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Prion biology and its implications for Alzheimer's disease therapeutics

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The deposition of extracellular amyloid β is one of the hallmarks of Alzheimer's disease and cerebral amyloid angiopathy. The formation of amyloid fibrils is one manifestation of the misfolding and aggregation of amyloid β into a prion conformation, which then induces the misfolding of additional copies of amyloid β in a self-propagating process. Prions were first discovered for the PrP protein[1,2] and are the cause of Creutzfeldt-Jakob and mad cow diseases. In 1994, soon after the discovery of PrP-prions, self-propagating forms of unrelated proteins in yeast and other fungi were found to have beneficial, rather than pathological, roles in these organisms.[3] Thus, prions mediate diverse processes in organisms separated by hundreds of millions of years of evolution. Given the early adoption of the term prion to describe these agents in all organisms, from fungi to humans, we do not agree with the suggestion to instead use the term proteopathic seed to describe aggregated proteins that adopt alternative shapes and undergo self-propagation, as Elsa Lauwers and colleagues[4] propose in their Personal View in *The Lancet*

Neurology. To remove any ambiguity, we propose that the prion nomenclature should include the misfolding protein—eg, tau-prion, α-synuclein-prion, and amyloid β-prion.

Lauwers and colleagues[4] argue that cerebral amyloid angiopathy is an amyloid β-prion disease. As in PrP-prion diseases, both Alzheimer's disease and cerebral amyloid angiopathy present in familial and sporadic forms, and amyloid β pathology can be transmitted to animals.[5,6] Human-to-human spread of amyloid β-prions can occur through iatrogenic transmission of cerebral amyloid angiopathy,[7] similar to PrP-prion diseases. However, iatrogenic transmission is rare compared with sporadic and familial Alzheimer's disease and cerebral amyloid angiopathy.[4] Moreover, acquired cerebral amyloid angiopathy is expected to be even rarer in the future, because of safeguards[4] that have eliminated the human-to-human transmission of PrP-prions. Looking more broadly at neurodegenerative diseases, a study with 1.5 million recipients did not show evidence of transmission of Alzheimer's disease by blood transfusion,[4] so a considerably larger sample size would be needed to reach a statistically significant endpoint. Thus, although Lauwers and colleagues[4] advocate for increased surveillance and epidemiological analyses, they also discuss the need to balance the cost–benefit relationships of such studies. Given the prevalence and burden of sporadic and familial Alzheimer's disease and cerebral amyloid angiopathy, large outlays of funds might be better directed to tackle these diseases than very rare iatrogenic cerebral amyloid angiopathy or yet-to-be-detected iatrogenic Alzheimer's disease. Lauwers and colleagues[4] also advocate for the uniform adherence to hospital safeguards against possible transmission; however, these safeguards are already implemented in many hospitals and laboratories worldwide.

Furthermore, Lauwers and colleagues[4] highlight progress in the development of animal and cellular models for evaluating the propagation of prions. Building on the cellular assays for tau-prions,[8] assays developed for amyloid β-prions showed that patient longevity and the severity of Alzheimer's disease are related to the infectivity of tau-prions and amyloid β-prions rather than the amount of insoluble, inert amyloid plaques in post-mortem brain samples (Alzheimer's disease is a double prion disease).[9] Thus, cellular and animal models provide insight into

pathways that either exacerbate or inhibit prion propagation, which might lead to cures for neurodegenerative diseases. Nevertheless, although animal and cellular models can reproduce many aspects of prion propagation, it is important to continuously ask how well these models reproduce the precise features responsible for disease and to make improvements as needed.

The detailed molecular structures of the amyloid fibrils formed by tau, α-synuclein, and amyloid β derived from human meninges have been reported.[10] Such precise structures will facilitate the design of new diagnostics and perhaps also therapeutics; the excitement caused by these structural studies is palpable. However, before drug design can progress apace, we must establish the relationships between the structures of large inert amyloid deposits, the corresponding infective prions, and the toxic species responsible for cell death. Indeed, there has been a litany of failures in Alzheimer's disease therapeutics—measuring inert products of Alzheimer's disease pathogenesis, such as plaques and tangles, has been unproductive.[9] Understanding the mechanism of prion spread and toxicity will lead to therapeutics that can potentially halt disease progression.

To quote Winston Churchill, "Now this is not the end. It is not even the beginning of the end. But it is, perhaps, the end of the beginning." Perhaps we are at "the end of the beginning," and within the foreseeable future, we will be able to initiate the development of effective therapeutics for Alzheimer's disease based on advances in amyloid β-prion biology.

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