Poster P.10.64

FULL ATOMISTIC MODEL OF PRION STRUCTURE AND CONVERSION

Biasini E.*

Dulbecco Telethon Institute & Dip. CIBIO, University of Trento ~ Trento ~ Italy

Full atomistic model of prion structure and conversion.
Since their discovery, prions have stood as enigmatic agents that defy the concepts of infectivity and genetic inheritance due to their capacity of propagating conformationally-encoded information in absence of nucleic acids (1). However, after more than 30 years of investigation, the high-resolution structure of prions as well as their mechanism of replication have remained elusive (2). In an attempt to fill this gap, different computational models have been proposed in the past, but they are now inconsistent with recently collected results (2).
In this work, using molecular modelling techniques, we constructed an all-atom model of a mouse prion integrating a wide array of updated experimental constraints, such as: (i) cryo-EM and X-ray fiber-diffraction, showing a folding compatible with a 4-rung-β-solenoid (4RβS) architecture (3,4); (ii) Circular dichroism and FTIR spectroscopy, which ruled out the presence of α-helices (5); (iii) Limited proteolysis, which mapped solvent-accessible residues as well as the presence of an intact disulphide bond (6,7); and (iv) The possibility of accommodating complex glycans, which was not accounted in the previous models (8). The stability of the new 4RβS model, assessed by Molecular Dynamics (MD) simulations, was found to be comparable to that of the β-solenoid architecture of Het-s, a naturally-occurring prion of yeast. Importantly, we coupled the information of the new 4RβS structure with a recently developed path sampling technique to perform a simulation of the conformational transition from PrPC, the normal form of the protein, to PrPSc, the misfolded and infectious conformation (9). The result is a transition pathway with atomistic resolution in which the C-terminal rung of the solenoid acts as a primary conversion surface for the N-terminus of PrPC, followed by a cascade of conformational changes where each newly formed rung templates the formation of the following one, ultimately leading to the complete conversion of PrPC into PrPSc. The new 4RβS model, together with the atomistic reconstruction of prion conversion, illuminate how the information encoded into the conformation of a protein could be inherited in a directional fashion, a concept underlying the infectious nature of prions (10). Furthermore, it provides an unprecedented opportunity for the rational design of anti-prion compounds acting by directly targeting the replication process.

Primo Modello Atomistico della Struttura e della Replicazione di un Prione

1. SB Prusiner. Science 1982; 216(4542):136-144.
2. H Wille and JR Requena. Pathogens 2018; 7(1):20
3. E Vazquez Fernandez et al. PLoS Pathog 2016; 12(9):e1005835
4. H Wille et al. Proc Natl Acad Sci USA 2009; 106(40):16990-16995
5. JR Requena and H Wille. Prion 2014; 8(1):60-66
6. E Welker et al. J Biol Chem 2002; 277(36):33477-33481
7. E Vazquez Fernandez et al. PLoS Pathog 2012; 14(1):e1006797
8. IV Baskakov and E Katorcha. Front Neurosci 2016; 10:358
9. G Tiana and C Camilloni. J Chem Phys 2012; 137(23):235101
10. Spagnolli et al. PLoS Pathog 2019; Jul 11;15(7):e1007864

Malattia di Creutzfeldt-Jakob

Coordinator: Emiliano Biasini
Duration (N. Years): 5
Starting year: 2015

Telethon Project (nr):

TCP14009

Disease Name:

Creutzfeldt-Jakob Disease

Keywords:

Prion, Neurodegeneration, Molecular Dynamics