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Prion, prionoids and infectious amyloid

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SUMMARY

"Amyloid" is a generic term and all amyloids, irrespective of amino acid sequence, are formed in a seeded nucleation mechanism in which a small aggregate (oligomers) of a few amyloid moieties (a seed or a nucleus) seed (nucleate) normal amyloid precursor moieties to change conformation to a β-sheet. All sporadic neurodegenerative disorders are diseases of old age. This epidemiological phenomenon is consistent with a view that spontaneous conformational change from soluble, monomeric precursor protein into an insoluble amyloid aggregate is accomplished via a seeded nucleation process characterized by a long lag phase. Several predictions can be made on the basis of this assumption. First, an increase of the precursor monomer concentration may favor nucleation and, thus, shorten the lag phase. Second, an increase in the number of seeds should lead to amplification of the nucleation reaction. There are several protein misfolding disorders – the most widely known include Alzheimer's disease, Parkinson's disease and other α-synucleinopathies, amyotrophic lateral sclerosis (ALS), frontotemporal dementias in which abnormally phosphorylated MAP-τ protein accumulates and finally, polyglutamine expansion diseases such as Huntington's disease and certain spinocerebellar ataxias. The proteins involved differ in each of these disorders but the molecular mechanism is almost exactly the same, a seeding–nucleation mechanism.

1. Introduction

"*A new era has come to microbiology as we have realized that the unconventional viruses of kuru, Creutzfeldt–Jakob disease (CJD), Gerstmann–Sträussler–Scheinker syndrome (GSS), scrapie, and bovine spongiform encephalopathy (BSE) are infectious amyloid proteins and that these transmissible spongiform dementias are brain amyloidoses*" [1].

The transmissible spongiform encephalopathies (TSEs) or prion diseases are a group of neurodegenerative (i.e. non-inflammatory) disorders that includes kuru (Fig. 1) [2], Creutzfeldt–Jakob disease (CJD), Gerstmann–Sträussler–Scheinker (GSS) disease, and fatal familial insomnia in man; natural scrapie in sheep, goats and mouflons; transmissible mink encephalopathy in ranch-reared mink; chronic wasting disease of deer, elk and moose in the USA and Canada; bovine spongiform encephalopathy or "mad cow disease" and its analogues in several exotic species of antelope and wild felids in zoological gardens; and feline spongiform encephalopathy in domestic cats (for review, see [3]).

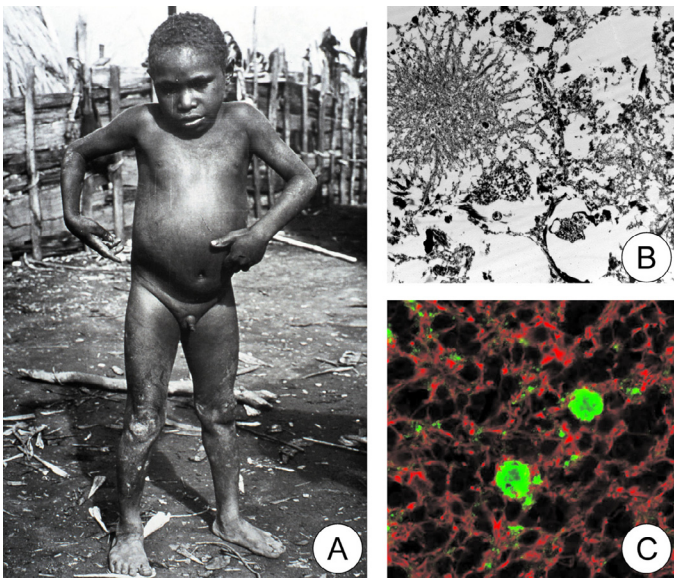

Fig. 1. (A) Kuru-afflicted child (courtesy the late D. Carleton Gajdusek); (B) an electron microscopic view of kuru plaque; amyloid fibrils are readily visible; original magnification, ×10,000; (C) confocal laser microscopy image of kuru plaques (green) surrounded by reactive astrocytes (red) (courtesy Dr. Beata Sikorska, Dept. Molecular Pathology and Neuropathology, Medical University, Lodz, Poland).

