The corruption and spread of pathogenic proteins in neurodegenerative diseases*

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SUMMARY

With advancing age, the brain becomes increasingly susceptible to neurodegenerative diseases, most of which are characterized by the misfolding and errant aggregation of certain proteins. The induction of aggregation involves a crystallization-like seeding mechanism by which a specific protein is structurally corrupted by its misfolded conformer. The latest research indicates that, once formed, proteopathic seeds can spread from one locale to another via cellular uptake, transport, and release. Impeding this process could represent a unified therapeutic strategy for slowing the progression of a wide range of currently intractable disorders.

INTRODUCTION

Most, if not all, age-related neurodegenerative diseases involve the misfolding and accumulation of specific proteins. This simple fact, though itself illuminating, raises numerous questions, the answers to which are in various stages of maturation. We will address two fundamental issues: The nature of the prime mover of protein aggregation in vivo, and the means by which proteinaceous lesions spread through the nervous system.

First, it is worth considering the dimensions of the protein misfolding problem. More than 50 diseases of abnormal protein deposition (broadly referred to as proteopathies, conformational diseases, or proteinopathies) have been identified in the brain and systemic tissues of humans (Table). Although these disorders vary widely in their clinical and pathologic manifestations, a common feature is the misfolding and abnormal aggregation of disease-specific proteins (1). Furthermore, the diseases may originate and progress within the body by a molecular mechanism resembling that of prion disease (below). The most prevalent risk factor for idiopathic (sporadic) proteopathies is advancing age, probably because the cellular regulation of protein production and disposal (protein homeostasis, or ‘proteostasis’ (2)) becomes increasingly compromised with age in certain tissues (2-4). Because life expectancy is rising in much of the world, the proteopathies collectively impose a growing burden on aging societies.

Many proteins fold into their native, biologically functional conformations shortly after they are generated; others, known as intrinsically disordered proteins, inherently lack a stable tertiary structure (5). Under pathogenic conditions such as amino acid substitutions, post-translational modifications (cleavage,
phosphorylation, etc.), protein crowding, or partial unfolding of structured proteins, some proteins are liable to misfold, self-aggregate and accumulate inside or outside of cells.

Amyloidosis, the most widely known embodiment of proteopathy, is a pathologic hallmark of many diseases (Table). Despite vastly differing amino acid sequences of amyloid-forming proteins, the amyloid deposits share particular features; a current definition of amyloid is “an in vivo deposited material, which can be distinguished from non-amyloid deposits by characteristic fibrillar electron microscopic appearance, typical X-ray diffraction pattern and histological staining reactions, particularly affinity for the dye Congo red with resulting green birefringence” (6). Previously, amyloid was considered to be exclusively an extracellular lesion, but the definition of amyloid continues to evolve (7); for instance, intracellular fibrillar deposits have been included in the latest definition (6). In any case, it is important to recognize that some proteinaceous lesions do not strictly conform to classical and/or current definitions of ‘amyloid’. Such lesions include (or previously included) neurofibrillary tangles (tau protein; (8)), Lewy bodies (α-synuclein; (9)), myopathic inclusion bodies (Aβ; (10)), and ectopic, aggregated transcription factors such as TAR DNA-binding protein 43 (TDP-43) and fused in sarcoma (FUS) (11). In addition, some ‘diffuse’ aggregates of proteins that have the ability to form amyloid (such as Aβ or the prion protein) do not show green birefringence after staining with Congo red, yet such aggregates are not normally found in the brain, and thus can be considered manifestations of a pathogenic process. Whether they are a stage in the development of amyloid or autonomous lesions (or both) remains uncertain; it is likely that protein aggregation can proceed along multiple pathways (12).

At the molecular level, aggregation often is associated with the conformational corruption (misfolding) of a protein, i.e., either a deviation from the native folded state or the induced folding of a disordered protein into a pathogenic conformer. Misfolding increases the tendency of the protein to self-assemble into stable, structured aggregates, and frequently renders it resistant to normal cellular clearance mechanisms. At the light-microscopic level, the morphology and localization of the lesions often are pathognomonic for the associated diseases (Figure 1), and it is possible that the supramolecular appearance of deposits reflects the secondary, tertiary and quaternary architecture of the misfolded molecules (12). In addition to the lesions that are observable by light microscopy, pathogenic proteins can exist as small, prefibrillar ensembles, collectively known as oligomers, which consist of only a few protein molecules and hence are less readily detected than are larger multimers (13-15). Because such soluble (and diffusible) protein assemblies can adversely affect cellular function and viability more potently than fibrils, they can profoundly influence the nature and course of proteopathic disease, even in the absence of visible deposits (13,14,16,17).

