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The broad spectrum of signaling pathways regulated by unfolded protein response in neuronal homeostasis

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ABSTRACT

The protein folding capabilities in the endoplasmic reticulum (ER) are disturbed by alternations in the cellular homeostasis such as the disruption of calcium ion homeostasis, the expression of mutated proteins and oxidative stress. In response to these ER dysfunctions, eukaryotic cells activate canonical branches of signal transduction cascades to restore the protein folding capacity and avoid irreversible damages, collectively termed the unfolded protein response (UPR). Prolonged ER dysfunctions and the downregulation of UPR signaling pathways have been accepted as a crucial trigger for the pathogenesis of various neurodegenerative diseases. Furthermore, recent studies have revealed that the UPR has a wide spectrum of signaling pathways for unique physiological roles in the diverse developmental, differential and lipidomic processes. A developed and intricate ER network exists in the neurites of neurons. Neuronal ER functions and ER-derived signaling mediate efficient communication between cell soma and distal sites through local protein synthesis, sorting and lipogenesis. However, relevant of ER-derived UPR signaling pathways in the elaborate mechanisms regulating neuronal activities, synaptic functions and protective responses against injury is not fully elucidated. In this review, we summarized our current understanding of how the UPR functions provide the appropriate signals for neuronal capabilities. We also reviewed how UPR dysfunctions lead to the pathogenesis of neurodegenerative diseases, and the possibilities ameliorating their toxic effects by targeting UPR components.

Contents

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1. Introduction

The endoplasmic reticulum (ER) provides an optimal environment for protein synthesis, folding, modification and assembly. This organelle has a unique system known as unfolded protein response (UPR), ensuring maintenance of the protein folding capacity (Kaufman, 2002; Ron, 2002). The UPR is activated in response to accumulation of unfolded proteins due to ER dysfunction, to ameliorate the ER environment and cellular conditions. Recent studies have extended the UPR roles from regulation of protein folding efficiency and maintenance of ER functions to manipulation of cellular homeostasis and biological functions such as cell development, differentiation, glycogenesis and lipid metabolism (Lee et al., 2008; Mao et al., 2011; Reimold et al., 2001; Vecchi et al., 2009; Wu and Kaufman, 2006; Zhang et al., 2006). Neurons have a highly developed ER in their neurites (Broadwell and Cataldo, 1983; Tsukita and Ishikawa, 1976). The extensive ER network in neurons presages that ER-specific competencies regulating local protein synthesis and sorting, lipogenesis, and calcium ion (Ca^{2+}) storage and proper release may deal with essential neuronal activities, maintenances and physiological functions. Here, we discuss the state of the diverse abilities and prospects of the UPR derived from the neuronal ER network in axons and dendrites, and how UPR signaling is engaged in the neuronal activities. We also mention how aberrations of neuronal homeostasis triggered by UPR dysfunctions lead to the pathogenesis of various neurodegenerative diseases.

