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Review

Redox signaling loops in the unfolded protein response

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ABSTRACT

The endoplasmic reticulum (ER) is the first compartment of secretory pathway. It plays a major role in ER chaperone-assisted folding and quality control, including post-translational modification such as disulfide bond formation of newly synthesized secretory proteins. Protein folding and assembly takes place in the ER, where redox conditions are distinctively different from the other organelles and are favorable for disulfide formation. These reactions generate the production of reactive oxygen species (ROS) as a byproduct of thiol/disulfide exchange reaction among ER oxidoreductin 1 (Ero1), protein disulfide isomerase (PDI) and ER client proteins, during the formation of disulfide bonds in nascent or incorrectly folded proteins. When uncontrolled, this phenomenon perturbs ER homeostasis, thus aggravating the accumulation of improperly folded or unfolded proteins in this compartment (ER stress). This results in the activation of an adaptive mechanism named the unfolded protein response (UPR). In mammalian cells, the UPR is mediated by three ER-resident membrane proteins (PERK, IRE1 and ATF6) and regulates the expression of the UPR target genes, which themselves encode ER chaperones, folding enzymes, pro-apoptotic proteins and antioxidants, with the objective of restoring ER homeostatic balance. In this review, we will describe redox dependent activation (ER) and amplification (cytosol) loops that control the UPR and the consequences these regulatory loops have on cell fate and physiology.

Contents

Abbreviations: AGR2, anterior gradient 2; ARE, antioxidant responsive element; ATF4, activating transcription factor-4; ATF6, activating transcription factor-6; ASK1, apoptosis signal-regulating kinase-1; BI-1, BAX inhibitor-1; BiP, immunoglobulin heavy chain-binding protein; CHOP, C/EBP-homologous protein; CANX, calnexin; CNC, cap 'n' collar; COPII, coat protein complex II; CRT, calreticulin; CSE, cystathionine γ-lyase; EDEM1, ER degradation enhancing mannosidase-like protein-1; EGF, epidermal growth factor; eIF2α, alpha-subunit of the eukaryotic translation initiation factor-2; ER, endoplasmic reticulum; ERAD, ER-associated degradation; Ero1, ER oxidoreductin 1; ERSE, ER stress-response element; ERQC, ER quality control; GADD34, growth arrest and DNA damage 34; GRP78, 78 kDa glucose-regulated protein; GRP94, 94 kDa glucose-regulated protein; GSH, reduced glutathione; GSSG, oxidized glutathione; HSP, heat-shock protein; IRE1, inositol-requiring protein-1; IP_3R1, inositol 1,4,5-trisphosphate receptor 1; JNK, c-Jun N-terminal kinase; Keap1, Kelch-like ECH-associated protein-1; MAP, mitogen-activated protein; MAPK, MAP kinase; MAPKK, MAP kinase kinase; MAPKKK, MAP kinase kinase kinase; MHC, major histocompatibility complex; MUC2, mucin 2; Neh, Nrf2-ECH homology; NRF2, nuclear factor-E2-related factor-2; PERK, protein kinase RNA-like ER kinase; PI3K, phosphoinositide-3-kinase; PDI, protein disulfide isomerase; PTP1B, protein-tyrosine phosphatase-1B; RIDD, regulated IRE1-dependent mRNA decay; ROS, reactive oxygen species; siRNA, small interfering RNA; sXBP1, spliced form of XBP1; S1P and S2P, site-1 and site-2 proteases; TCPTP, T cell protein-tyrosine phosphatase; TNF, tumor necrosis factor; TRAF2, TNF receptor-associated factor-2; Trx, thioredoxin; UPR, unfolded protein response; uXBP1, unspliced form of XBP1; XBP1, X-box binding protein-1.

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1. Introduction

The endoplasmic reticulum (ER) is the site in which secretory and membrane proteins acquire their proper conformation through the aid of molecular chaperones and folding enzymes. Correctly folded proteins exit the ER and are exported to the Golgi apparatus and the other intracellular organelle, whereas non-properly folded proteins are recognized by ER quality control (ERQC) machinery and retained in this compartment. Terminally misfolded proteins are transported from the ER into the cytosol through a dislocation channel and degraded by the ubiquitin–proteasome system (ER-associated degradation; ERAD). The accumulation of partially/non-properly folded proteins in the ER perturbs the homeostasis of this compartment, which in turn triggers the activation of an adaptive response named the unfolded protein response (UPR). The oxidative environment of the ER favors protein folding and in particular the formation of disulfide bonds between two cysteine residues in proteins by thiol oxidation. This specific redox environment is controlled by the presence of specific enzymes such as protein disulfide isomerases (PDIs), which are ubiquitously expressed in the ER and are responsible for the formation of disulfides bonds, or oxidoreductin proteins, which act by oxidizing directly PDIs through a direct disulfide exchange. These enzymatic activities maintain the ER protein redox homeostasis. The disruption of this redox balance, that can for instance be caused by challenging environments, leads in turn to a loss of ER homeostasis and the subsequent triggering of the UPR due to the accumulation of misfolded proteins in the ER (Fig. 1). The cytosolic signaling events comprised in the UPR can either directly modulate ER functions or participate in the regulation of specific transcriptional programs, the latter aiming collectively at restoring ER homeostasis. In this review, we focus on the UPR-mediated signaling pathways, the PDI family function in the ER, and the link between the redox status and UPR induction in the ER.

