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Proteopathic Strains and the Heterogeneity of Neurodegenerative Diseases

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Abstract

Most age-related neurodegenerative diseases are associated with the misfolding and aberrant accumulation of specific proteins in the nervous system. The proteins self-assemble and spread by a prion-like process of corruptive molecular templating, whereby abnormally folded proteins induce the misfolding and aggregation of like proteins into characteristic lesions. Despite the apparent simplicity of this process at the molecular level, diseases such as Alzheimer's, Parkinson's, Creutzfeldt-Jakob and others display remarkable phenotypic heterogeneity, both clinically and pathologically. Evidence is growing that this variability is mediated, at least in part, by the acquisition of diverse molecular architectures by the misfolded proteins - variants referred to as proteopathic strains. The structural and functional diversity of the assemblies is influenced by genetic, epigenetic, and local contextual factors. Insights into proteopathic strains gleaned from the classical prion diseases can be profitably incorporated into research on other neurodegenerative diseases. Their potentially wide-ranging influence on disease phenotype also suggests that proteopathic strains should be considered in the design and interpretation of diagnostic and therapeutic approaches to these disorders.

Keywords

Abeta; Alzheimer's disease; amyloid; Parkinson's disease; prion; synuclein; tau

INTRODUCTION

As humans grow old, the likelihood of developing one or more neurodegenerative diseases steadily rises (28). These clinically and pathologically heterogeneous disorders include Alzheimer's disease (AD), Parkinson's disease, Lewy body dementia, amyotrophic lateral sclerosis, frontotemporal dementia, Creutzfeldt-Jakob disease (CJD), and others. Virtually all age-related neurodegenerative diseases are characterized by the aggregation of specific proteins within or among the cells of the brain (17; 44; 68; 146). This process of abnormal protein self-assembly results in the formation of distinctive lesions that help to define each

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disease, including intracellular inclusions and/or extracellular masses of protein (Figure 1). Strong evidence now indicates that these neurodegenerative diseases arise and progress by a molecular mechanism closely resembling the corruptive protein templating that characterizes the classical prion diseases (68; 111; 126; 146).

In many instances, the pathogenic proteins form polymeric fibrils that assemble into clumps referred to as *amyloid*, (17; 152) a generic term for abnormal lesions that exhibit birefringence under the light microscope after staining with the dye Congo Red (Figure 2a), and a typical cross-β X-ray fiber diffraction pattern owing to a high content of β-sheet in the constituent proteins (31; 46; 129). Using electron microscopy, amyloids are seen as rigid, generally unbranched fibrils (Figure 2b) that often are superficially similar in appearance despite deriving from any of more than 30 distinct proteins that aggregate in various organs (17; 129; 152).

Notwithstanding their general similarity in size and shape, amyloid fibrils made of a given protein can show a degree of polymorphism (101) that reflects the organization of the peptide chains within the protofilaments (17), which, in turn, is influenced by certain intrinsic and extrinsic factors (101). The omnipresence of the cross-β configuration in amyloids is consistent with an essential role of the peptide backbone in amyloidogenesis, but the amino acid side chains also influence the ultimate structure of the assemblies (17; 75). Aggregated proteins sometimes do not have the classical properties of amyloid (129), but in all known instances, ectopic deposits of protein signal the probable presence of disease. Even some well-known pathogenic proteins only inconsistently form amyloid *in vivo*, such as the prion protein (PrP) (26), amyloid-β (Aβ) (7), transactive response DNA binding protein-43 kDa (TDP-43) (119), huntingtin (56), and α-synuclein (120). Furthermore, amyloidogenic proteins can exist in the form of small oligomeric assemblies that lack the fibrillar structure of amyloid but that nonetheless impair organ function (32; 34; 48; 56; 84; 118). Thus, the amyloid state is indicative of a proteopathic process, and an enhanced tendency to form amyloid is common in pathogenic proteins, but amyloid *per se* is not always obligatory for the manifestation of disease.

ALZHEIMER'S DISEASE AND THE AGGREGATION OF Aβ AND TAU

Alzheimer's disease is the most prevalent age-associated neurodegenerative disorder (114) and the most frequent form of amyloidosis in humans (41). The principal clinical attribute of AD is a progressive deterioration of cognitive function, usually over a period of 7–10 years (57). Analysis of biomarkers for AD indicates that the disease process begins in the brain two decades or more before the onset of demonstrable cognitive impairment (64). A definitive diagnosis of AD in a patient with dementia requires the presence of two canonical histopathologic lesions in the brain: Aβ (senile) plaques (heterogeneous structures consisting of extracellular deposits of multimeric Aβ peptide and a variable array of reactive cells), and neurofibrillary tangles (intracellular, fibrillar polymers of hyperphosphorylated tau protein) (Figure 1a). In addition to plaques, Aβ accumulates, albeit inconsistently, in the walls of brain blood vessels as cerebral amyloid angiopathy (CAA) (117).

Aβ is a cleavage product of the Aβ-precursor protein (APP), a 695–770 amino acid, single membrane-spanning protein that is expressed in cells throughout the body and is particularly

abundant in the nervous system (47; 127). APP is sequentially cleaved by an extra-membranous enzyme called β-secretase (β-amyloid cleaving enzyme [BACE]) and an intramembranous enzyme complex called gamma-secretase to yield Aβ fragments that are usually 40 or 42 amino acids long (Aβ40 and Aβ42, respectively). In addition, smaller populations of C-terminally and N-terminally truncated and/or modified Aβ fragments are present (107; 108). Although Aβ40 is the predominant isoform that is generated by brain cells, Aβ42 has two additional hydrophobic residues at the C-terminal end that greatly enhance its tendency to aggregate; for this reason, Aβ42 is thought to be the most culpable player in the early development of AD (57).