2. Key players in the UPR

The ER is a central organelle responsible for Ca^{2+} storage, lipid metabolism, protein synthesis and post-translational modifications of abundant secretory and membrane proteins. This organelle has a single and continuous membrane, and can be divided into the nuclear envelope, the ribosome-enriched rough ER and the smooth ER. Multiple cellular malfunctions such as disturbance of Ca^{2+} homeostasis in the ER lumen and expression of mutated proteins cause the accumulation of unfolded proteins in the ER lumen, resulting in the perturbation of ER functions. These abnormalities are known as ER stress (Kaufman, 2002; Ron, 2002; Rutkowski and Kaufman, 2004). Under ER stress, cells transduce signals dealing with unfolded proteins to induce chaperone activity, attenuation of protein translation, and degradation of unfolded proteins, referred to as the UPR (Fig. 1) (Kaufman, 2002; Ron, 2002; Ron and Walter, 2007). The three major canonical branches of the UPR are the inositol-requiring kinase 1 (IRE1) (Tirasophon et al., 1998), protein kinase R-like ER kinase (PERK) (Harding et al., 1999), and activating transcription factor 6 (ATF6) (Yoshida et al., 2000) pathways. These ER stress transducers localized at the ER membrane activate UPR signaling in response to ER stress. IRE1 has RNase activity that is preceded by its oligomerization and *trans*-autophosphorylation (Tirasophon et al., 1998). Activated IRE1 then processes a 26-nucleotide intron of *x-box binding protein 1* (*Xbp1u*) mRNA (unspliced *Xbp1*) to produce the mature *Xbp1s* mRNA (spliced *Xbp1*) (Calfon et al., 2002; Yoshida et al., 2001, 2003), generating the transcription factor XBP1s. XBP1s induces the expression of target genes including molecular chaperones and ER-associated degradation (ERAD)-related genes (Yoshida et al., 2003). PERK also oligomerizes and autophosphorylates in response to ER stress. The phosphorylated PERK directly phosphorylates the α subunit of eukaryotic initiation factor 2 (eIF2α), which inhibits the assembly of the *80S* ribosome and represses global protein synthesis (Harding et al., 1999, 2000; Shi et al., 1998). In contrast to most proteins, ATF4 escapes translational attenuation by eIF2α phosphorylation because ATF4 has open reading frames (ORFs) in its 5′-untranslated region. These upstream ORFs prevent translation of true ATF4 under normal conditions. The phosphorylation of eIF2α bypasses the pseudo ORFs and enhances the preferential translation of the true ATF4 (Harding et al., 2000; Vattem and Wek, 2004). This transcription factor promotes the expression of several genes involved in amino acid metabolism and the resistance to oxidative stress (Barbosa-Tessmann et al., 2000; Harding et al., 2000; Roybal et al., 2005). Additionally, ATF4 in turn drives the transcription of the transcription factor, CCAAT enhancer binding protein homologous protein (CHOP) (Harding et al., 2003; Ma et al., 2002; Wang et al., 1996). Continued expression of CHOP can induce cell death (Marciniak et al., 2004). ATF6 moves from the ER to the Golgi apparatus under ER stress conditions, and is subsequently processed by site-1 and site-2 proteases (Chen et al., 2002; Ye et al., 2000). The cleaved *N*-terminal fragments containing a basic leucine zipper domain translocate into the nucleus to act as a transcription factor. The ATF6 *N*-terminus is involved in the expression of ER molecular chaperones such as binding immunoglobulin protein (BiP) (Yamamoto et al., 2007; Yoshida et al., 2000). Prolonged or excessive ER stress leads to apoptosis via UPR signaling (Kaufman, 2002; Ron, 2002). Thus, the cell fate after ER stress is determined by the balance of cell survival and death signals regulated by the UPR. Interestingly, recent studies have uncovered novel UPR functions involved not only in dealing with unfolded proteins, but also in regulating beneficial outcomes including manipulations of biological functions and cellular homeostasis (Wu and Kaufman, 2006). In neurons, the well-developed ER networks are highly dynamic, showing constant remodeling and the intricate extension from cell soma to the distal segments of neurites (Broadwell and Cataldo, 1983; Tsukita and Ishikawa, 1976). The extremely elongated neuronal ER network and ER-derived signaling including the UPR have the potential to orchestrate the overall neuronal homeostasis through regulation of local events contributing to neurite capabilities. The perturbation of these signals can lead to neuronal dysfunctions, resulting in the development of neurodegenerative diseases.

3. Axonal regeneration and degeneration regulated by the UPR

Morphological observation of neurites has demonstrated that the rough ER is in the cell body, dendrites and proximal axon, and the distal axon is filled with smooth ER (Broadwell and Cataldo, 1983; Tsukita and Ishikawa, 1976). In peripheral neurons, mechanical injury and crush of distal axons promote the propagation of the Ca^{2+} oscillation. The propagated Ca^{2+} wave in response to the injury rapidly changes the environment of the distal axons, followed by initiating injury-responsive signals (George et al., 1995). For example, the acute alternation of Ca^{2+} concentration in cytoplasm and ER at the injury site elicits axonal degeneration via reactive oxidative species production and mitochondrial dysfunction (Villegas et al., 2014). Conversely, the retrograde propagation towards the cell body correlates with regenerative responses (Ghosh-Roy et al., 2010; Sun et al., 2014). In sensory neurons, at least one of the underlying factors of the Ca^{2+} wave induced by axonal injury is Ca^{2+} release from the axonal ER internal store through the ER-localized Ca^{2+} channels, Ryanodine and inositol trisphosphate (IP_3) receptors (Sun et al., 2014; Villegas et al., 2014). Ca^{2+} release from the ER, followed by its depletion in the ER lumen can induce ER stress. Indeed, several studies have demonstrated injury-induced UPR signaling, and the association between the key UPR factors and neuronal death and survival after axonal injury (Fig. 2). The locomotor recovery is reduced in *Atf4* or *Xbp1*-deficient mice after spinal cord injury (Valenzuela et al., 2012). The aberrant expression of these transcription factors leads to enhanced axonal

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