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Review

The impact of self-replicating proteins on inflammation, autoimmunity and neurodegeneration—An untraveled path

Dana Butnaru[a,*], Joab Chapman[b,c]

[a] The Zabludowicz Center for Autoimmune Diseases, Sheba Medical Center, Tel Hashomer, Israel
[b] Sheba Medical Center, Israel
[c] Robert and Martha Harden Chair in Mental and Neurological Diseases, Sackler Faculty of Medicine, Tel Aviv University, Israel.

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ABSTRACT

The central nervous system (CNS) in neurodegenerative diseases is a battlefield in which microglia fight a highly atypical battle. During the inflammatory process microglia themselves become dysfunctional and even with all the available immune arsenal including cytokine or/and antibody production, the battle is eventually lost. A closer look into the picture will reveal the fact that this is mainly due to the atypical characteristics of the infectious agent. The supramolecular assemblies of misfolded proteins carry unique features not encountered in any of the common pathogens. Through misfolding, proteins undergo conformational changes which make them become immunogenic, neurotoxic and highly infective. The immunogenicity appears to be triggered by the exposure of previously hidden hydrophobic portions in proteins which act as damage-associated molecular patters (DAMPs) for the immune system. The neurotoxicity and infectivity are promoted by the small oligomeric forms of misfolded proteins/peptides. Oligomers adopt conformations such as tubular-like, beta-barrel-like, etc., that penetrate cell membranes through their hydrophobic surfaces, thus destabilizing ionic homeostasis. At the same time, oligomers act as a seed for protein misfolding through a prion/prion-like mechanism. Here, we propose the hypothesis that oligomers have catalytic surfaces and exercise their capacity to infect native proteins through specific characteristics such as hydrophobic, electrostatic and π-π stacking interactions as well as the specific surface area (SSA), surface curvature and surface chemistry of their nanoscale supramolecular assemblies. All these are the key elements for prion/prion-like mechanism of self-replication and disease spreading within the CNS. Thus, understanding the mechanism of prion's templating activity may help us in the prevention and development of novel therapeutic strategies for neurodegenerative diseases.

1. Introduction

It has long been thought that neurodegenerative diseases are not associated with an inflammatory response. Oskar Fisher (1876–1942), one of the pioneers in the study of Alzheimer's disease (AD), after analyzing brain tissues of AD patients, could not find the typical morphological signs of inflammation seen in other tissues. He therefore exclaimed: "*Aber!—wo bleibt dann die entzündliche Reaktion*?" ("But, where is the inflammatory reaction?") [1].

The lack of the characteristic signs of a classical inflammation in neurological conformational diseases has been something that puzzled scientists from the beginning. Inflammation in the central nervous system (CNS) has a different appearance from that in the peripheral sites. Neither the prionic nor the other neurodegenerative diseases such as Alzheimer's disease (AD), Parkinson's disease (PD) present the four cardinal signs of inflammation: *rubor et tumor* cum *calore et dolore* (redness and swelling with heat and pain). They also lack the immune cell mediation represented by leukocytes migration out of blood vessels. Certainly, to outward appearance it may seem as Raine [2] expressed it, a banquet with the tables set for a meal before the guests have arrived; the guests being the infiltrating leukocytes, and the prepared tables, immune system signaling molecules and mediators [ibid].

The weight of evidence, however, strongly indicates that there is widespread inflammation within the brain following prion infection and/or amyloid formation, all mediated by brain resident cells, the microglia and astrocytes. [2–5]. The activation of resident immune cells

Abbreviations: (nAbs-PrPC), naturally occurring antibodies against cellular prion protein; (Aβ), beta-amyloid; (APP), amyloid precursor protein; (PrP^{C}), cellular prion protein; (PrP^{SC}), scrapie form of prion protein; (PAMPs), pathogen-associated molecular patterns; (DAMPs), damage-associated molecular patterns; (CJD), Creutzfeldt-Jakob disease; (CNTs), carbon nanotubes

* Corresponding author.
E-mail address: dana@danamedis.com (D. Butnaru).

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is rather a highly atypical inflammatory response when compared to the conventional, robust inflammatory response associated with acute/traumatic injury or even microbial invasion (e.g., bacterial meningitis) [2,3,6]. At the same time, it is worth noting that neurodegenerative diseases are chronic condition characterized by a slow build up of misfolded proteins with equally slow affectation of brain tissue.

This article deals with the problem of inflammation and its multiple facets in proteins misfolding diseases with special emphasis on the affectation of CNS by these entities. It also shows that premature neurodegeneration is not a mere question of low-grade chronic inflammatory processes against an infectious agent but goes beyond that. The third player involved in the game, the supramolecular assemblies of misfolded proteins, carries unique characteristics different from all the common infectious agents known so far.

2. Inflammation in neurodegenerative diseases

2.1. Characteristics of inflammation in CNS conformational diseases

Evidence for an early inflammatory response in the CNS of scrapie infected mice, for example, are supported by the observation of microglial activation, astrocytosis and neuroinflammatory genes upregulation which are present before any evidences of neuronal loss or signs of clinical illness [7–9]. Moreover, pharmacological depletion of microglia (macrophages of the CNS) which eliminates 78 to 90% of microglia from cortex led to accelerated vacuolation (spongiform changes), astrogliosis, accumulation of disease-associated prion protein and premature death in the scrapie infected mice [9]. In sporadic Creutzfeldt-Jakob disease (sCJD) mice, an early over-expression of IL-1β was detected at pre-clinical stages of inflammatory events [10].

In Alzheimer's disease patients, CNS inflammation consisting of high levels of TNF-α in the cerebrospinal fluid (CSF), is an early event in the pathogenesis of disease. The TNF-α levels increase in the CSF even before the diagnosis is made – as seen in subjects with mild cognitive impairment (MCI) who later developed AD [11]. In addition, patients with a rapid progressive subform of Alzheimer's disease (rpAD) had significantly elevated concentrations of microglial-produced inflammatory mediators in the sera (TNF-α, G-CSF and IL-13) when compared to classical Alzheimer's dementia [12].

