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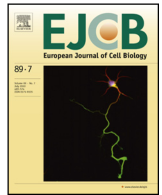

Review

The role of the endoplasmic reticulum stress in stemness, pluripotency and development

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ABSTRACT

The molecular machinery of endoplasmic reticulum (ER) integrates various intracellular and extracellular cues to maintain homeostasis in diverse physiological or pathological scenarios. ER stress and the unfolded protein response (UPR) have been found to mediate molecular and biochemical mechanisms that affect cell proliferation, differentiation, and apoptosis. Although a number of reviews on the ER stress response have been published, comprehensive reviews that broadly summarize ER physiology in the context of pluripotency, embryonic development, and tissue homeostasis are lacking. This review complements the current ER literature and provides a summary of the important findings on the role of the ER stress and UPR in embryonic development and pluripotent stem cells.

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Contents

1. Introduction 115
2. ER homeostasis and the molecular response to ER stress 116
3. The ER stress response in embryonic development 118
4. The ER stress response in pluripotency and differentiation 119
5. Conclusion 121
Conflict of interest statement 121
Acknowledgements 121
References 121

1. Introduction

The endoplasmic reticulum (ER) is the principal organelle involved in the synthesis, maturation, and post- or co-translational modification of secreted and membrane proteins, as well as in various metabolic processes including dynamic ion storage and biogenesis of membrane structures (Kleizen and Braakman, 2004). The rough ER (rER) is an extensive membranous network of cisterns, branched tubules, and flattened sacs that form a unique microenvironment consisting of oxidizing conditions and a high calcium concentration, which are necessary for the formation of disulfide bonds and supramolecular conformations of proteins (Ulianich et al., 2007). During proteosynthesis, nascent proteins are translated into the ER lumen where they are co-translationally and/or post-translationally modified with oligosaccharyl residues. These glycosylated motifs are targets for intra-ER chaperones, such as Calnexin and Calreticulin. Properly folded proteins are then addressed to the Golgi apparatus and to the extracellular surface by the secretory pathway or to other intracellular organelles (Ogata et al., 2006). Since the discovery of the ER by Albert Claude in the early 1940s (Claude, 1943) and a series of pioneering publications that identified the fundamental structure of the ER and suggested the proteosynthetic function of the ER (Porter et al., 1945) and liver and pancreatic microsomal structures (Palade, 1956; Palade and

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Siekevitz, 1956a,b; Zamecnik and Keller, 1954), the ER has been shown to be a complex hub that regulates numerous aspects of cellular life.

The ER machinery integrates various intracellular and extracellular signals including growth, differentiation, and inflammatory signals, and executes a unique set of molecular responses, which are conserved among various eukaryotes, including yeasts, plants, nematodes, insects, and mammals (for a detailed review see Ruberti and Brandizzi, 2014). The ability of the ER to sense properly folded and post-translationally modified proteins is at the core of a complex signaling network that evaluates the ER work load and initiates molecular responses to imbalanced homeostasis and ER stress.

2. ER homeostasis and the molecular response to ER stress

Disruption of ER homeostasis, the ER stress, may occur during cell differentiation, tissue development, and senescence or as a result of increased protein synthesis, perturbation of calcium homeostasis, DNA damage, altered redox status or the expression of mutant proteins (Zhong et al., 2011). In addition, exogenous chemical and physical inducers, such as hypoxia, glucose deprivation, and mechanical forces may cause ER stress. ER stress typically triggers a complex signaling process called the unfolded protein response (UPR) (Ulianich et al., 2007; Ozcan and Tabas, 2012). The common hallmarks of ER stress are proteosynthesis overload and attenuation of the secretory pathway by metabolic inhibition. Dilatations of ER cisterns, ribosome detachment, and abnormal cistern crosslinking (Fig. 1) have been described in many cell types, including somatic, cancer or stem cells, in the presence of various ER stress inducers (Duan et al., 2014; Horak et al., 2014; Kratochvílová et al., 2015). These molecular responses include upregulation of molecular chaperones, downregulation of mRNA translation, and degradation of misfolded proteins in a sequence of biochemical events termed UPR and ER associated degradation (ERAD). In cases of long-lasting ER stress, proapoptotic signaling pathways, which involve downregulation of Bcl-2 and induction of Bim or Puma, may be initiated (Kim et al., 2008).

UPR is initiated by three stress-sensing transmembrane proteins in the ER: 1) leucine zipper activating transcription factor 6 (ATF6), 2) inositol-requiring kinase/endoribonuclease 1 (IRE1), and 3) protein kinase RNA-like ER kinase (PERK) (Nishitoh, 2012). In unstressed cells, these sensors are maintained in an inactive state by the ATP-dependent ER chaperone GRP78 (BiP), which binds to their luminal domains. GRP78 belongs to the HSP70 family of heat shock proteins and is the most abundant protein in the ER lumen (Lane et al., 2014; Csala et al., 2012). Under physiological conditions, GRP78 binds to nascent or unfolded proteins through its peptide-binding domain and uses the energy from hydrolyzing ATP to promote proper folding and to prevent protein aggregation (Luo et al., 2006). When there are excessive amounts of misfolded proteins in the ER lumen, unbound GRP78 is depleted and bound GRP78 dissociates from PERK, ATF6, and IRE1. The release of GRP78 allows these transmembrane receptors to oligomerize, autophosphorylate, and activate their respective downstream pathways.

