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Opinion

Fascinating Stories of Prion Studies: From the Bench to Pharmaceuticals

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Introduction

Since the discovery of prion, continuous works have been undergone to uncover the true picture of prion protein and prion disease molecular mechanism. Several attempts were made to define the structure of prion protein and its association with prion diseases. X-ray, solution NMR, and other high-resolution techniques were employed to reveal the structure of the infective form of PrP. Although the putative PrPC structure of many species was reported, the absence of a crystallized form of PrPSc makes the understanding of the prion disease mechanism difficult. Recently, a group of researchers mimicked cellular PrP and discovered artificial recombinant human PrP that has infectivity potency [1,2]. This artificial rec.hPrP is expressed in bacteria in a reaction that seeded brain-derived sCJD prion [3]. The bioassay revealed vacuolization and loss of neurons, particularly in the hippocampus of mouse after several passages. Prior to this work, a study showed that extracted residue fragments of *Clostridium botulinum* -Rho [cPrD] had amyloid-forming propensities and can undergo conversion to a self-propagating prion conformation [4]. Similarly, research proposed PTMs as a source of novel conformations of ordered protein aggregates *in vivo*. In the study, GPI-anchor obstructs fibril assembly in WT mice while GPI-anchorless mice developed fibrillar, clinical, and pathological disease phenotype after a subsequent prion strain homogenate passage which decrease incubation period and conformational stability of PrP [5]. In the same way, research on cell lines transfected with wild and mutant hPrp expressed by *E. coli* revealed that N-linked glycosylation deficiency impairs the correct localization of human PrP at the plasma membrane, enhancing the protein's PK resistance and increasing aggregation ability [6].

The CRISPER-Cas9 technique assisted PrP knock-out PrP in mouse cell lines were reconstituted with PrPgenes from several animals and tested positive when infected with CDW. The authors concluded such a platform is a key approach to understanding the effect of multiallelic polymorphism in prion disease pathogenesis [7]. A research article reported a breakthrough finding of PrP transgenic Drosophila as a novel assay for mammalian infective prion [8]. Similarly, researchers reported the inflammatory potential of partially desialylated PrPSc was higher than normal sialylated PrPSc. This study was the first to demonstrate that PrPSc can directly trigger proinflammatory responses in microglia [9]. PMCA-based research strengthens the assumption made by Deleault NR et al. [9] showing the host-encoded stimulatory RNA molecules' effect on the pathogenesis of prion disease. In the report, disease phenotype, incubation period, and neuropathological features are distinct when a prion train was replicated in RNA-rich and RNA- free environment [10]. In 2018, a report was made on the potential therapeutic option for prion disease Prion Alliance. A review article concluded that miRNA-based therapies are the next potential options in treating prion disease through multiple mechanisms of action. The group announced that an antisense drug for prion disease

is under development. Antisense Oligonucleotides (ASOs) are short pieces of DNA (15-30 nucleotides) chemically modified to make the drug more potent and stable. They are designed to be the reverse complement (antisense) of the RNA sequence so that the ASO binds to RNA and blocks the translation of prion protein. ASO drug would be delivered by lumbar puncture, binding PrP RNA and lowering the amount of PrP in the human brain. Subsequently, research reported the efficiency of ASOs in slowing down neuropathogenesis and its effectiveness in extending survival rate even after end-stage clinical signs of prion-infected mice [11]. All the above recent advances were made in an attempt to eradicate, manage and treat prion disease and of course, halt the transmission. Regardless, it still remains enigmatic as prion and prion-like animal and human diseases get evolved. However, as briefly summarized, with the current advanced state-of-the-art technologies the eradication of the disease and effective treatment of current cases will not be far from reach.

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