After the onset and during the progression of neurodegenerative diseases the CNS inflammation usually accentuates. For instance, the accumulation of beta-amyloid (Aβ) and tau-protein in AD promote the activation of the complement system [13]. Neurons, astrocytes and microglia produce the complement proteins. In amyloid precursor protein (APP) transgenic mice lacking complement C1q there is less glial cell activation than in complement-sufficient mice [14]. The persistent microglial activation is dependent on amyloid load. The fibrillar Aβ alone was found to activate the Nlrp3 inflammasome in microglial cells in vivo [15]. The Nlrp3 inflammasome pathway through the release of IL-1b, IL-18 and IL-33 cytokines plays an important role in the neuroinflammation in Alzheimer's disease [15,16]. These cytokines are responsible for the initiation and perpetuation of the inflammatory responses. It has further been observed that anti-inflammatory substances such as curcumin which inhibit the Nlpr3 inflammasome pathway help treating and preventing Alzheimer's disease [17]. Reactive astrocytes also accumulate at sites of aggregated Aβ deposition [18].

In Parkinson's disease (PD), the substantia nigra has the highest density of activated microglia in brain. The nigral microglia are highly activated and clustered around dystrophic dopamine neurons (prepared to phagocytize neuronal debris) [19,20]. The α-synuclein released by neurons activates microglia playing a key role in initiation and maintenance of inflammation. However, there is an age-dependent decrease in microglial phagocytosis of α-synuclein oligomers [21,22]. Some reports [20,23] show no evidence of an activated microglia surrounding the Lewy body (LB)-bearing neurons. However, for the released, extracellular α-synuclein, microglia are the most efficient cells to clear and handle the aggregates [24].

The progression of non-motor impairment in Parkinson's disease was also characterized by inflammatory responses. Elevated levels of serum inflammatory markers such as the interleukin IL-6 correlated to worse depression and fatigue scores and the persistently higher levels C3 and C4 complement factors were associated with worse quality of life and memory ability [25].

In patients with sporadic Creutzfeldt-Jakob (sCJD) disease and prion-infected mice, there are also activated microglia with significantly increased expression of proinflammatory cytokines such as TNF-α, IL-1α, and IL-1β [26]. In turn, in genetic Creutzfeldt-Jakob disease (G114 V) and in fatal familiar insomnia, assays have rather demonstrated unchanged microglia [27].

2.2. Inflammation failure in neurodegenerative diseases

The unorthodox inflammation characterizing neurodegenerative diseases lacks the beneficial characteristics of classical inflammation. According to Raine [2], among the definitions of classical inflammation is that it *protects* and *promotes repair*. Although the reason for repair failure in neurodegenerative diseases is not well understood, one notion is that the impairment of the immune response against misfolded proteins in the form of microglial dysfunction leads to deposits formation in which prions and amyloids win the battle; another notion is that neuroinflammation through an excess of proinflammatory mediators (irrespective of the source: local or systemic) induces neuronal loss [20,28–32].

Microglial phagocytosis is compromised early in the course of disease, hampering the clearance of abnormal proteins [33,34]. This is (in part) due to the toughness and indigestibility of the β-sheet-enriched oligomers, fibrils and their intermediates (all resistant to the known proteolytic pathways) [33–35]. When Aβ deposits in Alzheimer's disease become more compact, microglia begin to show signs of dystrophy marked by shortened and less branched processes (usually deformed), cytoplasmic abnormalities (including spheroids) and even fragmentation of cytoplasm (*cytorrhexis* – which is infrequent in the normally aged human brain) [20,36]. This microglial pathology seen in AD patients has never been detected in mice APP-based models of AD [20,36]. Dystrophic (and senescent) rather than activate microglia are associated with tau pathology and precede neurodegeneration [37]. In addition, human AD brain autopsy reveals high incidence of microglial apoptosis [38].

In sporadic CJD, microglial pathology was also seen. Microglial cells presented an atypical phenotype characterized by tortuous cell processes and intracytoplasmic vacuoles, more accentuated in areas with spongiform change [39,40].

Another reason for repair failure in neurodegenerative diseases is synaptic structure and plasticity impairment. The aggregation and accumulation of misfolded proteins affect especially the synapses. Dendritic spine and synapse loss occur prior to the physical deterioration of neuronal structures [41]. In prion disease both PrP^{C} and PrP^{SC} locate at the synapses [41,42]. In Alzheimer's disease Aβ oligomers are especially toxic to synapses [43] and both the Aβ oligomers and protofibrils promote synapse dysfunction and neurodegeneration. As microglial cells are not electronically coupled with the neuronal cells, their biophysical independence permit microglia to monitor and respond to the morphofunctional state of synapses. Microglia sense altered synapses and eliminate them [40,41]. The “pruning” of synaptic endings by microglia is not necessarily detrimental but it may as well be neuroprotective or even part of neuron regeneration [44,45]; yet, in neurodegenerative disorders it affects the neurons in such a way that isolates them from the electronic stimuli and trophic factors [42].

Other factor that limits inflammation in neurodegenerative diseases is the apoptotic-like dendritic and axonal death and in last instance, neuronal death. It has long been thought that nerve cell death in these

disorders occurs by way of necrosis. Evidences [41,46] indicates that the process of apoptosis rather than necrosis primarily contributes to nerve cell death in neurodegeneration [ibid].

Lastly, the very process of protein aggregation in conformational disease marked by the formation of large insoluble aggregates may act as a protective mechanism to avoid cellular oxidative stress [47]. The apoptosis also prevents the formation of high levels of reactive oxygen species which are present in necrosis [46]. Consequently, the Aβ aggregates have time to accumulates and deposit among neurons forming plaques with little or ineffective inflammatory reaction against them.

At the final stage of diseases, prions and amyloids ultimately win against microglia. Microglia, the main agent in prion clearance is also the chronic reservoirs of infectivity [48]. The failure in degrading prions may transform microglia into a betrayer that spread the disease by virtue of their motility [28].

