Roles of Endoplasmic Reticulum Stress in Immune Responses

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The endoplasmic reticulum (ER) is a critical organelle for protein synthesis, folding and modification, and lipid synthesis and calcium storage. Dysregulation of ER functions leads to the accumulation of misfolded- or unfolded-protein in the ER lumen, and this triggers the unfolded protein response (UPR), which restores ER homeostasis. The UPR is characterized by three distinct downstream signaling pathways that promote cell survival or apoptosis depending on the stressor, the intensity and duration of ER stress, and the cell type. Mammalian cells express the UPR transducers IRE1, PERK, and ATF6, which control transcriptional and translational responses to ER stress. Direct links between ER stress and immune responses are also evident, but the mechanisms by which UPR signaling cascades are coordinated with immunity remain unclear. This review discusses recent investigations of the roles of ER stress in immune responses that lead to differentiation, maturation, and cytokine expression in immune cells. Further understanding of how ER stress contributes to the pathogenesis of immune disorders will facilitate the development of novel therapies that target UPR pathways.

Keywords: ER stress, immune response, inositol requiring enzyme 1 (IRE1), unfolded protein response (UPR), X-box binding protein 1 (XBP1)

INTRODUCTION

Secreted or transmembrane proteins are synthesized, folded, and modified in the endoplasmic reticulum (ER), which also plays crucial roles in lipid biosynthesis, calcium storage, and detoxification (Braakman and Bulleid, 2011; Chen et al., 2010; Marisa et al., 2018)(Fig. 1). Upon entry into the ER lumen, newly synthesized polypeptides are folded and modified to ensure precise conformations and function. Impairments of this process lead to ER stress due to the accumulation of misfolded- or unfolded-proteins in the ER (Byrd and Brewer, 2012). ER homeostasis is sensitive to multiple physiological and pathological processes, and perturbations have been associated with excessive protein synthesis, abnormal ER calcium content, lipid overload, hypoxia, oxidative stress, iron imbalance, nutrient deprivation, cancer, and infection (Kaufman et al., 2002; Marciniak and Ron, 2006; Martins et al., 2016).

Protein quality control is monitored by a complex system that modulates ER function to resolve ER stress and dysfunction. This protective mechanism is known as the unfolded protein response (UPR) and is an adaptive cellular response that elicits specific intracellular signaling pathways to protect against ER stress (Hotamisligil, 2010)(Fig. 1). The UPR restores ER homeostasis by attenuating protein synthesis or by inducing the expression of various genes encoding molecular chaperones and protein processing enzymes that promote protein folding and post-translational modification. Proteins that remain improperly folded are degraded by the proteasome through a pathway known as ER-associated degradation (ERAD)(Adachi et al., 2008). The UPR also enhances ER capacity by promoting expansions of the ER.
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**Fig. 1. ER stress and the unfolded protein response (UPR).** The endoplasmic reticulum (ER) is an essential organelle for protein synthesis, folding, and modification. The ER also plays important roles in lipid biosynthesis, calcium storage, and detoxification. ER homeostasis is disturbed by physiological and pharmacological stressors, and the resulting accumulations of misfolded proteins cause ER stress. ER stress triggers the UPR, which is an adaptive cellular response that is mediated by the three mammalian UPR transducers IRE1, PERK, and ATF6. Under conditions of ER stress, these proteins have various signal-mediated transcriptional effects that ameliorate ER stress. Proteins that are induced by IRE1, PERK, and ATF6 are involved in protein folding and ER expansion, and some attenuate protein translation. In addition, the UPR induces ERAD, which mediates degradation of unfolded proteins by proteasome. Under overwhelming conditions of ER stress, the UPR initiates apoptosis. IRE1, inositol-requiring enzyme 1; PERK, protein kinase R-like ER kinase; ATF6, activating transcription factor 6; ERAD, ER-associated degradation.

Membrane through increased expression of genes involved in lipid metabolism (Lee et al., 2008; Volmer and Ron, 2015; Walter and Ron, 2011). Finally, when these mechanisms fail to resolve chronic or overwhelming ER stress, the UPR stimulates apoptosis (Hetz, 2012).

Accumulating evidence suggests that ER stress is a major contributor to the pathogenesis of several diseases, including obesity, diabetes, cancer, neurodegenerative disorders, and inflammatory and autoimmune diseases, and can increase the severity of these (Hetz et al., 2013; Hotamisligil, 2010; Marciniak and Ron, 2006; Oyadomari et al., 2008; Özcan et al., 2004; Wang and Kaufman, 2012). Wherein sustained ER stress has been associated with the expression of pro-inflammatory cytokines and potential induction of inflammatory responses, causal relationships between immunity and ER stress remain an incipient area of interest (Smith, 2018). Herein, I discuss the underlying mechanisms by which ER stress affects immune responses, with a focus on differentiation and cytokine expression in immune cells and the etiology of immune disorders.

