal cells contributes to pathogenesis and is needed for disease progression [39].

6. Spongiform encephalopathy

Prion diseases, also termed transmissible spongiform encephalopathies (TSEs), comprises fatal, progressive and transmissible neurodegenerative diseases that affect humans and a wide variety of animals [40]. Although initially the TSEs were considered caused by a “slow virus”, in 1982 the Nobel Prize Stanley B. Prusiner showed that the responsible of this group of diseases was a protein that coined “prion” from the “protein-only” concept. In human prion diseases include Kuru, Creutzfeldt-Jakob disease (CJD), variant CJD (vCJD) –“after mad-crows disease–, Gerstmann-Sträussler-Scheinker (GSS) disease and fatal familial insomnia (FFI) (see Table 3) [40].

The prion disease is related to a 209 amino acids protein normally found anchored in the cell membrane by a C-terminal glycosylphosphatidyl inositol. The prion propagation is usually associated with post-transcriptional conversion of normal cellular prion protein (PrP^{C}) –soluble, protease-sensible and native form– to amyloid-like aggregated isoform (PrP^{Sc}) –less soluble and proteinase-K resistant– [12,41]. In the prion infectivity, the PrP^{Sc} transfers its amyloid conformation from the spleen to the central nervous system (CNS) in a biphasic model with the first phase characterized by widespread colonization of lymphoreticular organs and the second one involving the CNS and also probably the peripheral nerves, acting in concomitance with vesicle-associated infectivity, and cell-free, free-floating oligomeric or protofibrils infectious particles [40,41].

Table 3. Human prion diseases.

Disease	Etiology
Kuru	Infection
Creutzfeldt-Jakob disease	
Iatrogenic	Infection
Sporadic	Unknown
Familial	<i>PRNP</i> mutation
Variant	Presumed BSE infection
Gerstmann-Sträussler-Scheinker disease	<i>PRNP</i> mutation
Fatal familial insomnia	<i>PRNP</i> mutation

Extracted from ref. [40].

The human prion diseases are classified as infectious, inherited or sporadic disorders, depending on the clinical, genetic, and neuropathological findings. The clinical evolution is characterized by widespread neurodegeneration; therefore, affected individuals exhibit clinical symptoms of both cognitive and motor dysfunction. After infection and/or conversion triggering the disease undergoes a fast and progressive dementia, myoclonus, visual or cerebellar impairment, pyramidal/extrapyramidal signs, and akinetic mutism [40].

8. Conclusion

In the cell, the biological function is determined for the native protein fold. In this way, problems in the protein fold with the consequent apparition of misfolded species can disturb the essential cellular processes. The protein misfolding entailing the polypeptide aggregation into amyloid structures have been associated with an increasing number of human diseases as Alzheimer, Parkinson or prion diseases. Importantly, recent studies have shown that the amyloid aggregation process is not limited to disease-related proteins but appears to be a generic property of the proteins in both eukaryotic and prokaryotic cells. The possibility that the amyloid formation is a universal and omnipresent process shared for all life organisms entails important consequences in biology: (1) If the folding and aggregation compete in the cell, during the evolution the prevention of the protein aggregation have to be an essential selective mechanism of the regulation. (2) The fact that amyloid formation is an omnipresent process entails that the number of human genetic diseases associated to misfolding and aggregation could be much larger than previously thought. (3) Interestingly, as the paradigmatic case of the prion proteins that use the amyloid-like structure and the particular amyloidal properties to become self-perpetuating; in several cases, amyloid structures could have been selected during the evolution for functional purposes.

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