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Review

Endoplasmic reticulum quality control in cancer: Friend or foe

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ABSTRACT

Quality control systems in the endoplasmic reticulum (ER) mediated by unfolded protein response (UPR) and endoplasmic reticulum associated degradation (ERAD) ensure cellular function and organismal survival. Recent studies have suggested that ER quality-control systems in cancer cells may serve as a double-edged sword that aids progression as well as prevention of tumor growth in a context-dependent manner. Here we review recent advances in our understanding of the complex relationship between ER proteostasis and cancer pathology, with a focus on the two most conserved ER quality-control mechanisms–the IRE1α-XBP1 pathway of the UPR and SEL1L–HRD1 complex of the ERAD.

1. Introduction

In eukaryotic cells, approximately one third of the total proteome is folded to maturity in the endoplasmic reticulum (ER) prior to transportation to various subcellular or extracellular compartments. A myriad of chaperones, folding enzymes and nascent proteins crowd the molecular environment of the ER lumen all the while maintaining a delicate homeostasis in its protein folding machinery. Various perturbations to this equilibrium, including both physiological and pathological stimuli, can lead to an accumulation of misfolded proteins inside the ER, subjecting the cell to a condition called "ER stress" and activating a series of adaptive mechanisms to alleviate the stress and restore ER homeostasis. These mechanisms consist of two major ER quality control machineries, including unfolded protein response (UPR) and ER-associated degradation (ERAD) [1–3].

Originally discovered as a response to nutrient depletion, autophagy is a cellular process involved in the lysosomal degradation of cellular components and in the maintenance of energy homeostasis through recycling of amino acids and nutrients [4]. Several studies suggest that autophagy is activated as an adaptive mechanism in cells experiencing ER stress and may play a role in the maintenance of ER homeostasis in cancer [5,6]. However, as the role of autophagy goes beyond the ER [7], whether the effect of autophagy in cancer is related to its function in the ER remains to be established. Hence, as the role of autophagy in cancer has recently been extensively reviewed [8–10], it will not be the focus here.

Owing to a high proliferation rate, cancer cells often experience impaired ATP generation, hypoxia, hypoglycemia and specific mutations which may perturb ER homeostasis and trigger the activation of UPR [2]. Persistent ER stress often activates pathways that lead to cell death, effectively eliminating cells with a potential to go rogue. On the other hand, tumor cells may hijack the ER quality control machineries to provide survival signals required for neoplasm growth and eventually avoid cell death [11]. Researchers have considered targeting various components of UPR and ERAD as potent therapeutic means to specifically modulate the survival of cancer cells [12]. In this review, we will discuss the involvement of two most highly conserved branches of the ER quality control systems – the IRE1α signaling pathway of the UPR and the SEL1L–HRD1 complex of the ERAD – in cancer pathogenesis.

2. The IRE1α signaling pathway

IRE1 is a type-1 ER-resident membrane protein with bifunctional cytosolic kinase and endoribonuclease (RNase) domains [13,14]. In mammals, IRE1 exists in two isoforms, IRE1α [15] and IRE1β [16]. IRE1α is ubiquitously expressed and global knockout of the gene results in early embryonic lethality [17,18]. In contrast, IRE1β expression is limited to the gastrointestinal epithelial cells [19] and has no RNase activity toward the classical IRE1α substrate X-box binding protein 1 (*Xbp1*) mRNA [20]. While IRE1β knockout mice are viable, they are hypersensitive to experimental colitis [19], which may be in part due to reduced mucin biosynthesis [20].

Upon ER stress, IRE1α undergoes dimerization and/or oligomerization and trans-autophosphorylation, which triggers

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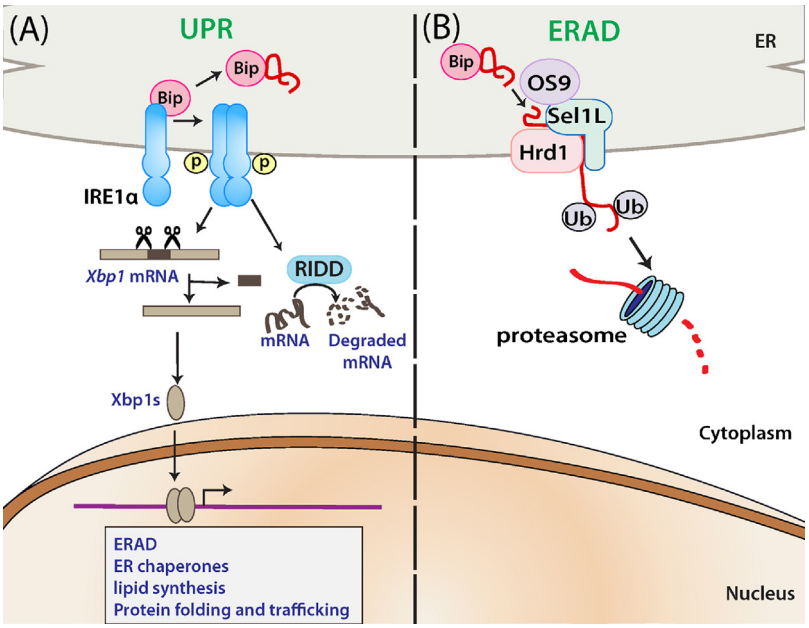

