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The stress of prion disease

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ABSTRACT

Prion diseases are fatal neurodegenerative disorders that include scrapie of sheep, bovine spongiform encephalopathy of cattle, chronic wasting disease of cervids, and Creutzfeldt-Jakob disease (CJD) of humans. The etiology for prion diseases can be infectious, sporadic, or hereditary. However, the common denominator for all types is the formation of a transmissible agent composed of a β-sheet-rich, misfolded version of the host-encoded prion protein (PrP^{C}), known as PrP^{Sc}. PrP^{Sc} self-replicates through a template-assisted process that converts the α-helical conformation of PrP^{C} into the disease-associated isoform. In parallel with PrP^{Sc} accumulation, spongiform change is pathologically observed in the central nervous system, where "holes" appear because of massive neuronal death. Here, we review the cellular pathways triggered in response to PrP^{Sc} formation and accumulation. Available data suggest that neuronal dysfunction and death may be caused by what originates as a cellular pro-survival response to chronic PrP^{Sc} accumulation. We also discuss what is known about the complex cross-talk between the endoplasmic reticulum stress components and the quality control pathways. Better knowledge about these processes may lead to innovative therapeutic strategies based on manipulating the stress response and its consequences for neurodegeneration.

This article is part of a Special Issue entitled SI:ER stress.

Contents

1. Introduction

Prions are infectious agents responsible for a group of rare, but devastating, neurodegenerative diseases that affect humans and animals. The underlying mechanism for prion formation is the post-translational misfolding of the cellular prion protein (PrP^{C}) into PrP^{Sc}, where PrP^{Sc} continues to propagate during disease by the conformational transfer of its β-sheet-rich structure to PrP^{C} (Prusiner, 1998). Recently, prion-like cell-to-cell spreading has been attributed to a number of disease-related proteins (Soto, 2012). Despite many similarities between prion disease and other neurodegenerative disorders associated with the cerebral accumulation of misfolded protein aggregates, prions remain unique because epidemiological data undeniably support its inter-individual transmission under natural conditions. Also, although the mechanism for protein aggregation and the end product appear to be similar, extensive data emerging over the past decade indicates

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that the cellular stress response occurring as a result of protein misfolding is not a generic response, but is dependent on the nature of the protein affected and its subcellular localization (*i.e.* PrP anchored to the cell surface, amyloid beta released extracellularly after the cleavage of the amyloid precursor protein, and the intracellular aggregation of tau or α-synuclein). Formation and accumulation of these protein aggregates produce differential responses in terms of cellular and endoplasmic reticulum (ER) stress (Hetz and Mollereau, 2014).

The biosynthesis of PrP^C is not distinct from other membrane-bound and secreted proteins. First, *PRNP* is transcribed in the nucleus and the corresponding mRNA is initially translated by the ribosomes until a 22-amino acid signal peptide is reached. This signal directs PrP^C to the ER lumen, where the remainder of the 253 amino acid protein (254 in some species) is synthesized (Cohen, 1999; Harris, 2003). In the ER, a single disulfide bond is formed between cysteine residues 179 and 214, while N-linked oligosaccharide chains of the high-mannose type can be added at amino acid residues 181 and/or 197. At the completion of synthesis, PrP^C is subjected to cleavage of the amino-terminal signal peptide, and a glycosylphosphatidylinositol (GPI) anchor is attached to replace a 22-amino acid carboxy-terminal GPI signal peptide that is simultaneously removed (Haraguchi et al., 1989; Stahl et al., 1987; Turk et al., 1988). During transit through the Golgi apparatus, the N-linked oligosaccharide chains and the GPI-anchor are modified to yield more complex structures that include the addition of sialic acid residues (Caughey et al., 1989; Stahl et al., 1992). By following the secretory pathway, mature PrP^C containing 209 amino acids is brought to the cell surface and generally localizes at lipid rafts that are rich in sphingolipids and cholesterol (Taraboulos et al., 1992a; Vey et al., 1996). Then, PrP^C cycles between the cell surface and intracellularly via endosomal vesicles (Peters et al., 2003; Sunyach et al., 2003; Vey et al., 1996).

The signaling cascade for cellular stress begins with increased retention of proteins in the ER (Fig. 1, left panel). Comparable to the systematic responses during other protein misfolding diseases, ER retained proteins are initially sent for degradation by the proteasome, autophagy, and/or lysosomes (Fig. 1, middle panel). When ER stress persists, the balance between protein synthesis and degradation is disrupted. A disturbance in proteostasis is revealed by an alteration in ER-calcium homeostasis, as well as increased levels of chaperones and foldases triggered to correct the ER misfolded proteins (Fig. 1, middle panel). A major objective of the unfolded protein response (UPR) is to reduce protein synthesis

