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Invited review

Targeting the unfolded protein response in neurodegeneration: A new approach to therapy

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ABSTRACT

Neurodegenerative diseases such as Alzheimer's disease (AD), Parkinson's disease (PD), Huntington's disease (HD), and the rarer prion diseases, share a number of key similarities, including aggregation of disease-specific proteins in the brain and neuronal loss. The focus of research in these disorders has centred on pathogenesis caused by individual proteins and their build up in their specific diseases, but there are also likely to be more generic pathways that are active in neurodegeneration across the spectrum of these disorders. The unfolded protein response (UPR) has recently emerged as one such pathway. The UPR is normally a protective cellular response that protects against endoplasmic reticulum (ER) stress, which occurs with the build up of misfolded proteins. Recent evidence indicates that in neurodegenerative disease this pathway becomes constitutively activated, preventing protein translation. UPR activation is found in post mortem brains in a variety of diseases, including AD, PD and prion diseases, and has also been found to be activated in mouse models of neurodegeneration and in various *in vitro* models. We propose that modulation of the UPR in neurodegeneration is therefore a promising target for future therapeutic treatments.

This article is part of the Special Issue entitled 'The Synaptic Basis of Neurodegenerative Disorders'.

1. Introduction

Neurodegenerative diseases are one of the greatest challenges facing society and medicine at present. Due to an ageing population, they are expected to increase in prevalence and are predicted to become the second most common cause of morbidity in the developed world by 2040. Alzheimer's disease alone is estimated to affect 25 million individuals worldwide (Wimo et al., 2003). Since Alois Alzheimer first described a specific form of dementia that would later bare his name, a great amount of research has been directed at deciphering the molecular and biochemical mechanisms that lead to neurodegeneration. Despite having distinct clinical, pathological and biochemical signatures, neurodegenerative diseases such as Alzheimer's disease (AD), Parkinson's disease (PD), Huntington's disease (HD), and the rarer prion diseases, all share remarkable similarities: protein aggregation in the brain and fatal neuronal loss. The build up of misfolded proteins is the major common feature; this group of diseases is often referred to as protein misfolding disorders. Each disorder exhibits a build up of disease specific misfolded proteins, amyloid-β (Aβ) in AD, α-synuclein in PD, huntingtin in HD or the prion protein (PrP) in prion disease. Much effort has been directed into elucidating how the build up of these specific misfolded proteins contributes to the pathology of their respective diseases. Aβ is known to be toxic to synapses, reducing synaptic transmission as well as the number of dendritic spines (Yu and Lu, 2012). The accumulation of α-synuclein can damage mitochondria, leading to cell death in the substantia nigra (Cookson, 2009). Expanded huntingtin can form inclusion bodies that interfere with normal cellular processes and induce the misfolding of proteins (Hatters, 2008). But as well as these disease-specific toxic mechanisms, are there more general similarities between these neurodegenerative diseases? Neurodegeneration starts with synaptic dysfunction, which leads to the loss of dendritic spines and the postsynaptic density, and ultimately to the failure of neuronal networks and neuronal cell death. Cellular processes such as protein recycling (Rubinsztein, 2006) and mitochondrial dysfunction (Lin and Beal, 2006) have already begun to explain some of the common footprints of neurodegeneration. Recently, the UPR has emerged as a central player in the pathology of prion disease (Moreno et al., 2012), and importantly, it is likely to be a shared common feature in neurodegeneration.

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1.1. The unfolded protein response

The unfolded protein response (UPR) is a protective cellular mechanism that is induced during periods of cellular and endoplasmic reticulum (ER) stress. Secreted and transmembrane proteins enter the ER as unfolded proteins to be properly assembled, or to be targeted for degradation. The UPR maintains the protein-folding homoeostasis within the ER, ensuring the proper functioning of the produced proteins, and therefore the cell. A variety of conditions can interfere with this process and cause ER stress, including amino acid deprivation, viral replication and, as the name suggests, the presence of unfolded proteins (Ron and Walter, 2007). This activates the UPR, which seeks to restore the normal functioning of the ER, using multiple strategies that act individually and in synergy. Chaperone proteins are produced to prevent protein aggregation and facilitate correct protein folding (Sitia and Braakman, 2003). Protein translation is temporarily reduced to lower the amount of proteins present in the ER (Zhao and Ackerman, 2006). Lipid synthesis is also stimulated to increase ER volume, and the degradation of unfolded proteins is induced by activating the endoplasmic reticulum-associated protein degradation (ERAD) pathway (Meusser et al., 2005).

1.2. The three arms of the UPR

When misfolded proteins accumulate within the ER, GRP78/BiP dissociates from three proteins that mediate the UPR stress response: protein kinase RNA (PKR)-like ER kinase (PERK), inositol-requiring enzyme 1 (IRE1) and activating transcription factor 6 (ATF6) (Lai et al., 2007). Dissociation of GRP78/BiP from PERK, IRE1 and ATF6 allows the activation of these factors resulting in the induction of three UPR-related pathways (Fig. 1).