Tau is a microtubule-binding protein that, in its normal state, is believed to stabilize cellular microtubules (132). In the tauopathies, tau misfolds and becomes hyperphosphorylated; in this state the molecules aggregate to form soluble oligomers and long, β-sheet-rich polymers that bundle together as neurofibrillary tangles. Tauopathy can afflict both neurons and glial cells (76), and occurs in association with numerous brain disorders other than AD. In the primary tauopathies, cognitive deterioration is linked to neurofibrillary tangles that generally exist in the absence of Aβ plaques (23; 76; 132). In many instances however, including AD, tauopathy appears to be secondary to various types of injury or stress to the brain (95).

For years the relative importance of Aβ and tau in the pathogenesis of AD has been the subject of debate (15; 79). The supposed antithesis of Aβ and tau in the AD scheme is, of course, a false dichotomy; abnormalities of both proteins are essential for the full clinicopathologic expression of AD (128). Although the number of tangles generally correlates more strongly with the degree of dementia than does the number of plaques (10; 25), genetic and biochemical evidence implicates the misfolding and multimerization of Aβ as the initial and indispensable occurrence in the ontogeny of AD (52; 57). This concept has been embodied in the *amyloid (Aβ) cascade* hypothesis, first formulated as such by John Hardy and colleagues (52; 53). The amyloid cascade hypothesis holds that Aβ aggregation is causative in AD, and other manifestations, including tauopathy, are downstream (more on this below).

Misfolded Aβ disrupts brain function in multiple ways. Studies in animal models show that Aβ plaques themselves have cytotoxic properties (94; 105), but, as in the case of many amyloidogenic proteins, Aβ also forms small, soluble, oligomeric assemblies that contribute to neuronal dysfunction and death (34; 48; 84). Hydrophobic amino acids are exposed on Aβ oligomers, facilitating toxic interactions with lipid membranes; as oligomers self-assemble into amyloid fibrils, their reactive surface area diminishes, rendering fibrils at least partially protective (128). With the proliferation and maturation of plaques, the equilibrium between insoluble fibrils and soluble oligomers is thought to shift in favor of generating oligomers, which then are free to impair the function of cells (128). A protective role of Aβ fibrils, however, by no means negates the centrality of Aβ aggregation in AD, as discussed below in a comparison with PrP prion disease. Additional evidence for a primary role of Aβ in AD has come from genetics.

AMYLOID, GENETICS, AND THE ORIGINS OF THE Aβ CASCADE HYPOTHESIS

In his description of amyloid in the early 1850's, Rudolf Virchow initially believed that amyloid (meaning "starch-like") resembled cellulose, but Friedreich and Kekule's 1859 report that amyloid consists mainly of protein profoundly re-oriented inquiry into the nature of the substance [see (112)]. The proteins in some systemic amyloidoses were eventually identified in the early 1970s (13; 130), and the Aβ that forms plaques and CAA was sequenced in the mid-1980's by Glenner and Wong (42) and Masters and colleagues (88). This knowledge quickly led to the localization of the gene for APP on human chromosome 21 (45; 72; 140), which, despite some early missteps (51), propelled genetic investigations of AD forward. In 1990, a missense mutation in the APP gene was linked to an autosomal dominant form of CAA (81; 143), and in 1991, for the first time a specific mutation (in the APP gene) was found to segregate with a familial form of Alzheimer's disease (43).

It is hard to overstate the significance of these discoveries for defining the subsequent course of research on AD. In furnishing the first indisputable evidence for a specific molecular abnormality as a causative feature of AD, they helped to clarify research objectives, establish a plausible framework for the development of disease-modifying therapies, and lay the groundwork for the creation of genetically modified rodent models of AD. In so doing, the genetic findings also kindled the formulation of the Aβ cascade hypothesis as the dominant mechanistic framework for understanding the causation and course of AD.

The Aβ cascade hypothesis was further solidified by the discovery of autosomal dominant transmission of AD due to mutations in the genes for presenilin-1 and presenilin-2. The presenilins are related components of gamma-secretase, the intramembranous enzyme complex that, in series with extramembranous β-secretase, liberates Aβ from APP (47; 127). Presenilin-1 is encoded on chromosome 14, and presenilin-2 is encoded on chromosome 1. The majority of autosomal dominant mutations associated with AD occur in the genes that code for the presenilins, especially presenilin-1 (51; 57). Indeed, all known AD-linked mutations affect the production, removal, trafficking, and/or tendency to aggregate of Aβ (52).

Most of the AD mutations – specifically those in the presenilins and the APP regions flanking Aβ - influence the processing of APP, but mutations within the Aβ segment often modify its aggregation potential and tissue specificity (47). Remarkably, a rare genetic variant in the APP gene that causes an amino acid substitution at position 2 of Aβ (A673T, according to APP770 numbering) reduces the production (67) and aggregation propensity (8) of Aβ, and also lowers the risk of developing AD (67). In contrast, substitution of valine for alanine at this position (A673V) *increases* the production and aggregability of Aβ, and in homozygous carriers causes an autosomal recessive form of AD (27). These genetic data leave little doubt that Aβ plays a critical role in hereditary forms of AD.

But autosomal dominant and recessive causes are operative in less than 1% of all AD cases (57). Is it possible that idiopathic AD arises by a different mechanism, i.e., one in which the aggregation of misfolded Aβ is not a pivotal feature? This seems unlikely. Genetic variations are estimated to contribute as risk factors in ~70–80% of all AD cases (95; 139; 155). Most of these myriad genetic variants individually have a small impact on overall risk (58), but

several together may have additive or emergent/interactive impact. By far the most salient genetic risk factor for AD is the E4 variant of apolipoprotein E (ApoE4) (158).