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2. Nomenclature

"*Various authors have exhausted the thesaurus to find terminology different from that used by their competing colleagues to describe the production of configurational change of host precursor proteins to β-pleated structure and polymerization of amyloid fibrillogenesis*; [...] *I have facetiously pointed out that the founders of virology define a virus as an obligate parasite of submicroscopic size requiring the informational and energy systems of the host for replication: this embraces viroids, virules, virettes, virinos, nucleating infections, and computer viruses*" [1].

Throughout this review, I will abandon the term "virus", even used in such a broad meaning as Gajdusek suggested, and use through it the interchangeable terms "TSE" or "prion diseases".

3. Prion diseases as a paradigm for brain amyloidoses

Prion diseases are caused by accumulation of abnormal misfolded isoform (PrP^{Sc}) of normal cellular protein (PrP^{c}). Thus, the conversion of PrP^{c} into PrP^{Sc} underlies the disease pathogenesis [4]. PrP^{c} is a highly conserved sialoglycoprotein encoded by a cellular gene mapped to chromosome 20 in man and chromosome 2 in mouse. The gene is ubiquitous; it has been cloned in numerous mammalian species, including marsupials, and there are analogues of this gene in birds, reptiles, amphibians, and fish. Recently, the *PrP* gene was cloned in several exotic species of mammals – Pekingese dog, Amur tiger, and African lion (for review, see [5]).

PrP plausibly is one of the most extensively studied proteins. Human PrP^{c} contains 253 amino acids encoded by an intronless open reading frame (ORF). Three forms of PrP^{c} exist – one completely translocated and two rather infrequent transmembrane variants, ^{Ctm}PrP and ^{Ntm}PrP; the sequence encoding residues 151–165 that form the transmembrane region is highly conserved. Furthermore, PrP^{c}, like βAPP (see below), undergoes endoproteolytic cleavage to yield the 17 kDa N-terminally truncated form C1, while PrP^{Sc} yields a slightly a larger peptide designated C2 [6].

In familial prion diseases, the mechanism is straightforward: the mutation within the gene encoding for PrP^{c} (PRNP) is responsible for the conversion by misfolding of PrP^{c} to PrP^{Sc} [7]. In sporadic prion diseases, the mechanism is totally unclear and either a somatic mutation or a spontaneous conversion has been suggested to explain the pathogenesis. Notwithstanding the cause, the conversion of PrP^{c} to PrP^{Sc} is conformational, likely yielding parallel, in-register-β-sheet forming, steric zipper motifs (for reviews, see [8,9]).

Prion diseases are amyloidoses – i.e. PrP^{Sc} meets the criteria for amyloid – the protein possesses cross beta-sheet conformation and its aggregates are congophilic and birefringent under polarized light and, by electron microscopy, aggregates of PrP^{Sc} form fibrils – called by Prusiner "prion rods" because of their elongated twisted appearance (Fig. 2) [9]. As early as the mid-1980s, D. Carleton Gajdusek, who won a Nobel prize in 1977, introduced the term "β-fibrilloses of the brain" or "transmissible amyloidoses" to stress the resemblance of "prion rods" to many different "non transmissible" amyloids. This similarity to other amyloids, in the form of amyloid plaques, was appreciated already in the 1950s, prior to the era of PrP protein chemistry, when similarities of kuru plaques to plaques in Alzheimer's disease prompted Gajdusek to call kuru "a galloping senescence of the juvenile". Prusiner also readily noticed similarities between prion diseases and Alzheimer's disease [10]. Thus, the idea is not novel, but as with many ideas it has evolved over the last quarter-century.