Activation of PERK leads to a reduction in global protein synthesis via the phosphorylation of eukaryotic initiation factor 2α (eIF2α) (Harding et al., 1999). This phosphorylation causes an eIF2α-mediated translational repression, which halts protein synthesis, helping to alleviate the overload of unfolded proteins inside the ER. There are also three other kinases that can phosphorylate eIF2α, each of which is activated by a different cellular stress: the double-stranded RNA-activated protein kinase (PKR) responds to viral infection (Clemens, 2004), general control non-derepressible-2 (GCN2) is activated during amino-acid starvation (Deng et al., 2002), and the heme-regulated inhibitor kinase (HRI) represses protein synthesis in heme-deficient erythroid cells (Han et al., 2001). Once the ER stress has been resolved and any unfolded proteins have been removed, the translational repression is reversed by dephosphorylation of eIF2α by the phosphatase GADD34 (Novoa et al., 2001). Although the phosphorylation of eIF2α causes the reduction in the synthesis of most proteins, some are upregulated, like activating transcription factor 4 (ATF4) (Blais et al., 2004). ATF4 is a key transcription factor involved in the regulation of genes related to protein folding, amino acid metabolism and redox control (Ma and Hendershot, 2003). Important targets of ATF4 include NRF2, which regulates the functions of a variety of antioxidant genes (He et al., 2001), and CHOP, which conversely is key in the activation of apoptotic pathways and cell death (Han et al., 2013).

There are two paralogs of IRE1: IRE1α and IRE1β (Wang et al., 1998). IRE1α is a kinase and endoribonuclease, that when activated, catalyses the splicing of the mRNA encoding the transcription factor X box-binding protein 1 (XBP1), removing a 26 base-pair intron (Calfon et al., 2002). This splicing changes the reading frame of the XBP1 mRNA, resulting in a potent transcription factor that regulates a subset of UPR targets genes involved in ER protein synthesis and folding, ERAD, autophagy and redox metabolism (Acosta-Alvear et al., 2007). IRE1β controls the site-specific cleavage of 28S rRNA, which contributes to translational repression (Iwawaki et al., 2001).

ATF6 has a CREB/ATF bZIP transcription factor domain at the amino terminus. Upon the accumulation of unfolded proteins in the ER, ATF6 is released from Grp78/BiP, and is trafficked to the Golgi apparatus where it is cleaved by site 1 and site 2 proteases at the

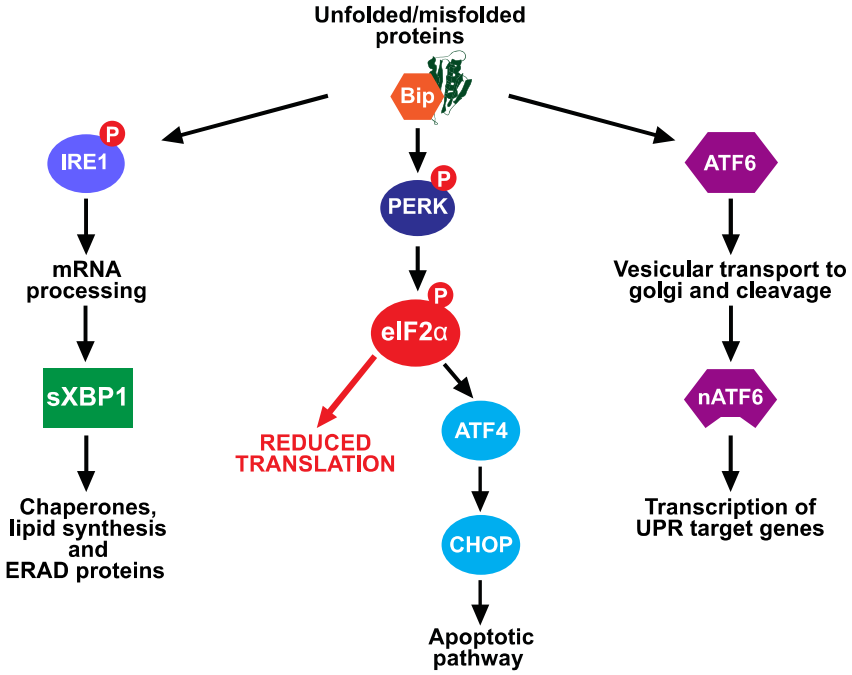

Fig. 1. Schematic of the unfolded protein response. After the detection of unfolded proteins by GRP78/BiP, the three arms of the UPR (PERK, IRE1 and ATF6) are activated. The PERK arm causes a reduction in global protein synthesis via the phosphorylation of eIF2α. Activation of IRE1 leads to XBP1 splicing (sXBP1) and the transcription of chaperones and ERAD proteins. ATF6 is cleaved to nATF6, which leads to the expression of a variety of UPR target genes.