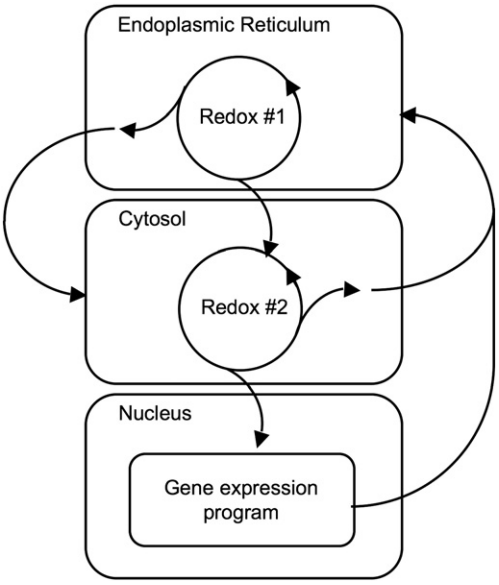

Fig. 1. Schematic representation of redox-mediated UPR activation and amplification loops — UPR signaling, including oxidative protein folding, is activated when misfolded proteins accumulate in the ER and the homeostasis of the ER is perturbed (Redox #1). The UPR and redox signals are transduced to the cytosol, which are related to both the UPR and oxidative stress response (Redox #2). These stress signals are subsequently transmitted to the nucleus to promote the expression of a series of UPR target or ROS-detoxifying genes (Nucleus), whose products will act in the ER. Taken together, the overloading of misfolded protein in the ER and the ROS production create several amplification loops to adapt cells against stress.

2. The unfolded protein response — description and activation process

In higher eukaryotic cells, newly synthesized polypeptides enter the ER through the translocation channels (translocon; Sec61). They are folded and assembled in the lumen of the ER. Only properly folded secretory proteins can reach the Golgi apparatus to be further modified and then are transported to their final destinations. The ER homeostasis is tightly regulated by the ERQC machinery [1]. In addition, the accumulation of incorrectly folded or unfolded proteins in this compartment (referred to as ER stress) induces the signaling mechanisms known as the UPR [2]. The UPR is conserved from yeast to human [3]. In mammalian cells, the UPR signaling is transduced by three ER-resident protein sensors namely the protein kinase RNA (PKR)-like ER kinase (PERK) [4], the inositol-requiring enzyme-1 (IRE1) [5,6] and the activating transcription factor-6 (ATF6) [7]. The most abundant ER chaperone, the immunoglobulin heavy chain-binding protein (BiP)/78 kDa glucose-regulated protein (GRP78) binds to the luminal domains of PERK, IRE1 and ATF6 in unstressed cells to maintain them in an inactive state [8,9]. When misfolded proteins accumulate in the ER, BiP preferentially binds to misfolded or unfolded proteins to assist their correct folding and consequently dissociates from the UPR sensors. These sensors released from BiP initiate the three main signaling cascades of the UPR.

2.1. PERK

PERK is type I ER membrane-associated protein, which has N-terminal luminal ER stress-sensing domain and C-terminal cytosolic kinase domain [4] (Fig. 2A). In response to ER stress, PERK is activated by *trans*-autophosphorylation and homodimerization to phosphorylate the alpha-subunit of the eukaryotic translation initiation factor-2 (eIF2α) on serine residue 51 [4]. The phosphorylation of eIF2α (Fig. 2B) results in translational attenuation to prevent additional load of newly synthesized proteins into the ER. Although eIF2α phosphorylation via PERK activation represses most mRNA translation and protein synthesis, PERK signaling selectively increases the expression of activating transcription factor-4 (ATF4), through the bypass of a micro-ORF upstream of ATF4 open reading frame [10], thus resulting in the transcriptional induction of C/EBP-homologous protein (CHOP; also known as GADD153) [10]. The production of CHOP induces in turn the expression of growth arrest and DNA damage 34 (GADD34) [11], which complexes with protein phosphatase 1 to dephosphorylate phosphorylated eIF2α and subsequently to promote recovery from translational attenuation. However, prolonged and excess extent of ER stress leads to apoptosis. CHOP also plays a role in apoptosis induction in response to ER stress [12]. PERK activation and eIF2α phosphorylation upon ER stress are negatively regulated by heat-shock protein (HSP) 40 family member $P58^{IPK}$ [13], which is under the control of XBP1 and ATF6 activation [14–16] to terminate translational attenuation. Whereas most of the PERK signaling is mediated through phosphorylation of eIF2α, additional transcription factor, nuclear factor-E2-related