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An on-pathway step explains the kinetic of prion amyloid formation

The pathogenic process of the transmissible spongiform encephalopathies diseases, is typically associated with the conformational conversion of the so-called prion protein (PrP). The protein-only model asserts that the misfolded isoform represents the infectious prion agent, self-propagating by binding to the normal PrP and inducing its conversion to the abnormal form [6]. This scenario was quantitatively described as a nucleation-dependent amyloid polymerization [4]. However, we obtained experimental results inconsistent with this theory. Indeed although the dynamics of polymerization resemble a simple nucleus-dependent fibrillogenesis, neither the initial concentration dependence nor off-pathway hypothesis fit completely with experimental results when submitted to theoretical models [1], comparable discrepancies were obtained by other [2,3,4,5]. We thus hypothesise the existence of an on-pathway before nucleation associated with a conformational change that generates intermediate conformations compatible with nucleation and polymerization. Using electron microscopy analysis, we observed odd-structures that behaved as precursor of the amyloid formation. We have developed a quantitative model with an explicit description of microscopic processes that takes into account our observations. Then, we confronted, under several conditions, the model predictions with the experimental data. It appears that they are in a good agreement. Several conclusions can be drawn from this model that better explain the nucleation kinetic barrier and prion misfolding. We discuss the consequences of the model in the light of the *in vivo* phenomenon.

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