Virus Research xxx (2014) xxx–xxx

Contents lists available at ScienceDirect

Virus Research

journal homepage: www.elsevier.com/locate/virusres

Prion and prion-like diseases in animals

Q1 Patricia Aguilar-Calvo[a], Consolación García[a], Juan Carlos Espinosa[a], Olivier Andreoletti[b], Juan María Torres[a,*]

[a] Centro de Investigación en Sanidad Animal (CISA-INIA), 28130 Valdeolmos, Madrid, Spain
[b] INRA, UMR 1225, Interactions Hôtes Agents Pathogènes, Ecole Nationale Vétérinaire de Toulouse, 23 chemin des Capelles, 31076 Toulouse Cedex, France

ARTICLE INFO

Article history:
Available online xxx

Keywords:
Prion
Amyloid
Amyloidosis
Protein misfolding
Protein self-templating
Prion-like transmission

ABSTRACT

Transmissible spongiform encephalopaties (TSEs) are fatal neurodegenerative diseases characterized by the aggregation and accumulation of the misfolded prion protein in the brain. Other proteins such as β-amyloid, tau or Serum Amyloid-A (SAA) seem to share with prions some aspects of their pathogenic mechanism; causing a variety of so called prion-like diseases in humans and/or animals such as Alzheimer's, Parkinson's, Huntington's, Type II diabetes mellitus or amyloidosis. The question remains whether these misfolding proteins have the ability to self-propagate and transmit in a similar manner to prions. In this review, we describe the prion and prion-like diseases affecting animals as well as the recent findings suggesting the prion-like transmissibility of certain non-prion proteins.

1. Introduction

Prion diseases or Transmissible Spongiform Encephalopaties (TSEs) are fatal neurodegenerative diseases that affect a diversity of mammal species including Creutzfeldt–Jacob disease (CJD), kuru, Gerstmann-Sträussler-Scheinker disease (GSS), and fatal familial insomnia (FFI) in humans, as well as scrapie in sheep and goats, bovine spongiform encephalopathy (BSE) in cattle, and chronic wasting disease (CWD) in deer and elk. Prion diseases are characterized by long incubation times (from months to decades), development of neuropathological alterations and symptoms primarily neurological including behavior abnormalities, motor dysfunction, cognitive impairment and cerebral ataxia. Prion diseases do not produce immune response and nowadays no effective therapies are available for their treatment.

Prion diseases are caused by the conversion of the physiological cellular prion protein (PrP^C) into a pathogenic β-sheets enriched isoform designated PrP^{Sc}, which is able to self-propagate by recruiting PrP^C. This conformational change confers PrP^{Sc} with an increased tendency to aggregate, insolubility in non-ionic detergents, high resistance to heat and chemical sterilization, and partial resistance to protease digestion. The concept of proteinaceous infectious particles, "Prions", was first recapitulated in the "Prion Protein Only Hypothesis" (Prusiner, 1982). To date, a number of studies have supported this contention, including the successful induction of neurodegenerative diseases just from recombinant amyloid forms of prions (Castilla et al., 2005; Colby et al., 2009; Legname et al., 2004) or in combination with certain lipids and RNA factors (Wang et al., 2010). Nevertheless, some findings suggest that the misfolded PrP^{Sc} protein alone is not necessarily infectious by itself and needs some cofactors to self-propagate (Deleault et al., 2012; Saa et al., 2012; Telling et al., 1995). Hence, some authors proposed that PrP^{Sc} formation and infectious agent replication might constitute two separated processes where infectivity could lay on other non-PrP structures (reviewed in Manuelidis, 2013).

Despite these arguments, prion diseases are entirely dependent on the expression of endogenous PrP^C, as confirmed by the total resistance of *prnp* knock-out mice to prion infection (Bueler et al., 1993; Prusiner et al., 1993). PrP^C is a glycosylphosphatidylinositol (GPI)-anchored plasma membrane protein encoded by the *prnp* gene which is well conserved throughout evolution in mammals (Nicolas et al., 2009). PrP^C is mostly expressed in central nervous system (CNS) but also in the lymphoreticular system (LRS), skeletal muscle, heart, kidney, digestive tract, skin, blood plasma, mammary gland and endothelia (Nuvolone et al., 2009). Despite its ubiquitous expression and distribution, its physiological function is not yet clear.