**THE SEEDED INDUCTION OF PROTEIN AGGREGATION**

An intriguing mechanistic commonality among the proteopathies is that some, and perhaps most, of them can be induced and propagated by corruptive protein templating, or seeding (12,15,18-21). Corruptive protein templating broadly refers to the structural alteration of a protein through interaction with a misfolded form of the protein, by a mechanism resembling seeded crystallization (22). The prion diseases are the prototype of this pathogenic process (17,23-25). Prion diseases are remarkable in that they can be genetic, idiopathic, or infectious (transmissible) in origin (23). The prion protein in its pathogenic form is enriched in β-sheet secondary structure, which modifies the physicochemical properties of the molecule. In this altered state, the protein is able to bind, and conformationally convert, other prion protein molecules. Over time, the pathogenic protein conformers multiply as the seeds continually corrupt prion protein molecules that are normally produced by cells (23). Transmission (‘infection’) involves the structural corruption of endogenous prion protein by interaction with exogenous seeds. Variations in the course and pathologic signature of prion disease suggest that the prion is not a unitary agent, but rather that prions can exist as polymorphic and polyfunctional strains (25-27).
Although prion diseases remain the only demonstrably infectious proteopathies (in the sense that some of them can be readily transmitted from one organism to another), recent in vitro and in vivo evidence indicates that proteins linked to clinically and pathologically dissimilar proteopathies can be induced to aggregate by mechanisms that, at the molecular level, bear striking similarities to the infectivity of prions (15, 19-21, 28-39). Some cerebral proteopathies that are thought to involve the prion-like induction of protein deposition include Alzheimer’s disease, Parkinson’s disease, Huntington’s disease, amyotrophic lateral sclerosis, frontotemporal lobar degeneration, and chronic traumatic encephalopathy (see (18) for review). Much of the information on this emerging pathogenic principle has come from experimental models, which generally do not recapitulate human neurodegenerative diseases in their entirety (40, 41). The models do, however, allow us to systematically examine the molecular underpinnings of protein aggregation and spread, and thus can uniquely enrich our understanding of the essential disease process.

The first evidence that a non-prion proteopathy might be inducible in the brain came from attempts to transmit Alzheimer’s disease to a New World primate, the common marmoset (*Callithrix jacchus*). Baker, Ridley and colleagues found that senile plaques and cerebral β-amyloid angiopathy are increased in marmosets 5-6 years following the intracerebral injection of Alzheimer brain homogenates (42). Unlike wild-type mice and rats, most nonhuman primates express the human-type Aβ sequence, and they naturally develop β-amyloid deposits in old age (41). Unexpectedly, the Aβ sequence in marmosets is predicted to have a substitution of histidine for aspartate at amino acid position 23 (http://www.ncbi.nlm.nih.gov/protein/296231956). Whether this change influences the susceptibility of marmosets to the exogenous (or endogenous) induction of Aβ aggregation is an intriguing open question.

The advent of transgenic mice expressing the human β-amyloid precursor protein (APP) established a more rapid, economical, and definitive model in which to test the hypothesis that Aβ deposition is inducible by exogenous seeds (30). In APP-transgenic rodents, Aβ-deposition can be instigated within a few months by the intracerebral infusion of brain extracts containing minute amounts of aggregated (multimeric) Aβ (29-31, 43-49). The collective evidence from the injection of brain extracts indicates that aggregated Aβ itself is the seeding agent (18). This conclusion recently has been borne out by the seeding of Aβ deposition in APP-transgenic mice by aggregated, synthetic Aβ (49), although, for unknown reasons, seeds consisting of synthetic Aβ are less effective than are seeds generated in vivo (31, 49). Interestingly, brain-derived Aβ seeds can occur as large, proteinase K (PK)-resistant aggregates as well as small, soluble, PK-sensitive aggregates, indicating that a diversity of Aβ multimers can induce cerebral Aβ-proteopathy (45), similar to prions (50). Their size, potency and diffusibility implicate soluble Aβ seeds in the expansion of Aβ lesions within the brain (45). Similarly, small assemblies of superoxide dismutase-1 (SOD1), the protein that misfolds and aggregates in familial, autosomal dominant forms of amyotrophic lateral sclerosis, appear to be particularly effective at seeding SOD1 aggregation in cultured cells (51).