Apolipoprotein E (ApoE) is involved in lipid transport throughout the body, and it is the main apolipoprotein in the brain (18). ApoE has three major isoforms in humans, designated ApoE2, ApoE3 and ApoE4. The *APOE* gene is on chromosome 19, and the *APOE4* allele dose-dependently increases the risk of AD (18). Worldwide, the most common isoform of the protein is ApoE3 (~78%), followed by ApoE4 (~14%) and ApoE2 (~8%) (83). Although the mechanism by which ApoE4 predisposes to AD is probably multifactorial (109; 158), bearers of *APOE4* begin to accumulate Aβ in the brain at least a decade earlier in life than do non-bearers (116; 147; 148). In this sense, *APOE4* appears to confer risk by expediting the Aβ cascade.

Whether hereditary or idiopathic, all AD involves the same core clinical and pathological features: progressive dementia in the context of Aβ plaques and neurofibrillary tangles. Notably, though, the characteristics of the lesions can vary within and among AD cases (see Proteopathic Aβ strains in Alzheimer's disease, below). The Aβ cascade hypothesis identifies Aβ as the prime mover in the pathogenesis of AD, but the means by which the protein actually causes disease has been uncertain. Here, parallels with the molecular attributes of PrP prions have established a compelling model for understanding how the transformation of Aβ leads to the dementia of AD.

THE PRION PARADIGM OF NEURODEGENERATIVE DISEASE

Prototypical prions are multimeric assemblies of misfolded PrP that impel the misfolding and aggregation of other PrP molecules by a process of corruptive molecular templating (110; 111). PrP, encoded by a gene on chromosome 20, is expressed in nervous and non-nervous tissues and can undergo a variety of post-translational modifications (98). PrP prions cause progressive, fatal neurodegenerative disorders that include CJD, kuru, Gerstmann-Sträussler-Scheinker syndrome (GSS), fatal insomnias, and variably protease-sensitive prionopathy in humans; in nonhuman species they include scrapie in sheep and goats, bovine spongiform encephalopathy (BSE) in cattle, chronic wasting disease in cervids, and several others (1; 60; 61; 90). The prion diseases are defined histopathologically by spongiform change, loss of neurons, astrocytosis, and the accumulation of PrP (Figure 3). Notably, however, these properties vary considerably among the prion diseases, as does the presence of accompanying anomalies such as tauopathy (26).

Prion diseases have long intrigued researchers because some of them – notably scrapie and kuru - are infectious with a very long incubation period. A frank immune response to infection is absent, and the infectious agent is unusually durable and resistant to harsh treatments such as radiation, heat and formaldehyde (110). Kuru is the prototypical infectious prion disease in humans. It is a rapidly progressive (usually 3–12 months) encephalopathy that was largely confined to the Fore linguistic/cultural group of Papua New Guinea in the 20th century. In early investigations, D. Carleton Gajdusek and Vincent Zigas noted that kuru had a strong tendency to run in families; hence, their leading hypothesis initially was that kuru was an atypical genetic ("heredofamilial") disorder [see (33)]. Several

incongruities, however, gave them pause – adult females were much more frequently affected than were males, but among children boys became ill nearly as often as girls. In addition, Gajdusek's exploration of the fringes of kuru territory disclosed occasional Fore females who developed kuru when married into neighboring (kuru-free) tribes, as would be expected for a genetic disorder, but they also made the contradictory observation that females from neighboring tribes sometimes manifested kuru after moving into Fore territory (33).

The experimental transmission of kuru to chimpanzees (38) ultimately substantiated the longstanding suspicion that endocannibalism – usually of deceased family members – caused the preferential spread of the kuru agent within families. Females and children were more likely than adult males to participate in the mortuary feasts (a.k.a. transumption) (153). Following the cessation of endocannibalism in the 1950's, the incidence of kuru began a long, slow decline; rare cases continued to appear into the 21st century (2), with incubation periods of some patients thought to exceed 50 years (22). Remarkably, the striking loss of Fore women and children during the kuru epidemic resulted in the selection of a polymorphism in the gene for PrP that protects against kuru, possibly the strongest example of genetic selection yet discovered in a human population (4).

The prion puzzle was complicated by the recognition that, in addition to infection, prion diseases also can be idiopathic or genetic in origin (110; 111). The infectivity of PrP prions is made possible by an unprecedented mechanism by which a pathogenic molecular conformation of PrP (PrP Scrapie [PrP^{Sc}]) structurally corrupts normal, endogenous PrP molecules (PrP Cellular [PrP^{C}]) by templated structural conversion (1; 110). Efficient transmission of prion disease is critically dependent on the compatibility of the host and the agent (110; 145; 150), and the host can influence the characteristics of the aggregates independent of PrP sequence differences (24). Functionally significant variations in prion traits are associated with differences in PrP amino acid sequence, protease sensitivity, resistance to denaturants, and glycosylation patterns (89; 150), but a crucial factor governing infectivity and phenotype is the molecular conformation of PrP^{Sc} (39; 103; 137). Such structural/functional variants of PrP prions are commonly referred to as prion *strains*, the heterogeneity of which is linked to heterogeneity in the presentation of the disease (21; 124). As is discussed below, other disease-related proteins share with PrP prions the capacity to form variant strains (17; 31; 137) (Figure 4).

PRION STRAINS

In 1961, Pattison and Millson noted that the disease phenotype caused by intracerebral inoculation of goats with scrapie-affected brain homogenates faithfully recapitulated the disease that had been seen in the donor (100). They surmised that the infectious agent – then supposed by most to be an unusual virus – existed in the form of variant, genetically defined viral strains that produced clinically distinct signs. In the same year, Chandler reported the first successful transmission of scrapie to mice (16). He made the important observation that the nature of the resulting disease – called either "scratching" or "drowsy" in goats – is governed by both the strain of inoculum *and* the type of host. Despite strong evidence even then that the infective agent was highly unorthodox (99), the existence of disease strains was

invoked for years afterwards as evidence that, in order to replicate in its alternative forms, the causative agent must be a microbe or virus. The emerging idea that prion strains are enciphered solely in the protein itself was met with incredulity by many researchers, as the complexity of strain characteristics was thought to require a nucleic acid genome (110). Although the maintenance of specific features through multiple passages is considered to be characteristic of microbial strains, an important attribute of prion strains is that they can be post-translationally modified and/or selected for by a different type of host (14; 151).