The mechanism by which PrP^C converts into PrP^{Sc} adopting the capacity to self-template is neither well-known. PrP^C can fold into a variety of thermodynamically stable PrP^{Sc} conformers (Prusiner, 1998; Wiltzius et al., 2009) whose mixture in a relative proportion may result in different prion strains (Angers et al., 2010). Each prion strain displays a specific disease phenotype (including incubation times, clinical signs, and histopathological lesions

* Corresponding author. Tel.: +34 91 620 23 00; fax: +34 91 620 22 47.
E-mail address: jmtorres@inia.es (J.M. Torres).

http://dx.doi.org/10.1016/j.virusres.2014.11.026
0168-1702/

and PrP^{Sc} deposition patterns in the brain) which is faithfully recapitulated upon serial passage within the same host genotype (Beringue et al., 2008b; Collinge and Clarke, 2007). Prion strains may arise upon replication and transmission by "mutation" and/or "adaptation". However, the molecular mechanism by which the range of PrP^{Sc} conformers would be produced and selected has not been yet elucidated. One possibility is that each PrP^{Sc} conformer might require a unique set of cofactors to propagate efficiently, and that the distribution and/or availability of these cofactors vary among different animal species, individuals or even distinct cell types. In line with this view, it was reported that different cell types within the same host can offer unique environments and selective pressures, each resulting in the emergence of different mutants as major constituents of the evolving population (Aguzzi and Sigurdson, 2004; Li et al., 2010; Mahal et al., 2007; Tremblay et al., 2004). On the other hand, studies in yeast have provided fundamental information for understanding the phenomenon of prion strain. A direct correlation between the frangibility (propensity to break) of yeast PrP^{Sc} fibrils and their rate of replication have been reported (Immel et al., 2007; Tanaka et al., 2004, 2006) and later extended to mammalian prions (Legname et al., 2006). Deciphering the structural features of PrP^{Sc} is a key issue to understand the molecular basis of prion formation, adaptation and propagation. Despite great efforts, the detailed tertiary structure of PrP^{Sc} is still unknown due to its insolubility and propensity to aggregate. Therefore, only partial structural information is available from low resolution techniques which failed to produce a shared explanation for the infectious capacity of prions (reviewed in Requena and Wille, 2014).

The ability to misfold and self-propagate is not exclusive of prion proteins. Several neurodegenerative and non-neurodegenerative disorders are associated with the accumulation of self-templating amyloid forms of specific proteins in various organs and tissues of animals and humans. This heterogeneous group of diseases, called amyloidosis, are caused by the conformational change of a physiologically soluble protein into a β-sheet enriched form which self-assembly into amyloid fibrils. Similarly to prions, this conformational change triggers insolubility, aggregation and resistant to physical denaturants favoring the amyloid deposition and disrupting the physiological function of the tissues/organs where accumulates. The pathology and pathogenesis of amyloidosis are highly variable depending on the protein that causes the disease and the factors provoking this misfolding.

To date, at least 28 different misfolding proteins, also called amyloid precursors, have been reported in humans and animals; including tau and Amyloid Precursor Protein (APP) in Alzheimer's disease, huntingtin in Huntington's disease, Serum Amyloid-A (SAA) in systemic amyloidosis or islet amyloid polypeptide in Type II diabetes mellitus. The exact mechanism through which these misfolding proteins are transformed and aggregated remains unknown but is reminiscent of prion replication. Thereby, amyloidosis have been labeled as "prion-like diseases" and included in the group of protein misfolding disorders (PMDs); where prion diseases belong. Moreover, increasing evidences attribute potential prion-like infectious properties to some of these amyloid precursors. In this way, tau, β-amyloid and α-synuclein have the ability to spread cell to cell, as demonstrated in mammalian cell cultures, in animals or even in humans (Costanzo and Zurzolo, 2013; Prusiner, 2012; Soto, 2012). In contrast, transmission between individuals has not been documented so far. The current key question is the possible infectious nature of these so-called "prion-like diseases" in a similar manner of prion diseases. In this review, an updated description of the prion and "prion-like diseases" affecting animals is presented. Pathogenesis of "prion-like diseases" in comparison with prion diseases as well as recent findings supporting the amyloidosis transmissibility are highlighted too.

