Pathologie Biologie 62 (2014) 96–99

Available online at
ScienceDirect
www.sciencedirect.com

Elsevier Masson France
EM|consulte
www.em-consulte.com

60th anniversary

Prions: A model of conformational disease?

Prions : une maladie conformationnelle ?

F. Morinet

Pôle Biologie-Pathologie-Physiologie, Université Paris Diderot-Paris Sorbonne Cité, Groupe Hospitalier Saint-Louis–Lariboisière - Fernand-Widal, Assistance publique–Hôpitaux de Paris, 1, avenue Claude-Vellefaux, 75010 Paris, France

ARTICLE INFO

Article history:
Received 22 November 2013
Accepted 17 February 2014
Available online 20 March 2014

Keywords:
Prions
Degenerative disease
Conformational disease
Folding
β sheet

ABSTRACT

The discovery that a protein could mimic viral and bacterial pathogens around 1980 by Stanley Prusiner was unexpected. Evidence shows now that Creutzfeldt-Jakob disease and related disorders are caused by prions. Prions and, for example neurodegeneratives diseases, arise from the same general disease mechanism. In each, there is abnormal unfolding and then aggregation of proteins. The protein conformational changes associated with the pathogenesis of protein misfolding disorders produce β sheet rich oligomers that are partially resistant to proteolysis and have a high tendency to form amyloid-like aggregates. It is important to distinguish between prions and amyloids: prions need not to polymerize into amyloid fibrils and can undergo self-propagation as oligomers. The prion diseases are characterized by the conformational conversion of PrP^{c} to PrP^{sc}, the fundamental even underlying prion diseases. Despite the obvious differences between prions and conventional infectious microorganisms, prions fulfill the Koch's postulates. Meaningful treatments are likely to require cocktails of drugs that interfere with the conversion of precursor into prions and enhance the clearance of prions; such an approach may find application in the more common degenerative diseases.

Mots clés :
Prions
Maladies neurodégénératives
Maladies conformationnelles
Repliement
Feuillet β

RÉSUMÉ

La mise en évidence qu'une protéine pouvait avoir un caractère infectieux dans le début des années 1980 par Stanley Prusiner était novatrice et tout à fait inattendu. Le terme de prion fut proposé ; il est maintenant admis que, notamment, la maladie de Creutzfeldt Jacob est due à une protéine prion. Le mécanisme commun des maladies dégénératives impliquant l'accumulation de protéines pathologiques fait intervenir un défaut de repliement de ces dernières, on parle alors de maladies conformationnelles. Ces protéines pathologiques sont riches en feuillet β et peuvent former dans certaines circonstances des fibrilles amyloïdes ; uniquement 10 % des maladies humaines à prions forment ces dépôts amyloïdes, loin de l'équilibre. Les maladies à prions résultent d'un changement conformationnel d'une protéine cellulaire PrP^{c} en une protéine pathologique PrP^{sc}. Cette protéine infectieuse remplit les postulats de Koch de manière analogue à un agent microbien. Il n'existe pas de traitement à l'heure actuelle pour les maladies à prions même si la piste structurale, c'est-à-dire inhiber le changement de conformation et l'accumulation de protéines pathologiques reste séduisante.

1. Introduction

My interest for prion and conformational disease dates back in 1986. Effectively as a medical doctor I was interested by unstable hemoglobins and during my PhD thesis I was confronted with inclusion bodies since I was producing capsid proteins of an eukaryotic virus, the Parvovirus B19, in bacteria [1] Also I was interested in the folding of proteins and I have read with a great interest in 1997 the paper of Carrell and Lomas in the *Lancet* concerning conformational disease [2]. These latter can be divided in aggregates and amyloidosis diseases. Prions induced aggregates and sometimes fibrils (10%).

Since 2000, I have been working on the regulation of viral expression by hypoxia, notably and always Parvovirus B19. Is it far

E-mail address: frederic.morinet@sls.aphp.fr

http://dx.doi.org/10.1016/j.patbio.2014.02.003
0369-8114/

from my interest in prions? Not at all; very recently Holmes published that the production of prion [MOT3^{+}] in yeast is eliminated by hypoxia [3], although the intimate mechanism remains at present not well defined.

2. Epidemiology

There are several types of human prion diseases, each beginning with pathological processes in a different brain region and leading to distinct functional deficits: cognition (Creutzfeldt Jacob disease [CJD]), movement control (Gerstmann-Straussler-Scheinker syndrome [GSSS]) or sleep and autonomic functions (fatal familial insomnia [FFI]).

But the most common human prion disease is sporadic CJD; it has an annual incidence range between one or two cases per million per year worldwide [4]. The disease duration varies, and major determinant of survival such as age at onset, gender and PRNP codon 129 genotype have been identified [5]. The PRNP is the chromosome gene located on the short arm of chromosome 20 encoding the prion protein (PrP). The one consistent pathological feature of the prion diseases is the accumulation of amyloid material that is immunopositive for PrP; the normal cellular PrP^{c} is a soluble protein rich in α helix whereas PrP extracted from the brains of affected individuals, PrP^{sc}, is highly aggregated and has a greater content of β-pleated sheets. The pathology of prion diseases shows varying degrees of spongiform vacuolation, gliosis and neuronal loss.