**THE SEEDED SPREAD OF PROTEIN AGGREGATES**

Emerging methods for mapping the connectivity of the human brain have begun to bolster the hypothesis that a pathogenic agent accesses networked sites via the brain connectome (52, 53). Earlier investigations of postmortem brains at various stages of apparent Alzheimer pathogenesis have suggested that neurofibrillary tangles and senile plaques proliferate systematically as disease severity increases (54-57). The olfactory system, because of its strong neuronal links to the medial temporal lobe (an area of severe pathology in Alzheimer’s disease) and its exposure to the outside environment, has been considered a possible focal point for the initiation of Alzheimer pathology (55, 58). Although the pattern of presumptive spread differs for the two protein pathologies - aggregated tau and Aβ (18, 54) - these observations suggest that a pathogenic agent somehow takes root in a particular place in the nervous system, and then...
migrates along connectional pathways by active neuronal transport or by passive diffusion. In a like manner, the orderly advance of symptoms, brain functional changes and associated lesions in amyotrophic lateral sclerosis (59,60) and Huntington’s disease (33,61) hints at a key role of neuronal connections as inadvertent conduits for disease-causing agents (38). The neuronal transport of pathogens has been well-established in virology, in that several viruses are conveyed by axonal transport to, and within, the central nervous system (62). Additionally, prions injected into the vitreous humor of the eye spread in the brain along defined visual pathways (63,64). Because early evidence for a similar mechanism in non-prion neurodegenerative diseases was indirect, and because it required assumptions about the staging of disease based on analyses of postmortem brains, definitive testing of the cellular transport hypothesis was not possible until the introduction of suitable animal models.

**The spread of Aβ proteopathy.**

In our original studies of Aβ seeding in APP-transgenic mice, we injected small amounts of dilute Alzheimer brain extracts unilaterally into the dorsal hippocampus (30,65). Four to six months later, the injected hippocampus had developed substantial seeded Aβ deposits (Figure 2B). At this point, we also noticed a small, isolated region of Aβ-immunoreactivity exclusively in the ventral entorhinal cortex, some distance from the extract-injection site (65)(Fig 2D). Mathias Jucker and Yvonne Eisele have shown that the reverse also holds, i.e., that injection of Aβ-seed rich brain extract into the ventral entorhinal cortex yields deposition in the hippocampal formation (18,29). The entorhinal cortex is a major neocortical relay station for information flowing to and from the hippocampus. Inasmuch as induced Aβ deposits were largely absent in other cortical regions of seeded mice at this timepoint, it is likely that the isolated immunoreactivity in the entorhinal cortex or hippocampus results from axonal transport of the proteopathic agent, although other modes of trafficking cannot yet be entirely excluded (18). Notably, one study has found that transgenic APP expression selectively in the entorhinal cortex induces behavioral impairments and hippocampal neuronal dysfunction indicative of trans-synaptic trafficking of endogenous Aβ (66). Furthermore, endogenously generated Aβ aggregates expand preferentially among interconnected brain regions in an APP-transgenic mouse (67). In this latter model, increased Aβ immunoreactivity appears first within cells, followed by diffuse, extracellular deposits in the subiculum and subsequently in axonally coupled regions.

Long-term studies indicate that, once initiated in one brain area, Aβ deposits continue to amplify and spread. One year following injection of Alzheimer brain extract into the dorsal hippocampus, Aβ-plaque load was substantially greater in the entorhinal cortex of the injected hemisphere than on the contralateral side (65). In an APP-transgenic mouse model that does not normally begin to deposit Aβ until 15 months of age, bilateral, focal injections of Aβ-rich brain extracts at 3 months of age cause, at 15 months of age, substantial Aβ pathology throughout most of the forebrain (44).

These studies in mouse models support the hypothesis that neuronal transport contributes to the systematic dissemination of pathogenic seeds within the Alzheimeric brain (54-57). Interestingly, infusion of Aβ seeds into the murine hippocampus instigates Aβ deposition also in the vasculature of the thalamus (29,31), suggesting that proteopathic seeds can migrate by diffusion along intracerebral perivascular drainage channels or through the bloodstream (29). An intravascular route of transit also is suggested by the finding that Aβ seeds delivered to the peritoneal cavity significantly increase brain Aβ load after a prolonged incubation period (43), although transport from periphery to brain by neurons has not been ruled out in this paradigm.