Prion strains in mammals have been classified as PrP variants that elicit typical pathogenic and phenotypic traits in the host (21; 39; 125). For instance, PrP^{Sc} is potentially amyloidogenic, but amyloid plaques *per se* are uncommon in most human and nonhuman prion diseases (26). Two exceptions are variant CJD (vCJD), which is transmitted to humans by exposure to the agent of BSE (154), and GSS, in which disease-associated amino acid substitutions facilitate terminal truncations of PrP that render the protein highly amyloidogenic (26). Interestingly, although tauopathy is inconsistent in occurrence and form in human prion diseases, the GSS cases are notable in that they manifest a type of tauopathy that is reminiscent of that in AD (26).

Genetic factors play a role in the pathobiology of prion strains by determining the primary sequence of PrP as well as the compatibility of the host and agent; for example, an amino acid polymorphism (M or V) at position 129 of PrP distinctly influences disease phenotype (39). Just as a rare variant in the primary structure of APP (A673T) can protect against AD (67), a G127V substitution in PrP is able to prevent prion disease (and therefore was strongly selected for by the kuru epidemic among the Fore people) (4). Amino acid sequence is one of several factors that influence a crucial trait that determines prion functionality: the multidimensional architecture of the molecules (3; 39). Recently developed thiophene-based probes can distinguish tertiary and/or quaternary molecular features of prion strains based on dissimilar fluorescence emission profiles when bound to aggregated PrP^{Sc} (87). Remarkably, prion strains can mutate and undergo preferential amplification under selection pressure (9; 21; 39; 40; 82). The notion that PrP prions and other proteopathic seeds exist in various states with distinct biological properties has considerable explanatory power for the protean nature of protein-based molecular information transfer (19; 20; 80; 92; 102; 111; 131).

PROTEOPATHIC Aβ STRAINS IN ALZHEIMER'S DISEASE

The deposition of Aβ in the brain can be stimulated in experimental animals by the introduction of seeds of aggregated Aβ (68). These seeds bear obvious structural and functional similarities to PrP prions. Specifically, Aβ seeds, like PrP prions, consist solely of a particular protein (Aβ rather than PrP); they are resistant to high temperature or formaldehyde (36; 93), they can spread within the brain and to the brain from the periphery (29; 30; 157), and they are extremely long-lived in the brain (156). These commonalities support the inclusion of Aβ seeds within the expanding prion family (111; 146). They also suggest that Aβ seeds might share with PrP prions the ability to aggregate into variant structural/functional strains. Although research on Aβ strains lags somewhat behind that of PrP prions, evidence is mounting that not all aggregates of Aβ are alike. Indeed, the

potential to generate conformationally distinct protein strains is considered to be a common property of aggregation-prone proteins (17; 31; 137).

A given protein can form amyloid fibrils of varying morphologies under the influence of different environmental conditions such as pH, temperature, ionic strength, and protein concentration, and the resulting fibrillar shapes are associated with differences in molecular arrangement (101). The molecular architecture of misfolded Aβ, like that of other amyloidogenic proteins, can be conveyed to newly formed fibrils by a process of templated structural conversion, or *seeding*, in a strain-specific fashion (85; 133; 149). Similar to PrP prions (above), strains of other pathogenic proteins are subject to conformational selection in which the morphotype best suited to a given environment prevails (101).

It is important to note that AD and other neurodegenerative diseases, unlike prion diseases, have not been demonstrated to be infectious under everyday circumstances. Recent reports have found evidence for the seeded induction of Aβ deposition in persons treated with cadaver-derived pituitary hormones (65) or who had received transplants of cadaver-derived dura mater (37; 50) – clearly extraordinary (and now discontinued) circumstances. The patients who were analyzed in these reports had died of iatrogenic CJD due to the presence of PrP prions in the biomaterials, and it appears likely that some of the materials also contained Aβ seeds (69; 77). However, the Aβ deposition in the recipients was not accompanied by tauopathy, and it cannot be known whether they eventually would have developed AD had they not succumbed to CJD. A study of human growth hormone recipients in the United States found no evidence of increased AD among surviving growth hormone recipients, at least as of 2008 (63). It will be instructive to monitor these patients over the coming years to determine if AD or other neurodegenerative diseases become disproportionately frequent with longer incubation periods.

Phenotypic variation in Aβ deposits

In the PrP prionoses, different strains of PrP^{Sc} often produce distinctive patterns of lesion configuration and distribution in the brain (26; 103). A key sign that vCJD is caused by a novel PrP prion strain, possibly originating from cows with BSE, was the discovery of unusual lesions called florid plaques in affected humans (62). As in the case of PrP prions, evidence is growing that Aβ can form strain-like variants both *in vitro* (91; 96; 97; 104; 142) and *in vivo* (54; 85; 93; 121; 123; 134; 149). Histologically, cerebral Aβ deposits in AD patients manifest considerable morphologic variation (Figure 5) that may be indicative of intra-individual strain-like differences in molecular structure (80).