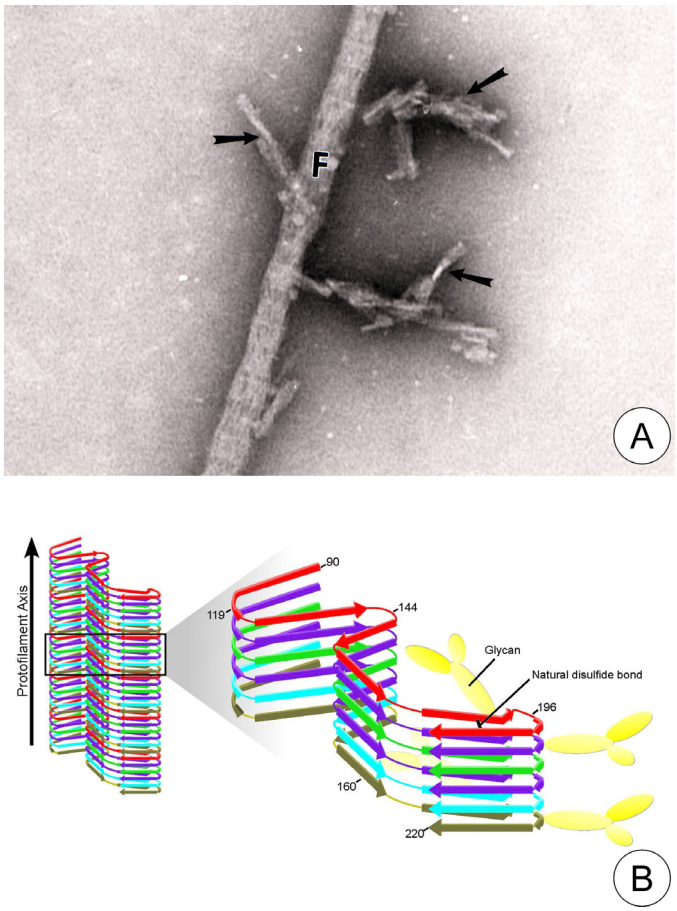

Fig. 2. (A) Prion rods (arrows) attached to a collagen fiber (F); original magnification, ×50,000; (B) a PrP^{Sc} view of the parallel, in-register-β-sheet forming steric zipper motifs. (Courtesy Dr. B. Caughey, Laboratory of Persistent Viral Diseases, NIH/NIAID Rocky Mountain Laboratories, Hamilton, USA.)

4. Amyloids and prionoids

"Amyloid" is a generic term and all amyloids, irrespective of amino acid sequence, are formed in a seeded nucleation mechanism in which a small aggregate (oligomers) of a few amyloid moieties (a seed or a nucleus) seed (nucleate) normal amyloid precursor moieties to change conformation to a β-sheet and, as the process perpetuates, it converts the normal precursor to more and more amyloid. Aguzzi termed those self-aggregate proteins "prionoids" [11] and this term will be used through the rest of this review. However, "true" prions differ substantially from all other prionoids – prions are infectious in the microbiological term in that they spread horizontally between individuals and cause real epidemics like kuru and vCJD in humans and BSE in animals, not to mention iCJD [12]. To discuss the problem more deeply, it is necessary to reflect on the term "infectious." According to the 28th edition of Stedman's Medical Dictionary, "*'infectious' denotes a disease due to the action of a microorganism*". Thus, in my mind at least, it is entirely wrong to describe any peptide as "infectious" even if those structures replicate. Paul Brown, in his lecture at the Neuroprion meeting in Montreal in 2011, said that you may think of rust as a parallel; rust on a metal surface expands (i.e., "replicates") but nobody would call it "infectious". Both Gajdusek and Lansbury and Caughey [13] evoked the metaphor of Ice-9, invented by Kurt Vonnegut in "Cat's Cradle", a metastable isoform of ice that converts all of the water in the world into Ice-9, causing a global catastrophe. Ice-9 is a metaphor to embrace all amyloids. Although there is no evidence of lateral case-to-case spreading of non-transmissible amyloidoses, there is one exception: transmission of AA (reactive or secondary) amyloidosis in captured cheetahs, where it may be responsible for some 70% of deaths [14]. Amyloid fibrils were detected in cheetah feces, which serve as a vehicle of transmission.