In the 1980s and 1990s, the UK outbreak of bovine spongiform encephalopathy (BSE) in cattle which origin is still remaining a mystery, and the subsequent human cases of a novel variant of CJD (vCJD) linked to the bovine disease were described [6]. 2012 looks like being the first year since 1995 without a reported case. All confirmed patients so far have had a particular prion protein genotype (methionine homozygotes at codon 129), but people who are either homozygous for valine or heterozygous at this codon might have a longer incubation time, so a second wave of vCJD related to consumption of contaminated meat remains a possibility. Effectively, from Kuru studies, another transmissible spongiform encephalopathy, which resulted from cannibalism in Papua New Guinea until 1950s, John Collinge and colleagues suggested that incubation periods of infection with human prions can exceed 50 years [7,8]. The total number of cases of vCJD in the UK in 1995–2011 was 176 with another 49 being recorded in 11 other countries. UK investments in prion disease between 1997 and 2010 was £30 million, more that for hepatitis B (£12 million) but less that HIV (£461 million) [9].

3. Conformational disease

A common feature of conformational diseases is that the proteins in the aggregates are usually devoid of helical regions, present in the form of β-sheets and contain high percentage of posttranslational modifications. In addition to prions' related diseases, there are others neurodegenerative diseases such as Alzheimer, Parkinson, Huntington's diseases and also cataract and type II diabetes [10]. In general these diseases are largely sporadic with late onset disorders although many of the diseases specific mutant proteins are expressed in embryogenesis.

The protein components of eukaryotic cells face acute and chronic challenges to their integrity. Eukaryotic protein homeostasis, or proteostasis, enables healthy cell and organismal development and aging and protects against disease. Because the fidelity of the proteome is challenged during development and aging, and by exposure to pathogens that demand high protein-folding and trafficking capacity, cells use stress sensors and inducible pathways to respond to a loss of proteostatic control; these include the Heat Shock Response, the proteasome and the Unfolded Protein Response. An age-associated decline in proteostatic control in concert with an increase in protein oxidation and modification that exacerbates aggregation challenges the maintenance of proteostasis during aging, offering a partial explanation for why many diseases are age onset.

4. A new paradigm

Before 1972, it was assumed that all infections were transmitted through the DNA and RNA carried by viruses and bacteria. Transformation continues to provide the most compelling evidence that the DNA is genetical material, a protracted saga which has begun in 1928 when Griffith reported that an non-virulent strain of the *pneumococcus bacterium* could be converted to a virulent strain using an extract of heat-killed virulent pneumococcus [11]. In 1944, Avery et al. reported that the active principle was a nucleic acid of the deoxyribose type [12].

Recent experiments in yeast showed that proteins could transform cells in the same format sense that is so convincing for DNA [13]. Yeast cells have a prion-like factor called [PSI^{+}]; it results from self-propagating aggregation of Sup35p, a protein required for efficient termination of translation. The [PSI^{+}] aggregates of Sup35p enhance the ability of ribosomes to read through non-sense mutations. The [PSI^{+}] prion propagates when a misfolded version of the Sup35 protein templates the aggregation of the properly folded Sup35 protein, thereby converting a [psi^{-}] cell to a [PSI^{+}] cell. Laboratories have also used procedures that enabled to purify Sup35p aggregates to transform a [psi^{-}] cell to [PSI^{+}] and this was a success. The [PSI^{+}] trait newly acquired by transformation is then transmitted from generation to generation. Infectivity with these aggregates is sensitive to proteinase but not to DNAse.

5. Lessons not from but for bacteria

Many biochemical pathways, from DNA replication to protein degradation, have been modeled first in bacteria. However, despite it has been long recognized that heterologous protein expression in bacterial cell factories results often in the formation of insoluble deposits composed essentially by the target protein known as inclusions bodies (IBs) as advocated in my introduction, only recently some groups have dared to exploit this well-characterized phenomena to model amyloid formation [14]. IBs bind Congo Red, the typical amyloid dye and low-resolution techniques denote the presence of signals corresponding to tightly packed intermolecular β-sheets, similar to those in amyloid fibrils. These IBs are toxic to neuronal cultured cells as amyloid material; Het-s, from the fungus *Podospora anserina*, was the first prion protein whose bacterial IBs were shown to display amyloid-like properties. The increasing medical and economic impact of aggregation – linked diseases in our society as notably Alzheimer and Parkinson diseases has fuelled the development of methods to identify chemical compounds that can interfere with amyloidogenic pathways. Assays using IBs are in development to identify and characterize amyloid modulators in large compound libraries [15].

In vitro, aggregation is irreversible under physiological conditions. Nevertheless, the cells of bacteria, plants, and fungi have evolved machinery to neatly extract polypeptide chains from large aggregates and refold them to the native state. Effectively, Rosenzweig et al. identified interaction sites within a chaperone system consisting of a HSP chaperone (bacterial Dnak) and a protein-remodeling adenosine triphosphatase of the AAA+ family (bacterial ClpB or yeast Hsp104) [16]. Nuclear magnetic resonance (NMR), crystallographic, and biochemical studies revealed a series