3. Autoimmunity and infectious proteins

There have been attempts to link several forms of prion and prion-like diseases to the spectrum of autoimmune diseases. Some research suggests that transmissible spongiform encephalopathies are in fact autoimmune disease caused by external agents showing molecular mimicry to neuronal tissues [49]. Microbes such as *Acinetobacter* and possibly *Pseudomonas* possess share chemical sequences which resemble myelin. Thus, the elevated levels of antibodies to *Acinetobacter* bacteria in bovine spongiform encephalopathy (BSE) affected animals and also in some patients with multiple sclerosis (MS) and probably sporadic CJD might validate the autoimmune hypothesis [ibid].

One step further was recently (2015) taken by Friedland [50] who used the same molecular mimicry concept to relate neurodegenerative diseases with microbial amyloids. The CNS amyloids share homologies with the highly conserved sequences and protein folding patterns of bacterial amyloids in the human gut [ibid]. The structural homology in molecular mimicry has generally been related to the primary structure of proteins (i.e., amino acid sequence). Friedland advocates for an expanding of the concept of molecular mimicry to include the secondary and tertiary structures of proteins as well as the nucleotide sequence of RNA in animal or plant viruses, in bacteria or food [50].

Human microbes such as *Escherichia coli* or *Salmonella enterica* generate amyloids type CsgA (curli fibers). Although CsgA and the Aβ1–42 peptide (the hallmark of Alzheimer's disease) do not share common amino-acid sequences, yet, they present conformational similarity in their PAMPs (pathogen-associated molecular patterns); consequently, they both are recognized by the same TLR2/TLR1 of the 13 different TLR-type receptors available and direct the same up-regulation of IL-17A- and IL-22-mediated pro-inflammatory-signaling [51].

Furthermore, the exposure to curli-bacterial amyloid triggered the formation of neuronal alpha-synuclein (the hallmark of Parkinson's disease) deposition in both gut and brain of rats. Even more, curli amyloid in the gut enhanced immune responses in rat brain characterized by microgliosis and astrogliosis with more expression of TLR2, IL-6 and TNF-α than in control groups [52]. The microbial amyloid problem becomes even more relevant considering the microbiota involvement in autoimmune diseases (along with microbiota manipulation as a therapeutic target) [53,54] and the similarities as well as connections between the brain and the “second brain” or gut. The enteric nervous system has been described as a “second brain”. It utilizes most of the same neurotransmitters found in CNS, such as acetylcholine, dopamine, serotonin, GABA, etc., and the longest nerve of the 12 cranial nerves, the *vagus* nerve (X), communicates the gut directly with the brain and vice versa.

The existence of natural antibodies (nAbs) against neuronal tissues and β-amyloids in neurodegenerative diseases has been confirmed by many studies. For instance, Chapman et al. [55] identified in the sera of Alzheimer's disease patients antibodies directed against the 200 kDa heavy neurofilament subunit (NF-H). These antibodies were highly specific for AD and were not found in controls with dementia type Parkinson's or multi-infarct dementia [ibid]. Also, Toh et al. [56] have found enhanced production of specific autoantibody to the 200-kDa and 150-kDa neurofilament proteins and also to the 200 − /150-kDa doublet in patients with kuru disease, Creutzfeldt-Jakob disease and other neurological disease such as Alzheimer's disease, Amyotrophic lateral sclerosis (Guam) Parkinsonism-dementia (Guam) and Subacute sclerosing panencephalitis over control subjects.

More antibodies which include anti-tau antibodies, anti α-synuclein, anti-Aβ, etc., were repeatedly found in neurodegenerative diseases [57,58]. Moreover, the controversy over the existence of a higher level of anti-Aβ antibodies in Alzheimer's disease patients compared to healthy individuals had recently (2015) ended. New research carried out by Söllvander et al. [59] has revealed that the number of plasma B cells producing anti-Aβ42 antibodies is significantly higher in AD patients when compared to healthy controls [ibid].

In prion diseases, prion-induced toxicity to neuronal cells depends on conversion of the normal cellular prion protein (PrP^{C}) to the pathological form, the PrP^{SC}. The polypeptide chains of PrP^{C} and PrP^{SC} are identical in amino acids composition, yet, they markedly differ in their folded structures (conformations). The PrP^{SC} expression is followed by further oligomerization and fibrillation with toxic effect on cells. Naturally occurring antibodies against cellular prion protein (nAbs-PrP^{C}) have been detected in the intravenous immunoglobulin (IVIg) formulations from healthy subjects [60,61]. In vitro the nAbs-PrP appear to be able to block the fibrillation of prion peptides into aggregates, to break down fibrils as well as to contribute to the clearance function of microglial cells without triggering an inflammatory response [ibid]. Autoantibodies to abnormal PrP^{SC} forms have not been detected. Now, with all optimism regarding the existence of nAbs-PrP, it should be mentioned that PrP^{C} is a janus-faced molecule. If by one side it is the key molecule in the pathogenesis of prion disease (through transformation into the pathogenic form, PrP^{SC}) [43], on the other side it is also necessary for normal synaptic function as it modulates the inflammatory responses, exerts antioxidative, antimicrobial, cytoprotective effects on neurons and other cells [62–65].

In patients with CJD, natural antibodies were barely detected. < 5% patients with sporadic CJD develop serum antibodies to neuronal antigens and, when positive, it is only at low titers [66,67]. In fact, the presence of low levels of autoantibodies may not imply pathogenicity or being related to a specific disease. Studies have revealed that vast majority of healthy subjects—young and old—have brain-reactive autoantibodies in their serum. > 90% of all human sera tested had abundant brain-reactive autoantibodies [68,69].

It is still under debate if some neurodegenerative diseases such as Alzheimer's disease or Parkinson's disease, amyotrophic lateral sclerosis, etc. are autoimmune in origin or not. Each category is incredibly complex and the boundaries between the two are not clearly defined. There is at least some overlapping between the autoimmune and neurodegenerative diseases [70,71]. Prusiner [72] gives the idea that the abnormal processing of neuronal proteins may evoke an autoimmune response, thus, leaving the issue open to further insights.

