

# Conformational conversion and prion disease

Liang Shen and Hong-Fang Ji

Because of mechanistic similarities between prion propagation in mammals and fungi, Tuite and Serio recently proposed (The prion hypothesis: from biological anomaly to basic regulatory mechanism. *Nature Rev. Mol. Cell Biol.* **11**, 823–833 (2010))<sup>1</sup> that similarly to fungal prions, which are thought to act as phenotype regulators, prions in mammals should be considered as a basic regulatory mechanism instead of a biological anomaly. However, by considering the behaviour of prions, we argue that the fact that mammalian and fungal prions use a similar mechanism of conformational conversion is not enough to suggest that they are not just infectious agents.

Conformational conversion of a protein from an  $\alpha$ -helix to a  $\beta$ -strand is usually associated with a major change in the tertiary structure, which may alter its physiological function and even be implicated in severe diseases. Prion diseases in mammals are one such example; they are caused by the conformational conversion of normal cellular prion protein (PrP<sup>C</sup>) into an abnormal isoform (PrP<sup>Sc</sup>)<sup>2,3</sup>. Some fungal proteins can, like prions, also exist in a range of stable conformations and transition between these states under physiological conditions<sup>4</sup>; thus, this type of protein is known as a fungal prion.

First, the conformational conversions of PrP<sup>C</sup> to PrP<sup>Sc</sup> in mammals may result in two outcomes: loss of function of PrP<sup>C</sup> and/or gain of toxicity of PrP<sup>Sc</sup>. If PrP<sup>C</sup> plays an important part in the regulatory pathways that control cellular phenotypes, similarly to fungal prions, loss of its function as a result of conversion to PrP<sup>Sc</sup> should lead to the development of neuropathological and phenotypic alterations that are similar to those seen in mammals with prion diseases. However, PrP-knockout mice, in which the

gene encoding PrP has been deleted, do not develop an overt phenotype other than resistance to prion diseases<sup>5–7</sup>. Thus, it seems unlikely that prion pathogenesis is simply due to a loss of PrP<sup>C</sup> physiological function.

In contrast to loss of function of PrP<sup>C</sup>, many studies suggest that toxic gain of function of PrP<sup>Sc</sup> gives rise to the pathogenic features of prion diseases<sup>8–10</sup>. It has been proven that the accumulation of PrP<sup>Sc</sup> is linked to apoptotic cell death in animal models and in humans<sup>8</sup>, and a PrP peptide (PrP<sub>106–126</sub>) has been shown to be neurotoxic to hippocampal cultures, mixed cerebellar cultures and primary neuronal cultures<sup>9,10</sup>. Some attempts to determine the infectious properties of aggregates produced *in vitro* from recombinant PrP found that PrP<sup>Sc</sup> infectivity was obtained *de novo* from recombinant mouse PrP<sup>C</sup> (PrP<sub>89–230</sub>), as shown by transmission studies to transgenic mice PrP<sup>C</sup> (PrP<sub>89–231</sub>)<sup>11</sup>. More recently, recombinant PrP<sup>C</sup> converted into a cross- $\beta$ -sheet amyloid was proven to induce prion diseases in hamsters<sup>12</sup>. Unlike mammalian prions, the conformational conversion of fungal prions does not cause diseases but instead modifies the functions of their protein determinants in a self-sustaining way<sup>1</sup>, implying that no toxic products are generated in this process. In addition, the conformational conversion does not seem to be specific to prions, as proteins that adopt different secondary structures under different conditions have not been shown to be associated with disease<sup>13</sup>. This indicates that conformational conversion is not intrinsically relevant to the occurrence of diseases.

In summary, owing to lack of PrP homologues in fungi, a conclusion on the potential role of mammalian prions cannot be drawn merely based on their mechanistic similarities to fungal prions. More clues regarding

the pathogenesis of prion diseases may be obtained from studies on non-mammalian prions<sup>14,15</sup>, as non-mammals also express PrP-encoding genes but do not develop prion diseases.

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## Competing interests statement

The authors declare no competing financial interests.