

CHRISTMAS LECTURE

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Prions: Minimalist pathogenic agents with maximum complexity

The term prion was coined by Stanley Prusiner to define a new biological agent that based its infectious behavior in their self-replicating abilities. While this feature is shared by many other infectious agents, this peculiar new pathogen was purportedly composed of a sole protein. This "heresy", referred as the protein-only hypothesis, attributed to a single protein the capability to display a wide diversity of structures with different pathogenic properties. For decades this hypothesis has motivated to the scientific community trying to decipher the heterodox features of this new pathogen. Recently the hypothesis has been demonstrated. The final probe has required of the replication of prions in a test tube by using the technique of PMCA (Protein Misfolding cyclic amplification), a method that allows the infectious agent can be amplified at the expense of a protein (PrP) which is found primarily on the central nervous system.

A key characteristic of prions is their ability to infect some species and not others. This phenomenon is known as transmission barrier. Compelling evidence indicates that the transmission barriers are closely related to differences in PrP amino acid sequences between the donor and recipients of infection. Unfortunately, the molecular basis of the transmission barrier phenomenon and its relationship to prion structures is currently unknown and we cannot predict the degree of a species barrier simply by comparing the prion proteins from two species. We have conducted a series of experiments using PMCA technique that mimics *in vitro* some of the fundamental steps involved in prion replication *in vivo*, albeit with accelerated kinetics. We have used PMCA to efficiently replicate a variety of prions from, among others, mice, hamsters, bank voles, deer, cattle, sheep, and humans. In addition, we have also generated prions that are infectious to species hitherto considered to be resistant to prion disease. These studies are being focused on understanding how these pathogens with an irreducible simplicity can self-replicate, display a diversity of conformations acquiring different properties and become infectious.

December 16, 2011
13.00 H
In CIC biomaGUNE