4. Exposed hydrophobicity—A potent driver of inflammation and neurodegeneration

Hydrophobic portions of biological molecules can act as universal damage-associated molecular patterns (DAMPs) [73]. The term *hyppos,* meaning “hydrophobic portions”, was coined by Matzinger and Seong in their 2004 article on hydrophobic danger signals [73].

In physiological conditions, hydrophobic portions of bio-molecules, “the hyppos”, are hidden from the aqueous environment by i) conformational folding, ii) insertion into membranes, or iii) by the help of accessory molecules (e.g., during lipid transport) [73]. Thus, native proteins have the hydrophobic amino acids buried (e.g., within the core of the globular proteins). Protein unfolding (and misfolding),

characterized by a transition from alpha-helix to a stretched β-sheet secondary structure, exposes the previously hidden hydrophobic residues. This makes proteins prone to aggregation [74], hydrophobicity being critical in driving aggregation (and also protein fibrilization) [75,76].

In Aβ1-42 peptide the regions that promote aggregation are two large portions of hydrophobic residues; the approx. Sequences are 15–21 and 31–37 respectively [74]. In α-synuclein, a 140-amino acid protein, the only hydrophobic region is around residues 61–95. The aggregation process by minimizing the total hydrophobic surface that is exposed to water [77], functions to partially hide and prevent the massive hydrophobic exposure and avoid cellular oxidative damage [47].

Hydrophobic polymers generate far more inflammation compared to non-hydrophobic polymers. This fact has long been known by the implant prostheses fabricants, as the control of hydrophobic interactions at interfaces has an essential role in the biomedical field [78,79]. Experiments have revealed that immediately after implantation, hydrophobic polymeric biomaterials acquire a layer of host proteins (such as albumin, immunoglobulin G, and fibrinogen) which appear to effectively "melt" into the surface. Hours later, the proteins adsorbed to most biomaterial surfaces cannot be removed even with powerful detergents [78]. Interestingly enough, the process of proteins adsorption onto the hydrophobic surfaces was followed by conformational and/or orientational changes in proteins structures followed by proteins aggregation [78–81].

Using the α-synuclein – an intrinsically disordered protein, Ouberai et al. [81], have shown that its adsorption on hydrophobic surfaces increases by 110% (compared to hydrophilic surface) leading to a different arrangement (packing) of the protein. A dense packing of α-synuclein was observed characterized by conformational re-orientation or deformation resulting in stronger protein-surface and protein-protein interactions [ibid]. Similarly, the Asp76Asn β2-microglobulin molecule, which is a natural variant of the human β2-microglobulin and the cause of hereditary systemic amyloidosis, forms amyloid fibrils within a few hours if exposed to a hydrophobic surface [82]. Moreover, it was shown that the new formed fibrils of Asp76Asn β2-microglobulin have the capacity to prime native wild-type β2-microglobulin conversion into fibrils [ibid].

On a related note, at nanoscale, the interaction between the hydrophobic walls of carbon nanotubes (CNTs) and blood proteins such as fibrinogen, immunoglobulin G and albumin leads to proteins adsorption onto the surface of CNTs followed by changes in proteins structures [83]. After only 10 min of protein-CNTs interaction, there was a significant change in the secondary structure with reduced α-helix and increased β-sheets for all three proteins [ibid].

Protein misfolding is accompanied by hydrophobic portions ("hyppos") exposure rendering the proteins potentially cytotoxic. All of the accumulated oligomers and fibrils (and especially the intermediates) of Aβ40/Aβ42, α-synuclein, β2-microglobulin, SOD1, prion protein PrP^{SC}, etc., in Alzheimer's disease, Parkinson's disease, dialysis-related amyloidosis, ALS, and respectively, prionic diseases, have important hydrophobic surfaces [73,76,84,85]. For instance, the α-synuclein *off-pathway* oligomers, which do not evolve into fibrils, have less hydrophobic surfaces than the *on-pathway* oligomers. The increase in surface hydrophobicity helps oligomers in the fibrillation process towards mature fibrils [84]. Moreover, the drug doxycycline, a tetracycline antibiotic, was shown to reshape toxic oligomers into less toxic, *off-pathway* oligomers by lowering the hydrophobic surface exposure [84], thus the efficacy of tetracyclines in prion infections [86]. Of note, another drug, the polymyxin B, an antibiotic for gram-negative bacteria, unites the highly hydrophobic bacterial LPS inducing changes in the supramolecular organization of LPS aggregates transforming them in hydro*philic* lamellar structures. In contrast, the toxic or autoimmune myopathy related to *hydrophobic* statins such as simvastatin is accompanied by an increase of *β-sheet* aggregates in muscles and liver [87–89]. In turn, with *hydrophilic* statins, the risk of myopathy appears to be much lower [89]. By the same token, the *hydrophobic* nature of the surface of silicone implants triggers proteins adsorption and denaturation onto the surface [90,91]. Silicone implants have been related to the onset of auto-inflammatory/autoimmune conditions such as the Autoimmune Syndrome Induced by Adjuvants (ASIA) [90–92]. Silicones behave as adjuvants [ibid].

Many prionic diseases are associated with changes in the hydrophobic core of cellular prion protein (PrP^{C}). The conformational conversion of the normal (cellular) form of PrP^{C} to a pathogenic and largely proteinase K resistant form, the PrP^{SC}, involves an increase in β-structure content with increase in exposed hydrophobicity [93]. The pathological form of prion protein (PrP^{SC}) exhibits a large hydrophobic surface. The extent of hydrophobic exposed area (i.e., high exposure) explains i) β-sheet oligomers instability along with their ii) tendency to organize into more stable higher order assemblies such as fibrils and, iii) to interact with cell lipid bilayer membrane forming pore-like structures at nanoscale [85].

