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ER stress signaling and neurodegeneration: At the intersection between Alzheimer's disease and Prion-related disorders

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ABSTRACT

Alzheimer's and Prion diseases are two neurodegenerative conditions sharing different pathophysiological characteristics. Disease symptoms are associated with an abnormal accumulation of protein aggregates, which are generated by the misfolding and oligomerization of specific proteins. Recent functional studies uncovered a key role of endoplasmic reticulum (ER) stress and the unfolded protein response (UPR) in the occurrence of synaptic dysfunction and neurodegeneration in Prion-related disorders and Alzheimer's disease. Here we review the common pathological features of both diseases, emphasizing the link between amyloid formation, pathogenesis and alterations in ER proteostasis. The potential benefits of targeting the UPR as a therapeutic strategy is also discussed.

1. Introduction

Efficient folding and quality control of proteins are required to sustain biological function in the cell. Abnormal protein aggregation is extensively associated with distinct pathological conditions, collectively known as protein misfolding disorders (PMDs) (Chiti and Dobson, 2006). PMDs include several cerebral and systemic amyloid diseases such as Alzheimer's disease (AD), Parkinson's disease, Huntington's disease, type-2 diabetes and transmissible spongiform encephalopathies or Prion-related Diseases (PrD) (Dobson, 2002; Soto, 2003). While AD is the most common form of dementia and affects more than 25 million individuals worldwide, PrDs are rare diseases, affecting on average one person per million people. Although the incidence and clinical characteristics between AD and PrD are different, both conditions are characterized by the misfolding and aggregation of specific proteins and share clinical and pathological features including neuronal loss, progressive cognitive decline and death (Braak and Braak, 1991; Prusiner, 1998). The major histopathological hallmarks of AD are the presence of amyloid plaques and neurofibrillary tangles (NFT) in the brain. Amyloid plaques are generated by the misfolding and extracellular deposition of a 42-residue peptide known as amyloid-β (Aβ), which is generated by the sequential cleavage of the amyloid precursor protein (APP) by β- and γ-secretases (Hardy and Selkoe, 2002). Creutzfeldt–Jacob disease (CJD) is the most common form of PrD. CJD involves the accumulation of a misfolded and protease-resistant form of the prion protein (PrP), and it is characterized by the spongiform degeneration of the brain, neuronal loss, and gliosis (Prusiner, 1998). An outstanding feature of PrDs is the mechanism of disease propagation: misfolded PrP is capable of spreading through the formation of self-propagating β-sheet-rich conformations of PrP (Prusiner, 1982). Recent evidence suggests that this intriguing form of transmission, initially described in PrD, may also occur in many neurodegenerative disorders including AD (Eisele et al., 2010; Kane et al., 2000; Langer et al., 2011; Meyer-Luehmann et al., 2006; Morales et al., 2011; Walker et al., 2002; Watts et al., 2014), which implies that a common pathological principle may underlie the progression and propagation of the pathology in both diseases (Soto, 2012). Accumulating evidence indicate that alterations in protein homeostasis (referred to as proteostasis) may underlie the progressive

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synaptic dysfunction in AD and PrDs, culminating in neuronal loss and irreversible brain damage (reviewed in Hetz and Mollereau, 2014). Therefore, understanding how the proteostasis network contributes to neurodegeneration represents an interesting target for disease treatment and prevention.

In addition to operating as a key compartment for protein folding and secretion, the ER is essential for maintaining proteostasis and buffer alterations in protein folding and synthesis. Several physiological and pathological conditions can perturb the protein folding process at the ER, where we highlight abnormalities in protein maturation, ER calcium homeostasis, ER-to-Golgi vesicular trafficking, or expression of certain mutant proteins (Walter and Ron, 2011). These conditions often lead to the accumulation of misfolded proteins in the ER lumen, giving rise to cellular condition referred to as "ER stress". Under ER stress, cells activate an adaptive response, the unfolded protein response (UPR), that increases overall protein-folding capacity, in addition to enhancing the efficiency of quality control and protein degradation mechanisms to reduce the unfolded protein load (Walter and Ron, 2011). Under chronic or irreversible stress conditions the UPR shifts its signaling toward cell death mechanisms by activating complex pro-apoptotic programs (Urra et al., 2013). The UPR is mediated by specialized stress sensors located at the ER membrane, which include inositol-requiring enzyme 1 (IRE1), activating transcription factor 6 (ATF6) and protein kinase RNA-like ER kinase (PERK). Each stress sensor controls a downstream transcription factor that induces the expression of a subset of partially overlapping target genes involved in stress adaptation or apoptosis. In the case of IRE1, its endoribonuclease activity catalyzes the unconventional splicing of the mRNA encoding the transcription factor X-box binding protein (XBP1), which induces genes related to protein folding, protein degradation, lipid synthesis and others (Acosta-Alvear et al., 2007; Lee et al., 2003). In addition, IRE1 can degrade specific mRNAs through IRE1-dependent decay (RIDD) (Hollien et al., 2009), and activate kinases such as JUN amino-terminal kinase (JNK) and the apoptosis signal-regulating kinase 1 (ASK1) (Urano et al., 2000). Under ER stress, ATF6 translocates to the Golgi apparatus where it is cleaved by proteases, releasing a cytosolic fragment that translocates to the nucleus and operates as a UPR transcription factor (Ron and Walter, 2007). Soluble ATF6 also can form heterodimers with XBP1 to induce the expression of specific genes (Shoulders et al., 2013).