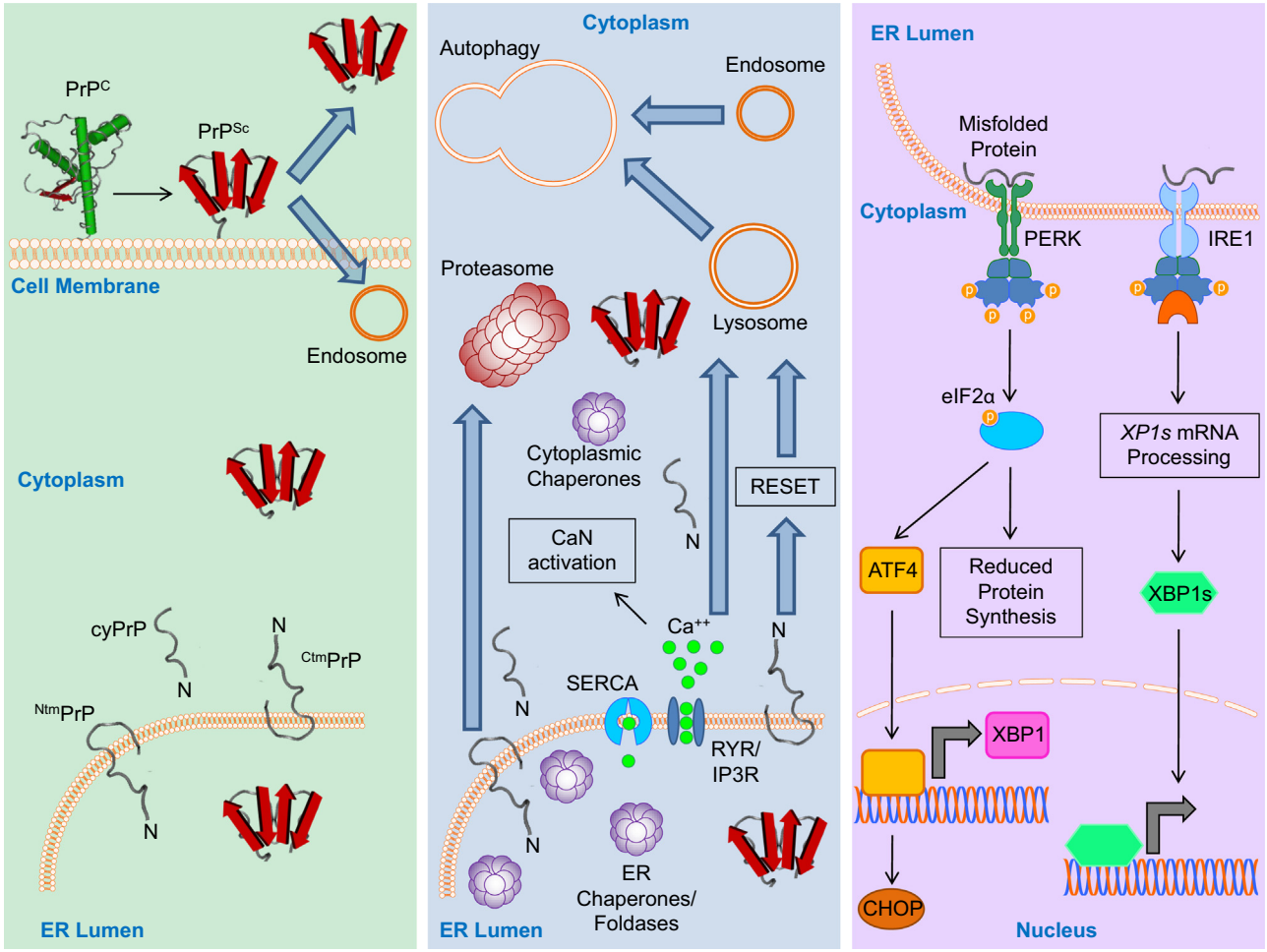

Fig. 1. The complex cellular stress pathways triggered by prion formation**.** The *left panel* shows that cellular stress can be initiated by the conversion of PrP^C into PrP^{Sc} or inefficient translocation in the ER forming ^{Ntm}PrP, ^{Ctm}PrP, and cyPrP. Once generated, PrP^{Sc} continues to propagate, being released from the cell surface, and cycle intracellularly in endosomal vesicles. As depicted, PrP species possessing similarities with infectious PrP^{Sc} suggests that PrP^{Sc} is also located in the ER and cytosol. The *middle panel* depicts the cell responding to the continued accumulation of PrP^{Sc} by transporting them for degradation by the proteasomes. Eventual exasperation of the proteasomes triggers degradative compensation from the lysosomes and through autophagy. The recently discovered RESET pathway may also degrade PrP by trafficking it to the Golgi, rapidly to the cell surface, and then to the lysosomes. In addition, levels of chaperones and foldases are drastically increased to correct the abundance of misfolded proteins, and ER-calcium (Ca^{++}) becomes depleted. The *right panel* illustrates the activation of the PERK and IRE1α/XBP-1 pathways of the UPR to reduce protein synthesis and generate transcription factors in attempt to recover balanced proteostasis. Persistence of ER stress ultimately will lead to neuronal dysfunction and death. Structures for PrP were adapted from the National Center for Biotechnology Information Molecular Modeling Database (MMDB ID: 19134).