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Hypothesis

Spontaneous conversion of PrP^{C} to PrP^{Sc}

Eugene Sulkowski

Roswell Park Cancer Institute, Buffalo, NY 14263, USA

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Octa-repeats of prion proteins (PrP) contain histidine and tryptophan residues which are known to function as ligands for transition metals. It is proposed that the spontaneous conversion of the PrP^{C} (cellular) isoform into PrP^{Sc} (scrapie) isoform may be triggered by the coordination of these metals.

Prion protein; Transition metal; Conformational isoform; Conversion of PrP^{C} to PrP^{Sc}; Prion disease

1. INTRODUCTION

Prion proteins (PrP) exist in two conformational forms: the 'cellular' form (PrP^{C}) of unknown function, and the 'scrapie' from (PrP^{Sc}) believed to be responsible for the degenerative neurological disorders of animals and humans [1]. The conversion of the PrP^{C} isoform into the PrP^{Sc} isoform may occur spontaneously (sporadic and familial diseases) or be brought about via conformational imprinting by exogenous PrP^{Sc} (transmitted disease).

What could possibly trigger 'spontaneous' conversion of a PrP^{C} isoform to a PrP^{Sc} isoform?

Any attempt at answering this question must encompass the recognition of a structural feature in a prion molecule which can constitute a nucleation site for that conversion. To this end one can avail oneself of the information emanating from several laboratories.

(i) There is a positive correlation between the multiplicity of octa-repeats in a prion protein and the predisposition to a prion disease [2,3].

(ii) The octa-repeats of prion proteins (sheep, mouse, rat, human, bovine, hamster) contain (Fig. 1) histidine and tryptophan residues [4].

(iii) The histidine and tryptophan residues may serve as ligands (electron donors) for the coordination of transition metal ions: Co^{2+}, Ni^{2+}, Cu^{2+} and Zn^{2+} [5,6].

Interestingly, the hexa-repeats of chicken prion-like protein (Fig. 1) contain histidine residues but lack tryptophan residues [7]. The resident tyrosine residues are unlikely to serve as ligands for the aforementioned transition metals. Previously, it was postulated that the binding of the transition metals to octa-repeats may cause a change in their conformation [8]. This is unlikely be the case with hexa-repeats.

Correspondence address: E. Sulkowski, Visiting Professor, Department of Molecular and Cellular Biology, Roswell Park Cancer Institute, Elm and Carlton Streets, Buffalo, NY 14263, USA. Fax: (1) (716) 845-8169.

2. HYPOTHESIS

The conformational changes induced by the coordination of transition metal ions to the octa-repeats of a prion protein will result in the spontaneous conversion of a PrP^{C} isoform into a PrP^{Sc} isoform: an agent of a prion disease [1].

One could envisage at least two different pathways for the $PrP^{C} \rightarrow PrP^{Sc}$ conversion within the framework of this hypothesis.

(i) The coordination of transition metals to a PrP^{C} molecule (monomer) results in a conformational change in its octa-repeat tandem; this change propagates itself to the remainder of a prion molecule with an attendant increase of its surface hydrophobicity; the dimerization of the prion monomers ensues. The overall result is the emergence of a PrP^{Sc} dimer [9,10].

(ii) The transition metals coordinate to a PrP^{C} monomer; a second PrP^{C} monomer (carrying no metals of its own) comes into contact with the first one and forms a 'metal sandwich' dimer [11,12]. A conformational change, resulting from this dimerization, leads to the generation of a PrP^{Sc} isoform.

Whatever the pathway might be, the present hypothesis stipulates that the binding of transition metals constitutes a sine qua non event in the triggering of the 'spontaneous' conversion of PrP^{C} to PrP^{Sc}. In all likelyhood, the PrP^{C} isoform may bind a limited number of transition metal ions without being converted into the PrP^{Sc} isoform. However, once a threshold number of

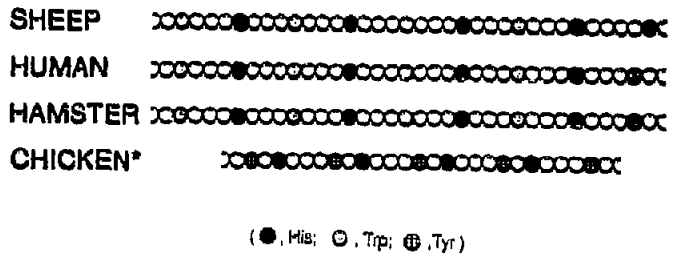

Fig. 1. The octa-repeats of mammalian prion proteins and a hexa-repeat of chicken prion-like* protein.

metals has been attained, the conversion would be triggered [2,3].

Should this be the case, one is immediately compelled to ask a pivotal, and testable, question: could transition metals induce the $PrP^{C} \rightarrow PrP^{Sc}$ conversion in vitro?

Some structural aspects of this hypothesis (binding of metals, conformational change, dimerization) could be probed with synthetic tandem repeats by physicochemical means (CD, NMR, chromatography, electrophoresis). Biological aspects could call for the construction of chimeric proteins (swapping of tandem repeats).

Would a prion protein, harboring an avian hexa-repeat tandem in place of its own octa-repeat tandem, be prone to undergo a conformational conversion? If not, then possibly the mere substitution of tryptophans by tyrosines in the octa-repeat tandem could also impede the conversion.

Would an avian prion-like protein, harboring a prion octa-repeat tandem in place of its own hexa-repeat tandem, undergo a conformational change and produce a pathogenic isoform? If so, then the substitution of tyrosines by tryptophans in the hexa-repeat tandem could alone lead to the emergence of a pathogenic isoform.

It should be pointed out that the postulated binding of transition metals will above all depend on the coordination by histidine residues [8]. Therefore, a radical reconstruction of the octa-repeat and hexa-repeat tandems should call for the substitution of resident histidines by amino acids which cannot function as the ligands for the transition metals. This must be somewhat tempered, however, by a possibility that the replacement of histidines might be detrimental to the putative physiological functions of the native tandem repeats. After all, the histidines are conserved in both hexa- and octa-repeats, pointing to their structural/functional importance. It is of note that chemical modification of histidines [13] inactivated PrP^{Sc} (earlier treated with proteinase K), but that biological activity of PrP^{Sc} was restored upon the reversal of that modification [14]. Thus, histidines residing outside the octa-repeat tandem have been previously shown to be important for the exogenous infection by prions. Parenthetically, this could possibly indicate the involvement of transition metals also in the PrP^{C}/PrP^{Sc} conversion brought about by conformational imprinting.

The octa-repeats have been recognized for some time as potentially important structural motifs of prion proteins on account of their content of glycine and proline residues [15–18]. This hypothesis, in turn, invokes the putative role of histidine and tryptophan residues. A conformational change induced by the coordination of transition metals, would par force encompass the contributions of all the constituents of the octa-repeats.

If the present hypothesis is valid, then a transition metal(s) could be recognized as the etiological agent(s) of sporadic and familial prion diseases.

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