2. Prion diseases in animals

Prion diseases may occur as inherited disorders, arise spontaneously or be acquired by infection. Transmissions within the same animal species but also between different species have been reported for some prion diseases and at least one of them, the bovine spongiform encephalopathy (BSE), is considered a zoonosis to date.

2.1. Scrapie

Scrapie is a TSE naturally affecting sheep, goats and mouflons (Jeffrey and Gonzalez, 2007); nowadays endemic in many countries worldwide. Scrapie is characterized by long incubation periods (2–5 years) and survival times ranging from 2 weeks to 6 months. Clinical signs comprise behavioral changes (fixed stare, isolation, hyperexcitability, loss of inquisitiveness), trembling, incoordination of gait, weight loss or emaciation, pruritus (main symptom in sheep, usually leads to wool loss) and impaired vision (Bellworthy et al., 2008; Dickinson, 1976; Hadlow et al., 1982). Neurological lesions deeply depend on scrapie strain, but generally include neuronal degeneration, non-inflammatory spongiform changes and astrogliosis detected mainly in diencephalon, midbrain, pons, medulla oblongata and cerebellar cortex (Hadlow et al., 1982). Apart from the nervous system, PrP^{Sc} deposition has been also observed in tonsils (Andreoletti et al., 2000), spleen (Hadlow et al., 1982), lymph nodes (van Keulen et al., 2008), nictitating membrane, muscles, placentas (Andreoletti et al., 2002), skin (Garza et al., 2014; Thomzig et al., 2007), mammary glands (Ligios et al., 2005), distal ilium, proximal colon (van Keulen et al., 2008); and more recently in pancreas, heart and urinary bladder (Garza et al., 2014).

Although vertical transmission was evidenced (Spiropoulos et al., 2014), the most likely route of prion infection seems to be the contact transmission between ewes and her lambs around the time of birth (Imran and Mahmood, 2011). Besides, the presence of scrapie infectivity in blood (Bannach et al., 2012; Dassanayake et al., 2011, 2012; Lacroux et al., 2012), saliva (Gough et al., 2011; Tamguney et al., 2012), milk (Ligios et al., 2011) and colostum (Konold et al., 2013) in conjunction with the high resistance of this prion agent against denaturizing factors contributes to its permanency in the environment, i.e. in soil (Saunders et al., 2012b), and consequently favors the horizontal transmission within sheep and goats herds.

Increased surveillance during the last two decades has led to the identification of a wide variety of scrapie disease phenotypes which are suggestive of scrapie strains. Moreover, an unusual type of scrapie was discovered in 1998 in Norway and therefore named atypical scrapie Nor-98 (Benestad et al., 2003). Currently, an increasing number of atypical/Nor98 scrapie cases have been reported in the majority of the European countries as well as in EEUU (Benestad et al., 2008) and New Zealand (Kittelberger et al., 2010). Its clinical signs are similar to classical scrapie disease; although generally less pronounced. Pruritus is uncommon and major clinical symptoms are ataxia and incoordination (Imran and Mahmood, 2011). Unlike classical scrapie, PrP^{Sc} deposition pattern in atypical scrapie infections is mild and restricted at the obex but more intense through cerebellum, substantia nigra, thalamus and basal nuclei (Moore et al., 2008).

Atypical scrapie has been proposed to have a spontaneous origin since is quite spread and often occurrers in older animals as single cases in a flock (Benestad et al., 2008; Fediaevsky et al., 2010; Hopp et al., 2006). Nevertheless, some findings have demonstrated the oral transmissibility of the atypical scrapie agent (Simmons et al., 2007, 2011). This fact, together with the presence of prion infectivity in different tissues (including in lymphoid tissues, nerves, and

Please cite this article in press as: Aguilar-Calvo, P., et al., Prion and prion-like diseases in animals. Virus Res. (2014), http://dx.doi.org/10.1016/j.virusres.2014.11.026