It is not the hydrophobicity per se what triggers a response from the immune system but rather the *revealed* hydrophobicity. The exposure of previously hidden hydrophobic patches in proteins may appear to the cells of immune system as if the proteins were putting on new clothes or better said, wearing the clothes inside-out. Hydrophobic portions ("hyppos") in proteins become DAMPs (damage-associated molecular patterns) when exposed in non-physiological condition: during, after or because of injury or damage [73]. As with any DAMPs, the *hyppos* serve as endogenous ligands for receptors such as Toll-like receptors (TLRs), scavenger receptors, C-reactive protein and others, activating them. The TLR4 itself has a large *hyppo* and a variety of apparently unrelated molecules that signal through TLR4 have in common important hydrophobic regions ("hyppos") [73]. Prions carrying large *hyppos* act as TLR4 ligands mediating innate immune activation and prion disease progression. Experiments [94,95] show that an impairment of glial and neuronal receptors, which difficult the cells sense of their environment, can facilitate prions outspread. Mice carrying a mutation in the TLR4 intracellular domain that prevents TLR4 signaling have a faster progression to scrapie disease compared with the wild-type control [94]. Also, the uptake of Aβ is reduced in TLR4 mutant microglia. In APP transgenic mice, the TLR4-loss of function increases oligomeric and fibrillar Aβ depositions without an increase in APP expression [96].

Most of misfolded proteins linked to neurodegeneration bind also the receptor of advanced glycation end products (RAGE) [97]. RAGE's extracellular region has an important number of hydrophobic pockets on the V-domain, as well as one hydrophobic cavity close to the C1 domain. In Alzheimer's disease, the Aβ through their hydrophobic regions interact with amino acid residues of the RAGE's hydrophobic V-C1 domain mediating neuroinflammation (via microglia) [98].

Janeway's *stranger model* joins the above-presented *danger theory* of Matzinger in the inflammatory process. Janeway's model suggests that immunostimulatory agents must be *non-self* in order to trigger immune activation [99]. This is valid in conformational diseases too where non-self molecular patterns can be afforded by the tertiary and quaternary structures of misfolded proteins. A modified self that exhibits new *hyppos* (or hydrophobic patches) can be recognized as non-self by the immune system. Prions adopt generic structures which are recognized by pattern recognition receptors (PRRs) that activate inflammation [100].

The chronic low-grade inflammatory process that occurs in Alzheimer's disease against the extracellular deposits of amyloid fibrils is akin to the inflammatory reaction against foreign bodies in the brain (with the abnormal fibrils acting as a foreign substance). This fact was first noted by Oskar Fisher in 1910 [1]. Based on current data on brain-machine interfaces, Tresco and Gerhardt [101] explained that the foreign-body response (FBR) against implanted electrodes in the brain shares common features with the Alzheimer's disease in terms of microglia activation, protein tau hyperphosphorylation and neuronal loss

[101,102]. Most of implantable electrodes have *hydrophobic* surfaces. It is thought that bioactive *hydrophilic* coatings may reduce inflammation and improve tissue integrity [103].

The role played by the hydrophobic endogenous biomolecules in neurodegeneration is not limited to these functioning as DAMPs for immune activation. Brain shrinking and the atrophy, the vascular degeneration in neurodegenerative diseases cannot be solely attributed to inflammation. The exposed hydrophobicity of protein aggregates perturbs the dynamics and structure of water in the brain. Brain is 80–85% water; water being the most abundant molecule in the human body. Protein misfolding and aggregation take place in the aqueous cellular environments of the brain. As shown by Rezus and Bakker [77], there is a *decrease* in the configurational space available to water molecules around hydrophobic solutes, water molecules in the vicinity of extended hydrophobic groups (> 1 nm) being effectively immobilized [ibid]. Consequently, an increase in the total hydrophobic surface in the extracellular space, as due to misfolded protein/peptides large aggregates, limits water's dynamics [104]. The Diffusion Weighted Magnetic Resonance Imaging (DW-MRI) studies have revealed that in prionic disease such as sporadic Creutzfeldt–Jakob disease (and perhaps other neurodegenerative diseases) there is an altered molecular motion of water characterized by a *restricted* diffusion of water [105,106]. Water molecules can be *restricted* by the presence of barriers, such as the hydrophobic cell membranes, myelin sheaths as well as by the presence of hydrophobic protein aggregates e.g., amyloids [105,107,108]. In particular, the restriction of water diffusion in Creutzfeldt–Jakob disease is caused by the decrease of extracellular space due to the large deposits of the abnormal forms of prion protein (PrP^{SC}) and also due to vacuolation (spongiform degeneration) [105,106]. Moreover, as shown by Lee et al. [106] the cerebral diffusion reductions may even precede the symptomatic onset of prionic diseases.

The very process of supramolecular self-assembly of misfolded proteins alters water dynamics. For instance, in amyloid fibrils formation, the self-assembly of the β-sheets—rich in hydrophobic groups—occurs rapidly and, the water in between the sheets is eliminated concurrently as the β-sheets associate with one another [109]. The expulsion of interfacial water (i.e., the water between two sheets or surfaces of e.g., proteins) is a key event in the oligmerization and fibril formation of Aβ peptides [109]. Moreover, the rate of protein aggregation increases significantly under conditions where limited hydration of molecules occur [110].

5. The phenomenon of prionic mechanism of self-replication: A *supra*-molecular basis

Brain inflammation in all its many facets is without a doubt an important part in the pathogenesis of neurodegenerative diseases. The anti-inflammatory drugs have the ability to slow down to some extent the disease course. Yet, the shrinkage, atrophy and vacuolation of the brain continue in a non-physiological manner; vascular degeneration (rather than vascular proliferation) is present, and microglia, the main player of cerebral inflammation, become ill as well. This shows that the remedy does not lie in merely anti-inflammatory measures. To be efficient, the treatment and, hopefully, the cure must also deal with the self-propagation mechanism of misfolded proteins.