**The spread of tauopathy.**

In Alzheimer’s disease and several other neurodegenerative disorders, the microtubule-associated tau protein polymerizes into abnormal cellular inclusions, most prominently as neurofibrillary tangles (8)(Figure 1A). The appearance of neurofibrillary tangles in the brains of Alzheimer patients follows a sequence that is, to a considerable degree, predictable by the axonal connectivity of the affected regions
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Neurofibrillary tangles are inducible by fibrillar tau in vitro (68), and, similar to the seeding of Aβ deposition in vivo, tangles can be exogenously induced by the infusion of brain extract containing abnormal tau filaments into the brains of mice expressing human tau transgenes (28). As with Aβ-seeding (31), the actuation of tauopathy is time- and brain region-dependent, and immunodepletion of tau from the donor brain extract blocks seeding. Remarkably, as the incubation time increases, intracellular tau lesions begin to emerge in nearby and/or axonally coupled areas, suggesting that neuronal transport mechanisms participate in the spread of seeds (28); some of these seeds, including tau oligomers, may be endogenous descendants of the original, exogenous protein seeds. As in the case of Aβ (above), endogenously generated focal tauopathy in genetically modified mice also appears to expand along interconnected neuronal pathways over time (69,70).

The spread of other proteopathic seeds.

The seeded induction of proteopathy may be an important pathogenic characteristic of other neurodegenerative disorders (for recent reviews, see (15,18,24,32-36,38,39,71,72)). For example, the aggregation of α-synuclein is typical of Lewy body disease/Parkinson’s disease, and analysis of postmortem brains suggests that synucleinopathy ramifies through the brain in a systematic fashion (73), albeit with some incongruities (74). The discovery of α-synuclein aggregates in the olfactory bulb and enteric nervous system, and the finding that the dorsal motor nucleus of the vagus nerve is afflicted early on, have suggested that a pathogenic agent may gain access to the brain via the nose or intestinal tract (75). In α-synuclein-transgenic mice, α-synuclein deposition can be seeded in enteric neurons by injections of brain extracts containing aggregated α-synuclein (76), but there is not yet direct evidence for the subsequent induction of lesions in the central nervous system by this route. When fetal dopaminergic neurons were transplanted into the striatum of Parkinsonian patients, some of the cells eventually manifested α-synuclein-positive Lewy bodies, indicative of the seeded induction of synucleinopathy in the transplanted tissue by proteopathic α-synuclein seeds stemming from the host (77,78). Confirmatory findings for the seeding and dispersion of synucleinopathy have been reported in vitro (79-81) and in experimental animals (79,80,82-84).

Amyotrophic lateral sclerosis (ALS), like other neurodegenerative disorders, has both genetic and idiopathic forms. Clinical observations suggest that ALS can arise focally in different regions of the nervous system, after which it spreads systematically (non-randomly) from one region to another (59,60). Autosomal dominant ALS often is associated with mutations in the gene for superoxide dismutase-1 (SOD1), and the inclusions in affected neurons contain aggregated SOD1; in most idiopathic ALS cases (and in a variant of frontotemporal lobar degeneration), TDP-43 is the predominant aggregated protein (38). Recently, mutations in the gene for FUS have been linked to ALS; because FUS and TDP-43 are DNA/RNA binding proteins involved in transcription, their ectopic aggregation hinders their normal activities in the nucleus, thus impairing the functionality of affected neurons (85). In this sense, the harmfulness of the aggregating proteins is related to a loss of normal protein function, rather than to a gain of toxic function. There is mounting in vitro evidence for the prion-like templated corruption of SOD1 (51,86,87) and TDP-43 (88). More broadly considered, because of their tendency to self-assemble and spread in the nervous system, RNA-binding proteins with prion-like domains may turn out to be implicated frequently in neurodegeneration (89).

Huntington’s disease is an autosomal dominant disorder that is caused by a supra-threshold expansion of an unstable CAG repeat region in the huntingtin gene, lengthening the stretch of glutamines in the protein. How mutant huntingtin disables neurons remains debated, but expanded polyglutamines render the protein prone to aggregation, and in general, the greater the expansion, the earlier the onset and more aggressive the disease (33,90). Evidence for the spread of huntingtin seeds in the nervous system remains indirect, but cell culture studies show that the cell-to-cell transfer of huntingtin aggregates can occur (below). Although Huntington’s disease is a prominent example,
there are multiple trinucleotide repeat expansion diseases (91) that may share this basic pathogenic mechanism.