Upon release from GRP78, the 90 kDa ATF6 protein is dispatched to the Golgi apparatus where it is processed by Site-1 and Site-2 proteases (Yoshida et al., 2006). The 50 kDa active soluble form of ATF6 is then transported into the nucleus and binds directly to the mammalian consensus sequence of the cis-acting ER stress response element (ERSE) and to conserved GRP promoters to activate ER chaperones, such as GRP78, GRP94, C/EBP homologous protein (CHOP), Calnexin, Calreticulin, and X-box binding protein 1 (XBP-1) (Kober et al., 2012). ER chaperones and their functions in protein folding are described in detail elsewhere (Ni and Lee, 2007; Halperin et al., 2014).

Activated PERK phosphorylates the α subunit of eukaryotic initiating factor 2 (eIF2α) leading to inhibition of general mRNA translation activity and protein synthesis, as well as to the subsequent diminution of nascent peptides entering the ER lumen (Lane et al., 2014). On the other hand, transcription of some genes, such as activating transcription factor 4 (ATF4), is triggered by phosphorylated eIF2α. ATF4 then activates transcription of the proapoptotic transcription factor CHOP (DDIT3, GADD153) which transitions the balance between anti- and pro-apoptotic members of the BCL2 family towards programmed cell death. CHOP can also induce apoptosis through death receptor 5 (DP5). In addition, CHOP activates transcription of ER oxidase 1α (ERO1α) and downregulates intracellular glutathione, thereby elevating levels of reactive oxygen species (Nishitoh, 2012; Kim et al., 2008). Activated ERO1α also ensures oxidative protein folding and enables the release of Ca^{2+} ions from the ER through the IP3 receptor, which can also initiate apoptosis. Another function of CHOP is to activate growth arrest DNA damage-inducible gene 34 (GADD34), which is responsible for dephosphorylating eIF2α and restoring protein translation (Marciniak et al., 2004).

When the PERK pathway is knocked-out, cells are exposed to more intracellular stress and are more sensitive to its lethal effects (Harding et al., 2000). In Wolcott–Rallinson syndrome, PERK is mutated and the eIF2α-ATF6-ATF4 axis is deregulated leading to uncompensated ER stress predominantly in the endocrine compartment of the pancreas and other tissues engaged in high-rate synthesis of proteins. Clinically, the absence of functional PERK causes neonatal or early-onset diabetes, bone dysplasia, and hepatic failure (Zhang et al., 2002; Julier and Nicolino, 2010). Moreover, PERK deficient cells show a rapid increase of IRE1-mediated UPR pathway (Harding et al., 2000).

The ER transmembrane protein IRE1 has endoribonuclease and protein kinase activity and its pathway is conserved among all eukaryotic models studied (Calfon et al., 2002; Yoshida et al., 2006). IRE1 activity is regulated by oligomerization, and the oligomerization state of IRE1 determines the molecular outcomes of IRE1 binding to cytoplasmic targets. Dimerization of IRE1 catalyzes alternative splicing of XBP-1 mRNA by the IRE1 endonuclease domain (Yoshida et al., 2001; Chen and Brandizzi, 2013). IRE1 removes a 26-nucleotide sequence from XBP-1 mRNA, which induces a shift in the reading frame leading to translation of the highly active basic leucine zipper transcription factor form of XBP-1. This spliced form of XBP-1 interacts with other bZIP transcription factors, such as c-Fos (Ono et al., 1991) and ATF6. The target genes induced by XBP-1 include ER enzymes, such as ER mannosidase alpha-like 1 (EDEM1), ER chaperones, as well as a variety of other genes, which are regulated in a tissue-dependent context (He et al., 2010). Upregulation of major transcription factors, such as AP-1, that enhances proliferation or immune responses, can then modulate directly the tissue microenvironment. Unspliced XBP-1 negatively regulates the spliced form of XBP-1 and the PERK pathway (Yoshida et al., 2006). IRE1 multimers catalyze the degradation of various RNAs, including microRNAs, mRNAs, and rRNAs, in cell- or tissue-specific manners by regulated IRE1-dependent decay (RIDD) mechanisms (Maurel et al., 2014). The kinase activity of IRE1 was identified under chronic ER stress conditions, triggering the proapoptotic pathway by assembling a signaling complex consisting of autophosphorylated IRE1, TRA2, and apoptosis signal-regulated kinase (ASK1). This signaling complex activates c-Jun NH2-terminal kinase (JNK) and its downstream targets (Urano et al., 2000).

UPR mediates an adaptive process that directly reduces the amount of misfolded proteins in the ER lumen. Substantial proportions of the proteins that enter the lumen of the ER are excluded by rigorous quality control mechanisms and are eliminated as defective ribosomal products (DRiPs) (Schubert et al., 2000). ERAD is

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