The prion/prion-like mechanism of transmission is defined as the recruiting of native proteins by a prion with subsequent conversion of them into a likeness of itself. It involves the propagation of prion's own secondary and tertiary structures (spatial conformation) through a self-templating process [111] (which includes the many conformational characteristics of the incoming prion, i.e., proteopathic strains).

Prionic corruption does not involve the amino acids sequence (primary structure) of a given protein which remains the same but only the folding of the protein. The principal characteristic of prions (and amyloids in general) is that different amino acids sequences in proteins can lead to the same, generic folding [112]. That is markedly different from what happens with native proteins in which a specific sequence of amino acids dictates and leads to a unique, specific folding [112].

As stated by Ventura (2017) [111] the most stable conformation that a protein can adopt is *not* the (complex) native state, but the highly repetitive and densely stacked amyloid fibril. The β-amyloids along with the prionic states of proteins do not constitute a superior level of proteins/peptides organization, but rather a *thermodynamic sink* [111] in which multiple proteins can get trapped [ibid].

This section of the article provides in four logical steps a perspective on how and why proteins 'sink' from their native folding state into a non-physiological generic arrangement that enables them entrap other proteins in the way converting them in a likeness of themselves, in other words, the prion's templating activity.

5.1. Most toxic oligomeric and protofibrils assemblies have cylindrical architectures

The failure of the "amyloid cascade hypothesis" led to the emergence of the "oligomer cascade hypothesis". During the "amyloid cascade hypothesis" intense efforts were made to understand fibril formation and the biological activities of fibrils. Early work showed that Aβ was not toxic unless it formed fibrils [113,114]. The new "oligomer cascade hypothesis" asserts that small entities such as oligomers and protofibrils (of α-synuclein, Abeta40, Abeta42, tau protein, IAPP, etc.) rather than mature fibrils are the real culprits behind disease propagation. This is because oligomers: first, self-replicate (prion-like characteristics) acting as seed and second, insert into lipid bilayers permeating membranes through a β-barrel pore-forming [115], both linked to their cytotoxicity [Fig. 1].

Even though the lexicon to describe the suprastructures of beta-sheet-rich oligomers (and protofibrils) may differ [119], most of descriptions point to common characteristics of oligomers such as tubular-like structures with a hollow core, as for example: cylindrical architecture [120], annular porelike assemblies [121,122], fibril-like [123], hexagonal pores with hydrophobic surfaces [124], six-stranded β-barrel-like morphology [125,126], nanotubes that pack into a hexagonal lattice [127], nanotubes [43]. The β-sheets are the building blocks of such supramolecular structures.

The landscape of oligomers and protofibrils is more divers including spherical, globular, ellipsoid oligomers [125]; however, the most toxic species seem to have open endings that allow them permeabilize membranes (i.e. membrane-permeabilizing activity).

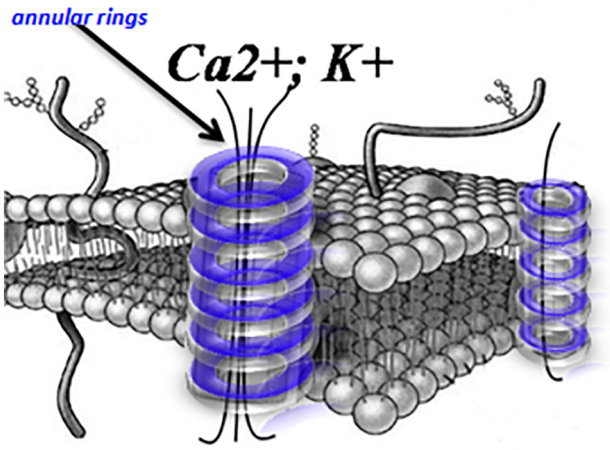

Fig. 1. Oligomers penetrate membranes.
The Aβ, tau, α-synuclein, etc., oligomers self-organize into ring-shaped structures (e.g., hexamers, dodecamers) with hydrophobic side chains facing the plasma membrane, permitting uncontrolled leakage of ions into and/or out of the cell, thus destabilizing ionic homeostasis [115–118].

5.2. Oligomers mimic molecular chaperone

Molecular chaperones are instrumental in protein de novo folding/re-folding in vivo. Chaperones are generally described as homo- or hetero-oligomers consisting of many subunits usually combined in ring-like (toroidal), cylinder or hollow sphere quaternary structures. Chaperones have important hydrophobic patches [128,129]. The existence of many exposed hydrophobic clusters serve as sites for the fixation of target proteins and allow molecular chaperones to exert their functions [129,130].

The supramolecular structures of oligomers mimic the cylindrical structure and/or function of molecular chaperons [127,130,131]. The cylindrical, barrel-like superstructures of some Aβ oligomers are not just imitating the toroidal architecture of molecular chaperones but they rival in complexity and size with the chaperones specifically, with GroEL chaperonin [127]. The presence of GroEl alone (and in absence of the GroES co-chaperonin or ATP hydrolysis), as explained by Marchenkov and Semisotnov [129], suffices for the effective GroEL-assisted protein re-folding. Moreover, GroEl can refold large proteins that exceed the dimensions of the inner cavity [129]. Similarly, the partial occlusion of the inner cavities e.g., of the eukaryotic chaperonin CTT with antibodies has no effect on the rate and yield of protein re-folding [132]. This shows that molecular chaperons may not always require i) the use of the inner cavity to refold proteins, ii) the double ring structure, iii) ATP hydrolysis. This way, the chaperone structure being reduced to a simple cylinder with an active outer surface.

Although the main role of chaperones is to correct protein folding, some chaperones produce toxic Aβ oligomers. Prefoldin (PFD), an archaeal molecular chaperone from *P. Horikoshii* OT3, produces high-molecular-mass of soluble Aβ oligomers in vitro which are highly cytotoxic similar to those found in Alzheimer's disease brains [133]. Human PFD also induced formation of soluble Aβ oligomers but 30–40% less toxic (yet, still 60–70% toxic) to cultured rat pheochromocytoma (PC12) cells or to cortical neurons from embryonic C57BL/6CrSlc mice [134]. Eukaryotic PFD is homologous to archaeal PFD and is expressed in the human brain. Both possess a similar/identical structure consisting of a double β-barrel assembly with six long and protruding coiled coils with hydrophobic residues that interact with the substrate.