Genetic Determinants of Structurally Variant Aβ Assemblies

Genetic mutations that substitute amino acids within Aβ can engender distinct disease phenotypes. The first evidence that a mutation in the gene for APP can cause disease arose from investigation of a rare familial form of cerebral amyloid angiopathy in the Netherlands (81; 143). A G->C nucleotide change (the “Dutch” mutation) alters amino acid 22 of Aβ (APP: E693Q), causing Aβ deposition in the cerebral vasculature (81; 143), which leads to catastrophic cerebral hemorrhage by approximately 50 years of age (86). In contrast, the “Arctic” mutation at the same locus (yielding E693G) results in clinical AD but with

profuse, atypical Aβ plaques lacking the classical dense amyloid core (70). As mentioned earlier, different amino acid substitutions at position 2 of Aβ either cause dementia (27) or protect against it (67); these findings collectively confirm that not all multimeric Aβ is the same at the molecular or histologic level, and that molecular differences can influence the nature of the disease. The amino acid sequence is a strong determinant of folded protein structure, but, as in the case of PrP prions, the amino acid sequence of Aβ need not be altered in order for the aggregated protein to manifest different structural and functional properties (141). In addition to germline mutations and polymorphisms, the role of somatic mosaicism (12; 35) and/or epigenetic modifications (78) in the ontogeny and heterogeneity of AD and other neurodegenerative disorders is a nascent and promising topic for further investigation.

Aβ Strains in Idiopathic Alzheimer's Disease

The hypothesis that Aβ is able to aggregate into diverse strains is supported by the differential affinity of amyloid-binding agents for Aβ lesions. Pittsburgh compound B (PiB) (*N*-methyl-[^{11}C]2-(4′-methylaminophenyl)-6-hydroxybenzothiazole) is a radiolabeled diagnostic imaging agent derived from the histochemical dye Thioflavin-T. PiB crosses the blood-brain barrier and, at low-nanomolar concentrations, selectively binds with high affinity and stoichiometry to Aβ plaques (73) and CAA (66) in humans. Unexpectedly, deposits of human-sequence Aβ in APP-transgenic mice are deficient in high-affinity binding of PiB (74). Similar observations were made in species that naturally accumulate human-type sequence Aβ with age. For example, nonhuman primates deposit high levels of Aβ in plaques and CAA as they grow old (55; 123), yet the lesions lack significant high-affinity PiB binding, suggestive of post-translational differences in misfolded Aβ among species (123). Although monkeys show some cognitive decline with age (6), they do not manifest the full behavioral and pathologic phenotype of AD, most notably the presence of widespread cerebral tauopathy. These findings together suggest that the degree of high-affinity PiB binding reflects post-translational characteristics of misfolded Aβ, and thus could furnish clues to the uniquely human vulnerability to AD (80; 122; 123).

The affinity of PiB binding to Aβ appears also to vary among humans with AD (59; 121). In one extraordinary occurrence, a patient who had died of AD was discovered to have very high levels of Aβ in the brain, yet virtually no high-affinity binding of PiB (121). Though histopathologically unexceptional, biochemically this patient had an especially high ratio of Aβ40:Aβ42; indeed, the amounts of various Aβ fragments could be an important determinant of the strain-like character and pathogenicity of aggregated Aβ (108). While the existence of this PiB-negative case would seem to argue against high-affinity PiB binding as a marker of pathogenic Aβ, it is worth noting that the manifestation of clinical disease in this case occurred in the context of Aβ levels that were an order of magnitude greater than in other AD cases (121).

Several other experimental approaches have added to the evidence for Aβ strains in humans. Using a biophysical method developed for the analysis of PrP prions, Safar and colleagues reported that a rapidly progressive form of AD is associated with specific structural properties of the aggregated Aβ, especially Aβ42 (20). Lu, Tycko and colleagues used Aβ

derived from two clinically distinct AD cases to seed the formation of daughter fibrils, which consisted of synthetic Aβ40, that were remarkably distinct when analyzed by solid-state nuclear magnetic resonance and electron microscopy (85). These studies, along with those of PiB and conformation-sensitive dyes, substantiate the conclusion that not all Aβ aggregates are alike, and that strain-like variations of amyloidogenic proteins can markedly influence the bioactivity of the assemblies (142).

Experimental Induction of Aβ Strains

Aβ deposition can be seeded in the brain by a prion-like process when brain extracts containing aggregated Aβ are injected intracerebrally into APP-transgenic mice expressing human-sequence Aβ (71; 93). In the absence of seeding, APP-transgenic mouse models normally begin to manifest cerebral Aβ deposits at a predictable age. In the seeding paradigm, however, injection of a small amount of Aβ-rich brain extract into the brains of host APP-transgenic mice induces accelerated Aβ deposition that then spreads from the site of injection (49; 157). As in humans with AD, APP-transgenic mice exhibit molecular structural differences in Aβ; these strain-like characteristics are preserved when the Aβ is seeded into suitable transgenic host mice (36; 54; 93; 134; 149).

Two different lines of transgenic mice used in the Aβ-seeding studies (APP23 mice (135) and APP-PS1 mice expressing human APP and human presenilin-1 (113)) develop Aβ plaques that differ morphologically under the light microscope (54). When a small amount of Aβ-laden brain extract from one of these models is injected into the brain of the other model, the seeded lesion morphologies and the molecular architecture of the Aβ as assessed by thiophene-based amyloid probes reflect characteristics of both the seeding extract and the host mice (54). Interestingly, the exogenous seeds also modified the relative amounts of Aβ40 and Aβ42 in the Aβ deposits that were induced in the host mice (54). Brain extracts from AD patients carrying either the Swedish or Arctic mutation were shown to seed distinct Aβ pathologies that could be serially propagated and preserved after multiple passages (149). These observations, along with evidence that soluble Aβ aggregates differ in normal aging and Alzheimer's disease (106) and can form assemblies that retain their properties after repeated passage *in vitro* (104), support the concept that Aβ aggregates resemble PrP prions in their ability to form and propagate functionally variant strains. Furthermore, tauopathy can be cross-seeded by pre-aggregated Aβ seeds (144); it will be informative to determine whether distinct Aβ strains differentially seed tauopathy in animal models. Here again, a systematic comparison to PrP prion diseases, in which tauopathy is inconsistent and heterogeneous (26), could provide clues to the molecular relationship between Aβ deposition and neurofibrillary tangles in the Aβ cascade.

