Molecular Mechanisms of Prion Diseases

Efrat Levy*

Department of Psychiatry and Pharmacology, New York University School of Medicine, New York, USA

***Corresponding author**: Efrat Levy, Department of Psychiatry and Pharmacology, New York University School of Medicine, New York, USA, E-mail: elevy@nyulangone.org

Received: November 16, 2021; **Accepted**: November 30, 2021; **Published**: December 07, 2021

About the Study

Prion diseases are invariably fatal neurodegenerative disease of humans and animals. They are unprecedented in the history of medicine because the infectious agent that causes them is a protein molecule that is devoid of a nucleic acid genome. The earliest recorded prion disease is scrapie, first described in the 18th century in sheep and goats and subsequently recognized to be infectious by laboratory transmission to rodents [1]. The name is derived from the tendency of affected animals to rub their fleece against rocks, trees or fences. The mode of transmission of scrapie in the wild is still unclear, although it is known that susceptibility is strongly influenced by the polymorphisms of the sheep prion protein gene.

Based on the great deal of biochemical and molecular genetic work over the past 25 years, it is now recognized that the prion protein can exist in two distinct conformations; the normal cellular form and the infectious form. The two forms have the same primary amino acid sequence and post translational modifications, but differ in their conformations. Although it is clear that the conformations differ, it has proven difficult to determine an atomic-scale structure using high-resolution structural techniques such as NMR and X-ray crystallography, due to mainly the aggregated and heterogeneous nature of the infectious protein. Recently cryoelectron microscopy was used to create a three-dimensional reconstruction of infectious prion fibrils. Recent works demonstrated that these fibrils were composed of two protofilaments with four-rung beta-solenoid as the underlying subunit [2]. Other models have been proposed, most notably structures comprising parallel, but these are based on the noninfectious forms of prion protein amyloid.

The prion hypothesis is now supported by an extensive network of experimental findings. Historically, perhaps the most persuasive piece of evidence was the discovery that mice in which the gene encoding prion protein is ablated are completely resistant to prion disease, demonstrating that endogenous type is an essential substrate for prion propagation. Moreover, it was shown that the species tropis, of prions could be manipulated by the introduction of different prion protein-encoding transgenes into mice. Prions exemplify a mechanism for propagation of biological information that is independent of nucleic acid and that has been found to occur in other organisms including yeast, filamentous fungi and bacteria. Self-templating changes in protein conformation have recently been shown to participate in a number of physiological phenomena, including innate immunity, formation of membraneless cellular organelles and possibly even memory formation in the brain. A prion-like mechanism may also underlie the spread within the central nervous system of protein aggregates involved in other neurodegenerative diseases including Alzheimer's disease, Parkinson's disease and tauopathies [3].

Human prion diseases exist in sporadic, genetic or infectious forms, whose origins can rationalized in terms of the molecular theory of prion propagation. The common prion disease of humans, sporadic Creutzfeldt-Jakob disease has a worldwide occurrence of one case per million people per year. It is characterized by a rapid progressive dementia and myoclonus. Once symptoms appear, patients typically succumb within 1 year. Neuropathologically, sporadic Creutzfeldt-Jakob disease is characterized by abundant spongiform change in the brain, with minimal accumulation of prion protein containing amyloid plaques [4ofSentrainctelatedpriondiseasenofhuma,geneticCreutzfeldt-Jakocdisea