5.3. The exposed hydrophobic surfaces of oligomers are involved in their toxicity and infectivity

The oligomers formed in neurodegenerative diseases (e.g., Abeta, alpha-synuclein, PrP^{SC}, SOD1, IAPP, etc.) have high surface exposure of hydrophobic residues. These hydrophobic surfaces of oligomers promote insertion into membrane and are responsible of their toxicity [115–118]. An increase in exposed surface hydrophobicity correlates with more toxicity. For example, the addition of Zn^{2+} to Abeta40 or Abeta42 oligomers led to oligomeric forms with higher level of hydrophobic surface exposed on the protein surface (ZnAβ oligomers) [135]. These ZnAβ oligomers were more toxic (as measured in human neuroblastoma BE(2)-C cells) and had also altered immunoreactivity [ibid].

The exposed hydrophobicity of oligomers is also related to their infectivity through a prion/prion-like mechanism. Prions themselves are by definition *oligomers* (i.e., beta-sheet-rich oligomers) [136]. The efficacy of tetracyclines in reducing prion infectivity was tested and the results showed that reduced infectivity was related to the reduction in the hydrophobic surface exposed by the oligomers [84,86].

The overall toxicity of oligomers correlates with a combination of both surface hydrophobicity and size; the most toxic oligomers have high hydrophobicity and small size [137].

5.4. The catalytic surfaces of nanotubes as a place for protein misfolding—A hint into the prionic mechanism of transmission

The nanotubes-protein interaction has a destabilizing effect on protein folding. Multiple studies on proteins interaction with carbon nanotubes (CNTs) have shown that nanotubes have catalytic surfaces that induce conformational changes in the secondary and tertiary structure of native proteins [138–142]. For instance, the interaction between Aβ40 peptide and the hydrophobic surface of CNTs promotes in Aβ40 peptide a structural transition from a random coil to a β-sheet which curves and coats the CNT [139]. Similarly, the interaction of tau protein with the surface of CNTs led to an increase of β-sheet content with pronounced conformational changes in tau protein [142]. The bovine serum albumin and lysozyme interaction with CNTs had also resulted in a decrease of α-helix secondary structure with increase in β-sheets [141,143].

New research (2015) showed that the destructive effect of CNTs on the secondary structures of proteins increases with the decrease of nanotubes diameters. The loss in α-helical and gain in β-sheet content was more accentuated on the surfaces of smaller-diametered nanotubes ranging from 40 to 10 nm [144]. These small diameters of carbon nanotubes are similar to the nanoscale diameters of neurotoxic oligomers ranging (approximately) from 3 to 25 nm [145,146]. One fundamental characteristic of these small-sized nanoparticles is that possess larger specific surface areas (SSA) dictating a more dramatic structural rearrangement in the secondary and tertiary structures of native protein which interact with them [144]. This fact is in accordance with the recent shift in the Aβ cascade hypothesis in which the toxicity of small oligomeric species increases with the decrease in their size (diameter and height) [146].

The adsorption of proteins onto nanosurfaces is the first step in a chain of events leading to protein's native structure destabilization with subsequent unfolding/misfolding. The specific surface area (SSA), surface curvature and surface chemistry of nanotubes are all important factors in protein absorption and oligomerization [147,148]. But, the driving forces for proteins adsorption and destabilization onto the nanotubes surfaces are mainly three: i) hydrophobic interactions, ii) electrostatic interactions and iii) the π-π stacking interactions (also called *pi stacking* which refers to attractive, noncovalent interactions between aromatic rings) [138].

On the side of proteins, it is worth mentioning that, proteins do not have all the same propensity to misfolding. The misfolding of the proteins interacting with hydrophobic nanosurfaces is protein specific. Moreover, natively folded proteins are vulnerable to prion infection (only) during the extremely short periods in which native proteins unfold as part of their various physiological activities [personal communication].

At nano-scale, size appears to be more important than content [146]. The formation of tubular (or spherical) nanostructures by organic molecules, (e.g., organic nanotubes of Phe-Phe – in which Phe-Phe is the core recognition motif of Alzheimer's β-amyloid polypeptide) resembles the tubular (and spherical) carbon and inorganic structures (e.g., carbon nanotubes) [149]. The study of carbon nanotubes interaction with proteins gives a hint about organic nanotubes interaction with proteins. This is important because, as shown by several studies [43,127], some of protein toxic super-assemblies such as protofibrils and oligomers are in fact organic nanotubes [ibid]. Moreover, as stated by Nicoll et al. [43], Aβ nanotubes are present in human brain and have an important role in disease (e.g., synaptic dysfunction [ibid]).

Of note, it has recently (2013) been confirmed by Cohen et al. [150] that Aβ42 fibrils also have *catalytic surfaces*. Fibers are different from oligomers in that they lack the hollow structure which characterizes oligomers and protofibrils. Although the catalytic surfaces of mature fibrils are not involved in the conformational conversion of native proteins, they promote the growth and conversion of monomers into oligomers and oligomers into mature fibrils [ibid]. The catalytic