CONCLUSIONS: THE WIDENING SPECTRUM OF PROTEOPATHIC STRAINS

The heterogeneity of age-related neurodegenerative diseases has defied a straightforward explanation. In Alzheimer's disease, multiple factors probably contribute to phenotypic variability. These include genetic, epigenetic, and environmental risk factors, as well as the location of the primary protein aggregation event(s) in the brain, and, especially in very old patients, the co-existence of separate pathogenic processes. Research increasingly supports

the likelihood that the molecular architecture of the aggregated Aβ protein also plays a part in disease heterogeneity.

In addition to Aβ and PrP, burgeoning evidence indicates that other disease-associated proteins exhibit strain-like heterogeneity, including tau (11; 138), α-synuclein (102), superoxide dismutase-1 (5), and amyloidogenic proteins outside the nervous system, such as insulin (136) and possibly AA amyloid (152). A key, open question is the mechanism by which variant strains are linked to variant disease phenotypes, but high-resolution structural definition of PrP prions and other seeds remains a challenge. Emerging and evolving methods for interrogating protein structure, such as spectroscopy, surface reactivity, cryo-electron microscopy and others should help to define conformational elements and intermolecular contact points that contribute to the pathogenicity of the proteins (115). In this regard, it is important to investigate amyloid generated both *in vitro* and *in vivo*, as the latter includes auxiliary substances that can influence the form and function of the material (152). From a broader perspective, it will be profitable to establish the variety and prevalence of proteopathic strains in the general population, as the conformation of the protein assemblies could influence the course of disease and the efficacy of therapeutic interventions.

For decades, the prion diseases have presented a compelling model for the concept that a single protein, through the assumption of myriad forms, can yield diverse disease phenotypes. Integration of the prion concept into our thinking about other neurodegenerative diseases is likely to spawn needed insights into their origin, clinicopathologic course, and idiosyncrasies. This more cohesive research effort could accelerate the discovery of unified therapeutic strategies that can be applied to the many diseases of protein aggregation that currently lack effective treatment.

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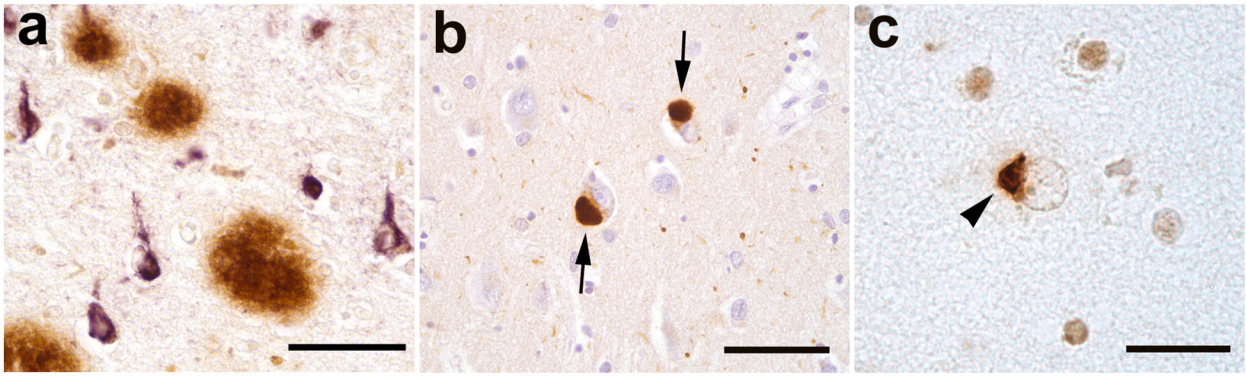

Figure 1.

Abnormal protein deposits detected immunohistochemically in three human neurodegenerative diseases. **a**: Extracellular Aβ (senile) plaques (brown) and intracellular neurofibrillary tangles (purple) in Alzheimer's disease. **b**: Intracellular Lewy bodies (arrows) in Lewy body dementia. **c**: Ectopic (cytoplasmic) mass of TDP-43 (arrowhead) in amyotrophic lateral sclerosis. Nissl counterstain (blue) in **b**; Bars = 50μm in **a** and **b**, 20μm in **c**.