Activation of PERK leads to the direct phosphorylation of the ubiquitous eukaryotic translation initiation factor 2α (eIF2α) to rapidly attenuate translation and reduce the ER lumen protein overload. This mechanism also induces the translation of ATF4, a transcription factor that controls the expression of genes involved in apoptosis, autophagy, amino acid metabolism, and antioxidant responses (Walter and Ron, 2011). In summary, the UPR integrates information about the intensity and duration of the stress stimuli, coordinating several critical responses to buffer fluctuations in protein folding, a process often altered in neurodegenerative diseases such as AD and PrDs.

2. Protein aggregation in AD and PrD

Although PMDs are characterized by the deposition of aggregates that consist of different proteins – amyloid-beta (Aβ) and tau proteins in AD and misfolded prion protein (PrP^{Sc}) in PrDs – several shared morphological, biological, and biochemical features have been described. The misfolded proteins in both diseases often contain stacks of β-sheets organized in a polymeric arrangement (Soto et al., 2006). Moreover, the typical molecular arrangement of these aggregates consists of clusters of misfolded proteins organized into cross-β structures, which can form patterns of deposition known as amyloid fibrils or diffuse/dense plaque-like deposits (Blake et al., 1996; Parchi et al., 1999; Soto, 2003). These particular structural dispositions confer several adverse properties, such as proteotoxicity and disrupted protein clearance mechanisms. Additionally, because β-sheets can be stabilized by intermolecular interactions, misfolded proteins have a high tendency to form oligomers and larger polymers, which facilitates the accumulation of inclusions.

The main risk factor for developing most amyloid-related disease is aging (Cuanalo-Contreras et al., 2013; Finkel, 2005), which suggests that older tissues and cells are more prone to form and accumulate misfolded protein aggregates. In fact, a global reduction in the buffer capacity of the protein homeostasis network is observed during aging in model organisms (Douglas and Dillin, 2010). However, it is unknown whether the age-dependent accumulation of insoluble proteins is a cause of cellular dysfunction resulting in aging or a consequence of the progressive decline of proteostasis. Overall, during the last two decades, a large body of histopathological, genetic, and biochemical studies have provided accumulating evidence that favors a critical role for protein misfolding and aggregation in AD and PrDs. The generation of transgenic animal models for rare genetic variants observed in familial cases of AD and PrDs have validated the involvement of protein misfolding and aggregation in these diseases (Price et al., 1998). However, the exact molecular mechanisms driving neuronal dysfunction in PMDs remains poorly understood.

Mutations in three genes have been linked to the development of rare familial and early onset forms of AD (Bertram and Tanzi, 2008). These genes encode for APP and presenilin (PSEN) 1 and 2. The mechanisms explaining the overproduction of Aβ peptide in familial AD (FAD) cases are starting to be elucidated, but little is known about the etiology of the most common sporadic forms of the disease (SAD). Given that FAD and SAD cases share several common clinical and histopathological characteristics, it is likely they also share common pathological mechanisms. Gradual changes in the steady-state levels of Aβ peptide in the brain are thought to initiate the amyloid cascade (Karran et al., 2011; Selkoe, 2004). In AD and PrDs local accumulation of soluble oligomers and fibrils are though to operate as a central initiator of neuronal dysfunction and in the long term cell death (Walsh and Selkoe, 2004). Aβ and PrP oligomers and fibrils associate with synapses and alter their function; they also can impair calcium homeostasis, and trigger detrimental processes, such as excitotoxicity, oxidative stress, ER stress and local inflammation (Cornejo and Hetz, 2013; Halliday and Mallucci, 2014; Hetz and Soto, 2006; Karran et al., 2011; Selkoe, 2001). In summary, protein misfolding and aggregation are common features of AD and PrD that may also result in the engagement of similar degenerative pathways, were we highlight the ability to self-propagate abnormal conformations and the irreversible perturbations to the ER protein homeostasis.

3. Protein misfolding amplification and transmissibility

Several groups have shown that the infectious properties of misfolded prion aggregates follow a kinetic profile, which is known as the nucleation-dependent mechanism (Come et al., 1993). This process involves two different phases, where the first stage or "lag phase" involves the slow formation of the initial stable misfolded aggregates. Here, small oligomeric structures referred to as "seeds" are formed through unfavorable intermolecular interactions between monomers. In the lag phase, the build-up of multimeric structures is slow and corresponds to the rate-limiting step leading to further aggregation. Subsequently, in the second stage or "elongation phase" the recruitment of new units to the growing aggregates takes place in an accelerated fashion until a plateau level of polymerization is observed. This seeding–nucleation process can be accelerated by the addition of

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