**Cellular mechanisms underlying the spread of seeds, and prospects for therapy.**

The means by which seeds are taken up, released, and/or transferred by cells remain poorly defined, and are likely to be governed by the cell types involved, the cellular localization of implicated proteins, and the nature of the seeds. While the etiologic details of the different proteopathies may vary, clarification of cellular trafficking could inform the search for therapeutic agents designed to slow the spread of disease (24,33,38,51,81,88,92-98). Cell culture models have been particularly informative for this purpose; for example, in vitro experiments show that rather large aggregates of huntingtin are able to enter the cytosol from the extracellular milieu (32,98), indicating that cell membranes are unexpectedly permeable to proteopathic seeds (32). Furthermore, direct neuron-to-neuron transfer of oligomeric Aβ has been demonstrated in cultured hippocampal neurons (99). Impeding the ability of seeds to template conformational corruption could limit the spread of pathology, and therapeutic agents might be designed to target specific proteins in order to minimize side-effects.

Simple models, such as yeast, can be helpful in illuminating cellular operations (100), but ultimately, the insights gained in cells and in cell-free systems must transfer to living mammals. Many gaps remain in our knowledge of the hypothesized prion-like properties of aggregation-prone proteins in diverse maladies (38). Fortunately, none of the non-prion proteopathies have yet been shown to share the (relatively) facile infectivity that characterizes prions. Nonetheless, similarities in the pathogenic process at the molecular level argue that the concept of corruptive protein seeding could yield fundamental insights into the origins and progression of many common neurodegenerative diseases of old age.

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FOOTNOTES

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The abbreviations used are: Aβ, Amyloid-β; APP, Aβ-precursor protein; ALS, amyotrophic lateral sclerosis; CADASIL, cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy; CAG, cytosine, adenine, guanine; FUS, fused in sarcoma; PBS, phosphate-buffered saline; PK, proteinase-K; rf, rhinal fissure; SOD1, superoxide dismutase-1; TDP-43, TAR DNA-binding protein 43.
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Table. Some Diseases Involving Protein Misfolding and Ectopic Deposition in Various Systems

AA amyloidosis, AH (heavy chain) amyloidosis, AL (light chain) amyloidosis, Alexander disease, Alzheimer's disease, amyotrophic lateral sclerosis, aortic medial amyloidosis, apoA1 amyloidosis, apoA2 amyloidosis, apoA4 amyloidosis, CADASIL, cardiac atrial amyloidosis, cataract, cerebral amyloid angiopathies, corneal lactoferrin amyloidosis, critical illness myopathy, cutaneous lichen amyloidosis, dialysis amyloidosis, familial amyloidotic neuropathy, familial British dementia, familial Danish dementia, familial visceral amyloidosis, fibrinogen amyloidosis, Finnish hereditary amyloidosis, frontotemporal dementia, Huntington's disease and other polyamino acid diseases, hereditary lattice corneal dystrophy, inclusion body myositis/myopathy, lysozyme amyloidosis, medullary thyroid carcinoma, odontogenic (Pindborg) tumor amyloid, Parkinson's disease, pituitary prolactinoma, primary systemic amyloidosis, primary cutaneous amyloidosis, prion diseases, pulmonary alveolar proteinosis, seminal vesicle amyloid, seipinopathy, senile systemic amyloidosis, serpinopathy, sickle cell disease, synucleinopathy, tauopathy, type 2 diabetes
FIGURE LEGENDS

FIGURE 1. Proteopathic lesions in Alzheimer’s disease and Lewy body disease. A: Senile plaque (arrow) and neurofibrillary tangles (one is indicated by the arrowhead) in the brain of a patient with Alzheimer’s disease. The plaque consists of a core of compact Aβ-amyloid (pink) surrounded by abnormal neurites (brown/black) and reactive glial cells (not readily visible). Naoumenko-Feigin/Periodic acid-Schiff stain. B: Lewy body (arrow) that is immunoreactive with an antibody to α-synuclein (brown) in the brain of a patient with Lewy body disease. Note also the fine, filamentous, α-synuclein-immunoreactive neurites scattered about the neuropil (one is marked with an arrowhead). Section is counterstained with hematoxylin (blue). Bar = 50μm for A and B.

FIGURE 2. Seeded induction and spread of Aβ deposits in a Tg2576 APP-transgenic mouse. The hippocampus on the right (B) was injected with 2.5μl of a 10% Alzheimer cortical extract when the mouse was 3 months of age (the hippocampus on the left side (A) received a control injection of PBS). At the age of 9 months, the mouse was sacrificed and brain sections immunostained using an antibody to Aβ. An isolated patch of Aβ is present in the entorhinal cortex ventromedial to the rhinal fissure (rf) on the extract-injected side (arrow, D) but not on the control side (C). Bar = 200μm for all panels.
Figure 1
Figure 2
### Table. Some Diseases Involving Protein Misfolding and Ectopic Deposition in Various Systems

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