Fig. 1. Schematic diagrams depicting the roles of IRE1α in UPR and SEL1L–HRD1 in ERAD. Upon sensing ER stress, IRE1α undergoes dimerization or oligomerization, and trans-autophosphorylation, activating its cytosolic endonuclease activity. Subsequently, IRE1α alternatively splices *Xbp1* mRNA to generate Xbp1s which translocates into the nucleus and regulates different genes. Furthermore, activated IRE1α can selectively degrade particular mRNAs by a process called regulated IRE1-dependent decay (RIDD). Unlike IRE1α-XBP1 pathway, physiological significance of other IRE1α pathways are not well established. (B) Misfolded proteins in the ER lumen are recognized, ubiquitinated and retrotranslocated by the HRD1–SEL1L ERAD complex to the cytosol for proteasomal degradation. Bip and OS9 may be involved in the recognition of misfolded substrates.

conformational change and activation of its RNase domain. Activated IRE1α splices 26 nucleotides from *Xbp1* mRNA, leading to translational frameshift and the generation of an active transcription factor XBP1s. Subsequently, XBP1s enters the nucleus, where it transactivates various target genes, including those involved in protein folding, ERAD, protein trafficking, and lipid biosynthesis (Fig. 1) [21]. Additionally, IRE1α has been shown to degrade a subset of mRNAs via a process called Regulated IRE1-Dependent Decay (RIDD) (Fig. 1) [22–25]. Moreover, IRE1α cleaves some premature microRNAs as a means of regulating apoptosis [26] as well as its own mRNA level [27,28]. The physiological significance of these extra-*Xbp1* activities of IRE1α in vivo remains poorly characterized.

Similar to IRE1α-deficient mice, global deletion of XBP1 leads to embryonically lethal in mice [17,18,29]. Using cell type-specific knockout mouse models, studies have demonstrated a critical role of IRE1α-XBP1 pathway in secretory cells, most notably B cell-derived plasma cells and pancreatic β cells. Mice with B cell-specific *Xbp1* deficiency show a profound defect in plasma cell production, along with decreased levels of antigen-specific immunoglobulin [30–32]. Intriguingly, IRE1α deficiency in B cells affects not only plasma cell differentiation, but also early stage of B cell development [17]. While VDJ rearrangement occurs normally in XBP1$^{-/-}$ B cells [30], this event is severely defective in the pro-B cell stage of IRE1α$^{-/-}$ B cells [17]. The authors propose that the cytoplasmic domain of IRE1α may directly regulate transcriptional activation of genes involved in VDJ recombination such as *Rag1* (recombination-activating gene 1), *Rag2* (recombination-activating gene 2), and *TdT* (terminal deoxynucleotidyl transferase).

In vitro, IRE1α can be activated by glucose in a concentration-dependent manner [33] and hyperactivation of IRE1α by high glucose may lead to insulin mRNA degradation in pancreatic β cells [34]. Intriguingly, β cell-specific deletion of *Xbp1* in mice results in islet atrophy and hyperglycemia associated with impaired β cell proliferation, insulin maturation and secretion at basal level [35]. Moreover, deficiency of XBP1 caused constitutive hyperactivation of IRE1α, leading to attenuation of *insulin* mRNA via RIDD. On the other hand, while IRE1α deficiency in β cells causes disruption in glucose homeostasis and impairs β cell proliferation under metabolic stress, it did not affect pancreatic structure or islet area [36]. These differential phenotypes observed in β cell specific IRE1α- and XBP1- null mice suggest that each component of this pathway may have its own unique function in cellular physiology. Alternatively, it points to a possible role of the unspliced form of XBP1u, whose physiological role awaits further investigation. Taken together these studies highlight the indispensible role of the IRE1α-XBP1 pathway in ER expansion and survival of highly secretory cell types.

3. The role of IRE1α-XBP1s signaling pathway in cancer

Table 1 and Fig. 2 depict various possible molecular mechanisms underlying the role of IRE1α in cancer. The role of IRE1α in cancer is best illustrated and characterized in multiple myeloma (MM). MM is a malignant proliferation of plasma cells in the bone marrow and share phenotypical characteristics with long-lived plasma cells. Due to abundant synthesis of secretory proteins in the ER, MM cells are hypersensitive to the activation of UPR that aggravates as the disease advances [37]. Thus, these cells require a large capacity of folding and disposal in the ER and are particularly sensitive to compounds targeting proteostasis. IRE1α activation can contribute to cancer progression in several pathways mediated by its substrate XBP1s, which is highly expressed in MM [38]. Blocking of IRE1α RNase activity by IRE1 inhibitors such as STF-083010 or 4μ8C or similarly reducing XBP1 expression by proteasome inhibitor or toyocamycin, an XBP1 inhibitor, attenuates the growth of MM cells, via apoptosis [39–42]. Conversely, forced expression of XBP1s in B cells promotes multiple characteristics of myeloma pathogenesis with lytic bone lesions, plasmacytosis and increased monoclonal antibodies [43]. More than 1000 genes are upregulated in XBP1s-transgenic myeloma cells compared to non-transgenic B cells, including Cyclin D1, Cyclin D2, MAF and MAFB, many of which are known to be involved in human MM pathogenesis. In clinical studies, human MM patients with high ratio of *Xbp1s* mRNA to