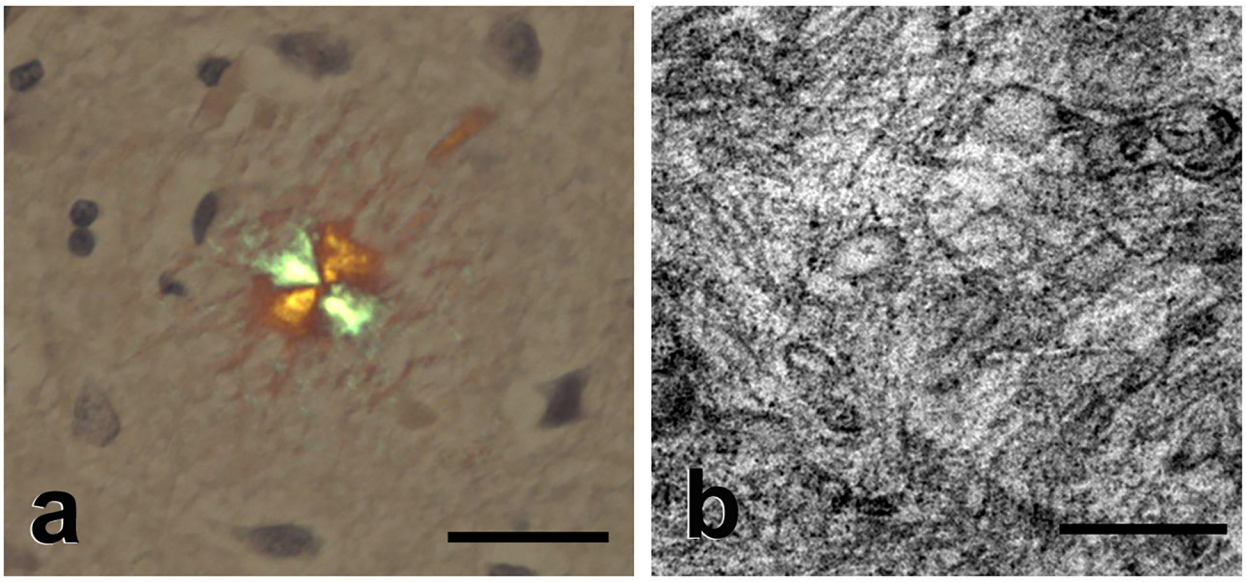

Figure 2.

Amyloid. **a**: Light micrograph of an amyloid plaque in the brain of an Alzheimer patient showing characteristic orange-green birefringence under illumination using crossed polarizing filters (Congo red stain, Nissl counterstain (blue); Bar = 50μm). **b**: Electron micrograph of massed amyloid fibrils in a plaque from an Alzheimer patient. The average width of amyloid fibrils in vivo is 7–13 nm (17). Bar = 200 nm.

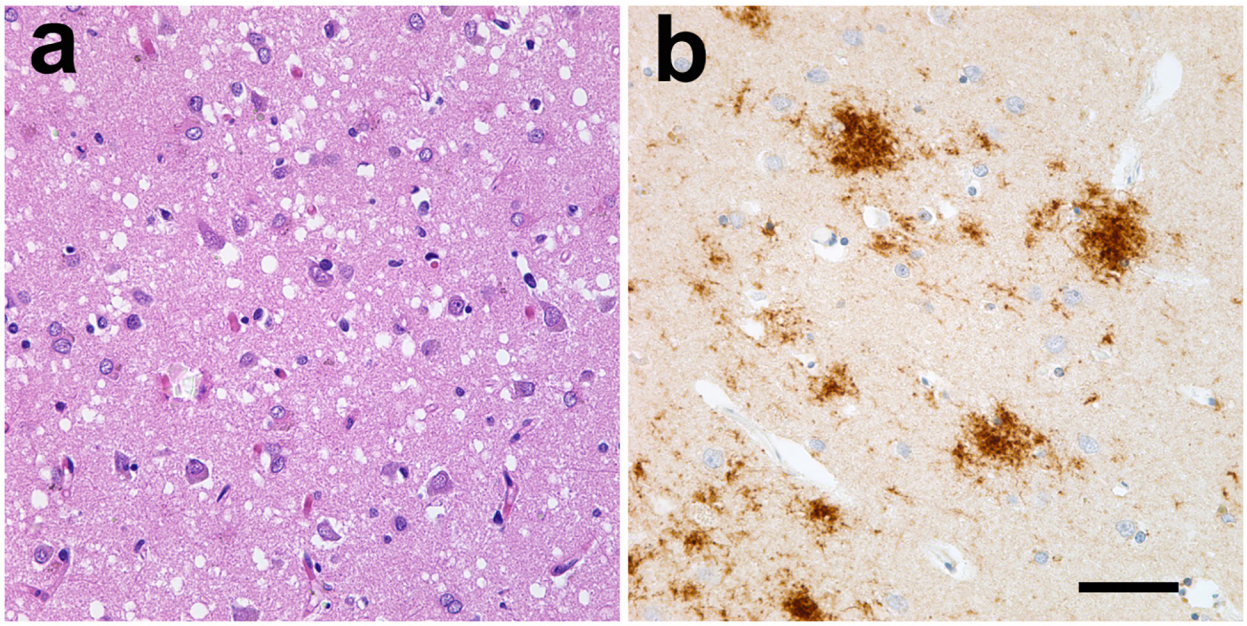

Figure 3.

The pathology of Creutzfeldt-Jakob disease. Common features of CJD are spongiform degeneration (seen as holes in **a**; hematoxylin and eosin stain) and the variable accumulation of prion protein (**b**; PrP immunostain, brown, Nissl counterstain, blue). Both types of lesion vary in type and extent among patients, and amyloid *per se* is rare in most cases of human prion disease. Bar = 50μm for both panels.