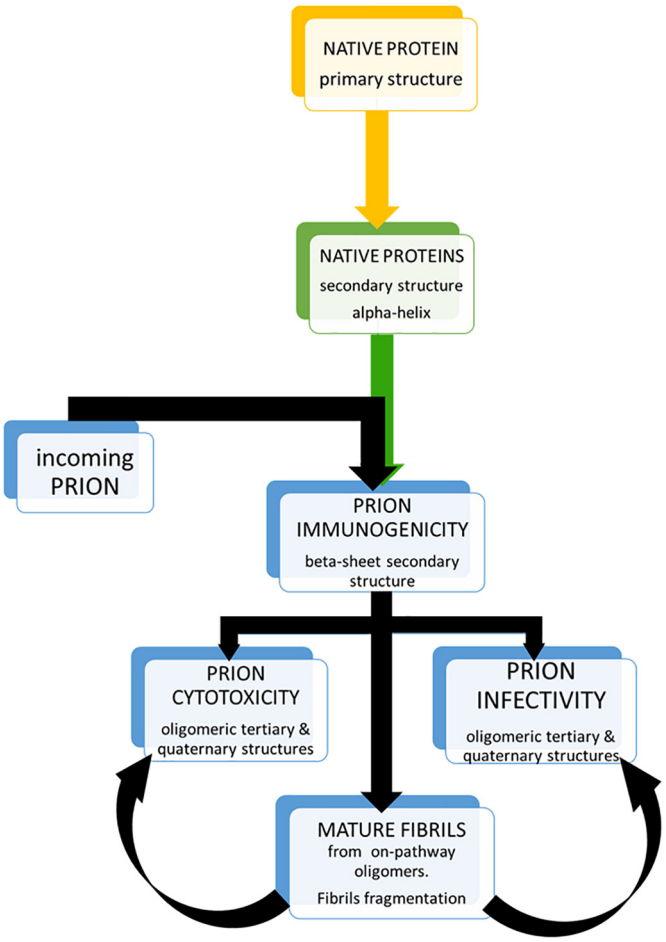

Fig. 2. Prion corruption of natively folded proteins.
Converts proteins into immunogenic, cytotoxic and highly infective agents like themselves. Starting with the corruption of the secondary structure, proteins undergo further re-arrangements in the tertiary and quaternary structures leading to oligomer formation. The change in the secondary structures that exposes hidden hydrophobic portions in protein suffices for protein immunogenicity, the hydrophobic exposed regions acting as damage-associated molecular patters (DAMPs) [73]. The rearrangements in the tertiary and quaternary structures lead to the formation of oligomers and promote both the cytotoxic activity (through a membrane-permeabilizing activity) as well as the infectious activity (apparently through their catalytic surfaces) of misfolded proteins [115–118,153]. A secondary nucleation process involves the (on-pathway) oligomers evolving into mature fibrils. These fibrils have large phenotypical heterogeneity [112]. However, mature fibrils can also disaggregate into toxic and infectious oligomers. Fibril propensity to fragmentation (brittleness or frangibility) is closely related to the strength of prionic infectivity strain [152,153]. Smaller aggregates, which are more readily generated by strains that form fragile particles, are markedly more infectious than larger aggregates [ibid].

surfaces provided by Aβ42 fibrils worked by lowering the kinetic barriers that under normal circumstances hinder their de novo formation [ibid].

In short, the mechanism proposed for prion self-replication is the following. Similar to carbon nanotubes or molecular chaperones and even to organic β-amyloid fibrils, the organic nanotubes –part of the supramolecular structures of oligomers and protofibrils in disease – [43]) have *catalytic surfaces*. The interaction of proteins with such organic nanotubes would lead to proteins adsorption onto nanotube surfaces. The adsorption, which is dependent on hydrophobicity, π-π stacking interactions, surface area and curvature, etc., would induce conformational conversion in native proteins (e.g., fibrinogen, tau) and other peptides (e.g., Aβ40, Aβ42). Proteins/peptides are expected to lose part of their α-helix secondary structure, gain β-sheet-rich structures and oligomerize; both changes fulfilling the two fundamental characteristics of prion's definition as formulated by Prusiner in 2013 [136]. The newly formed oligomers may further perpetuate the cycle.

6. Final remarks

If in the past the main enemy for the immune system was represented by foreign invaders (e.g., bacteria, viruses, parasites, etc.), nowadays, the increasing incidence and prevalence of neurodegenerative disorders in our world shows that we are facing a different type of enemy, more subtle but invariably lethal: a changed, modified form of the *self* represented by the misfolded proteins. Through misfolding, a protein loses its native folding which constitutes protein's own identity and adopts the generic folding of β-amyloids. The switch from the native α-helix secondary structure to a β-sheet is followed by changes and re-arrangements in the higher levels of protein organization including the tertiary and quaternary structures. These newly adopted conformations by the proteins, also known as proteopathic strains, enable them to replicate and propagate through a self-templating process making proteins infectious. The small oligomeric forms of misfolded proteins rather than the mature fibrils are known today to be the most toxic and infectious forms of misfolded proteins [Fig. 2].

The conversion of a normal cell-surface glycoprotein (PrP^{C}) into a conformationally altered isoform (PrP^{SC}) renders the glycoprotein (and other proteins through it) less utile for the body and highly infectious. PrP^{C} to PrP^{SC} conversion is characterized by a reduction in the α-helical content and increase in β-sheet secondary structure with further re-arrangements in the tertiary and quaternary structures leading to oligomer formation.

Most toxic oligomers have high catalytic surfaces and exercise their capacity to infect native proteins through specific characteristics such as hydrophobic interactions with native proteins, electrostatic and π-π stacking interactions as well as the specific surface area (SSA), surface curvature and surface chemistry of their nanoscale tubular supramolecular assemblies. The PrP^{SC} oligomers are not just highly infectious but they form toxic aggregates that impair neuronal functionality and trigger inflammation. The PrP^{SC} alone by directly contact with microglia can trigger inflammatory response [151]. As with the PrP^{C}, so with other proteins involved in disease such as α-synuclein in Parkinson's disease, Aβ40/Aβ42 and tau protein in Alzheimer's disease, etc.; misfolding leads to loss-of-function and altered protein topology.

The misfolding problem does not stop at local level. Misfolded proteins entrap other proteins in the way (of the same amino acid sequence or even different through *heterologous* seeding) forming large proteinaceous deposits in the CNS.

Like the pieces of a domino game that fall down one after another, so the β-sheet-rich oligomers recruit and corrupt native proteins in an unending chain of misfolding events leading to profound and irreversible changes in the body economy.

Conflict of interest

None.

Financial disclosure

None.

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