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Alzheimer's Disease Pathogenic Proteins, Prionoids and Prions

Luc Marc*

Faculty of Immunology, Vrije Universiteit Brussel Pleinlaan, Brussels, Belgium

Editorial

Prior to the development of molecular genetics, the types of misfolded proteins that build up in the brain as soluble deposits to cause neurodegenerative disorders in the elderly were used to describe these diseases. The deposits were stacks of well organised -sheets, which is how amyloid is defined physically. There are distinct nuclear, cytoplasmic, and extracellular compartments where each kind of amyloid resides. Since the development of molecular genetics, several of these neurodegenerative disorders have been connected to causative genes, and in a startlingly high percentage of cases, these causal genes expressed the same protein that made up the amyloid fibrils that defined the neuropathology in the disease. With the exception of PrPSc, there is no experimental proof that the pathogenic proteins causing the neurological decline that kills patients in neurodegenerative diseases-prions or prionoids-are prions or prionoids. Neurofibrillary tangles, intracellular amyloid aggregates that appear when tau adopts a new -sheet shape, have been linked to cognitive decline for more than a century. This century-old theory, however, was debunked in 2005 when it was discovered that reducing soluble tau in a mouse model of neurodegenerative disease with neurofibrillary tangles prevented the loss of neurons and improved memory function, despite the startling finding that the prion-like neurofibrillary tangles continued to grow [1,2].

The self-replicating prion protein variants that build up in a number of central nervous system transmissible disorders, including scrapie and Creutzfeldt-Jakob disease. Despite the fact that prions are unique infectious agents devoid of nucleic acids encoded by the virus, their identification was based on an archaic paradigm. The neurological function of a person with prion disease gradually deteriorates over time, finally leading to death. Prusiner discovered that the most lethal inoculates included fibrillar aggregates of a proteolytic fragment of the prion protein, PrP27- 30, by methodically sorting through brain samples from scrapie-infected hamsters. The scrapie isoform of the prion protein, PrPSc, an aggregated, alternatively folded conformer of the cellular prion protein, PrPC, is where this fragment originates, according to current knowledge [2].

Prions fit the description given above because they were first identified as real infectious pathogens by means of microbiological techniques. The original protein can seed compartments both *in vitro* and *in vivo* that contain it in a monomeric soluble state, while many other proteins can aggregate into geometrically ordered structures. It would be oversimplified to equate the ability to seed with the term "prion." In contrast to genuine prions, which have produced epidemics in sheep, cows, mink, cats, and people (including iatrogenic and "variant" Creutzfeldt-Jakob disease), any inorganic crystal can seed a supersaturated solution of its cognate salt. The culprits of these disorders were not recognised as prions for many decades because to their obvious infectious traits—communicability and contagiousness—and many famous scientists thought of them as "slow viruses". Understanding the normal physiological functions of ataxin-1, a nuclear protein, led to the discovery of the mechanism through which PolyQ/ataxin-1 destroys neurons. Ataxin-1 in its pathogenic form does not exist in a misfolded form; it does not have any novel secondary structures or -sheets that are not typically found in the brain. Its pathogenic consequences result from changes in its binding affinities with its normal nuclear partners, the transcriptional regulators Capicua and the regulator of RNA splicing RMB17,22, which change the transcriptome and, presumably, have an impact on the viability and function of neurons. Patients with Alzheimer's disease and prion disease both experience progressive, deadly types of dementia. However, mice exposed to PrP prions pass away, while mice exposed to A prions do not [3,4].

Aggregates are harmful, but they affect certain biological pathways in different ways. In contrast to PrP prions, the pathogenic pathway for A aggregates in humans may not be present in mice. Aggregates are not always harmful; rather, cellular malfunction that results in a neurological disorder is brought on by variations in parent proteins. The parent proteins' misfolded or aggregated versions do not necessarily make up these pathogenic variations.A widespread decline in protein synthesis caused by the deregulation of eIF2a, a mammalian translation initiation factor, is linked to catastrophic brain dysfunction in prion disease. It is thought that this amazing finding represents the process via which PrP prions ultimately cause neurotoxicity. The question of whether the self-replicating substance that causes prion illness is physically identical to the neurotoxic entity has come up repeatedly. In this regard, they recently suggested the moniker "PrPL" to designate a putative moiety that is distinct from PrP but may be neurotoxic [5].

When mice produce too much A, two different types of cognitive impairment appear. The first kind is seen in animals with aggressive amyloid deposition-an excess of A prionoids-in which the accumulated amyloid plaques and their associated cytopathology behave like a massive, brain-damaging lesion. Plaque centres no longer contain any neurons, and the 50-micron halo surrounding the cores is made up of twisted, dystrophic neurites and dendrites that have lost some of their spines. Therefore, it is not surprising that cognition varies inversely with plaque load above a specific threshold.

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Conflict of Interest

The author reported no potential conflict of interest.

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***Address for Correspondence:** Luc Marc, Faculty of Immunology, Vrije Universiteit Brussel Pleinlaan, Brussels, Belgium; E-mail: marc.luc@up.ac.za*

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