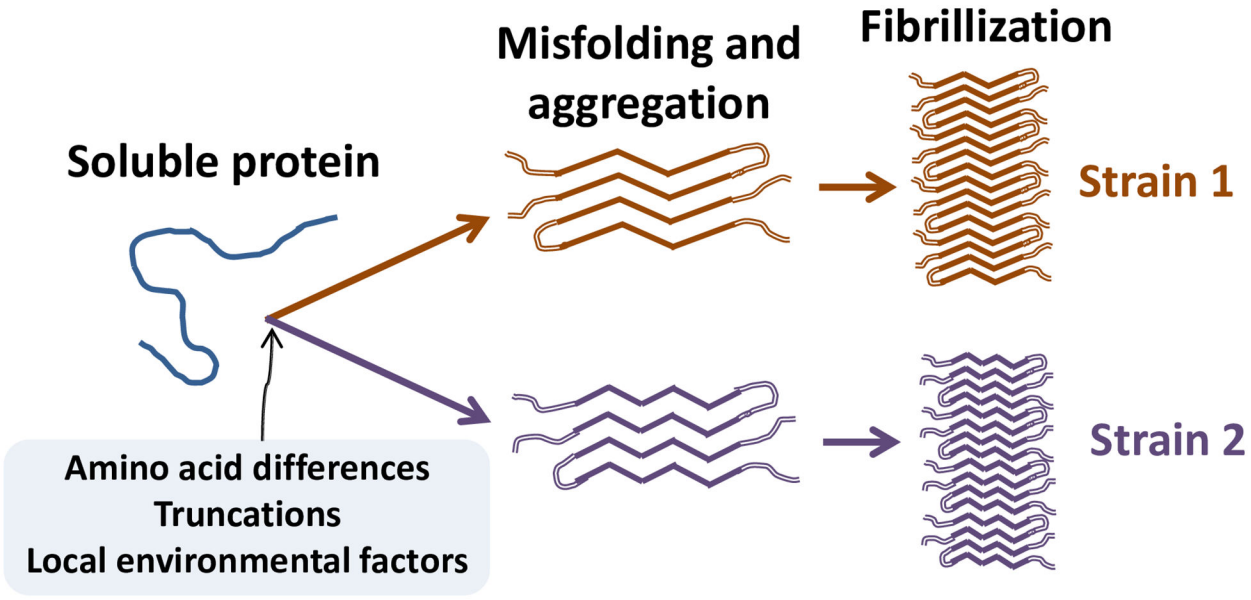

Figure 4.

Schematic diagram of proteopathic strain formation. Pathogenic proteins are most likely to misfold from an unfolded or partially folded state. The path to a given strain is influenced by such factors as sequence differences, truncation of the protein, post-translational modifications, and the milieu in which the seeds form and propagate. As the molecules acquire excess β-sheet, they bind to one another and multimerize into small oligomers, protofibrils, and/or amyloid fibrils. In addition to their influence on disease presentation, different molecular strains are sometimes reflected in the presence, distribution, and/or morphology of resultant lesions in the brain.

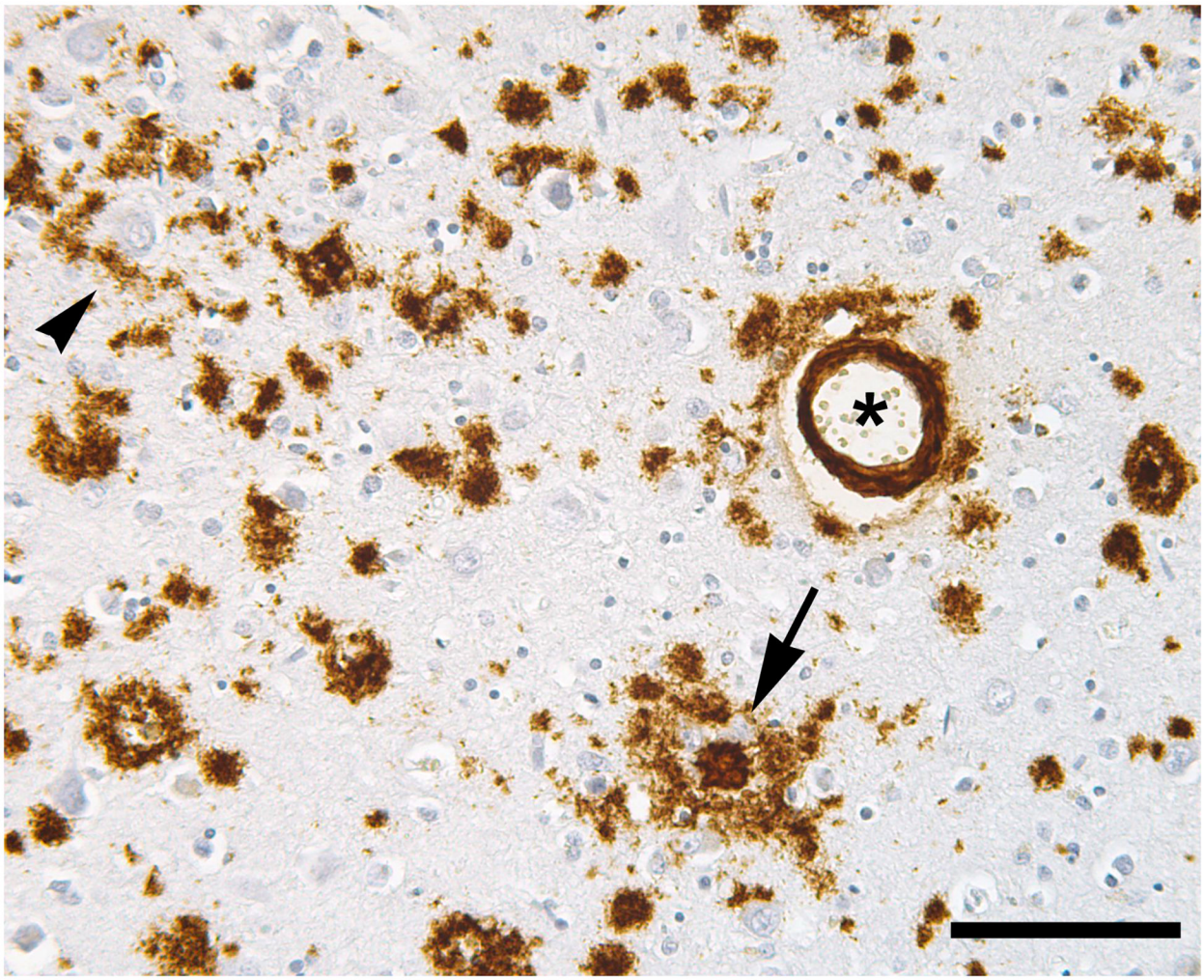

Figure 5.

Aβ deposits in AD are heterogeneous. A dense-core (amyloid) plaque is marked by an arrow, a cluster of diffuse Aβ deposits by an arrowhead, and a blood vessel with mural and perivascular Aβ by an asterisk. Immunostain for Aβ (brown); Nissl counterstain (blue). Bar = 100μm.