**GENERAL MECHANISMS OF THE UPR**

ER stress is recognized by the ER-resident proteins inositol-requiring enzyme 1 (IRE1), protein kinase R (PKR)-like ER kinase (PERK), and activating transcription factor 6 (ATF6) (Bettigole and Glimcher, 2015) (Fig. 2). These transmembrane proteins are major transducers of the UPR in mammals and mediate multiple distinct signals from the ER to the cytosol. As a UPR initiating response to perturbations of protein folding, the ER chaperone Grp78 dissociates from the ER luminal domain and binds to the unfolded protein to prevent aggregation (Bertolotti et al., 2000; Ron and Walter, 2007; Shen et al., 2002). Various pharmacological agents have been shown to disturb ER functions. Among these, tunicamycin (Tun) prevents N-linked glycosylation, thapsigargin (Tg) depletes Ca\(^{2+}\) from the ER by inhibiting the sarco/endoplasmic reticulum Ca\(^{2+}\)-ATPase (SERCA) pump, dithiothreitol (DTT) interferes with the formation of protein disulfide bonds, and MG132 inhibits the proteasome (Oslowski and Urano, 2011) (Fig. 1).

The proteins IRE1 and PERK are central type-I transmembrane proteins of the UPR. IRE1 has Ser/Thr kinase and endoribonuclease (RNase) domains in the cytoplasmic region, and comparisons of yeast IRE1 with the mammalian homologs IRE1\(^{\alpha}\) and IRE1\(^{\beta}\) reveal a high level of conservation (Fig. 2A). Whereas IRE1\(^{\alpha}\) is expressed in most cells and tissues, IRE1\(^{\beta}\) expression is primarily restricted to epithelial cells of the gastrointestinal tract (Kaufman et al., 2002). The ER-luminal domain of the yeast IRE1 senses misfolded proteins following dissociation of Grp78 and via direct interactions with unfolded proteins, but does not bind to unfolded proteins in mammals (Oikawa et al., 2009). Subsequent IRE1 oligomerization induces autophosphorylation in the kinase domain, and the resulting RNase activity of IRE1 leads to unconventional splicing of yeast HAC1 or mammalian X-box binding protein 1 (XBP1) mRNA (Yoshida et al., 2001). XBP1 mRNA encodes the short unstable protein "unspliced form XBP1" (267-amino acids), and IRE1-mediated excision of 26 intronic nucleotides produces the spliced form that encodes "XBP1s" (371-amino acids). Due to the resulting translational frame-shift, this protein contains a novel carboxyl terminus (Calfon et al., 2002; Lee et al., 2003). Specifically, XBP1s contains a basic leucine zipper (bZIP) domain in the C-terminus and acts as a transcription factor for UPR-related genes, including the ER chaperones ERdj4, HEDJ, Grp58,
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Fig. 2. Signaling pathways of the UPR. ER-resident proteins IRE1, PERK, and ATF6 sense ER stress and deliver distinct signals from the ER to the cytosol. Under normal conditions, Grp78 binds to the ER luminal domains of sensor proteins and inhibits their activation. However, Grp78 dissociates from the sensors in response to ER stress and binds to unfolded proteins, leading to activation of the sensors. (A) IRE1 pathway: IRE1 has Ser/Thr kinase and RNase domain in the cytoplasmic region, and ER stress induces IRE1 oligomerization and autophosphorylation of the kinase domain. The RNase domain of activated IRE1 performs unconventional splicing and cleaves 26 intronic nucleotides from XBP1 mRNA in mammalian cells. This splicing induces a translational frame-shift, and the truncated XBP1 mRNA encodes XBP1s, which contains a new carboxyl terminus. As a transcription factor, XBP1s activates UPR-related genes including ER chaperones, ERAD components, and lipid-biosynthetic enzymes. (B) PERK pathway: PERK is a protein Ser/Thr kinase that undergoes oligomerization and autophosphorylation of the kinase domain under conditions of ER stress. Activated PERK phosphorylates eIF2α at serine 51, resulting in general inhibition of protein translation. However, phosphorylated eIF2α selectively increases the translation of ATF4, which upregulates CHOP and GADD34 mRNA. As a negative feedback mechanism, GADD34 promotes dephosphorylation of eIF2α to restore protein synthesis following elimination of ER stress. However, failure to alleviate ER stress leads to CHOP-mediated apoptosis. (C) ATF6 pathway: ATF6 has a bZIP domain in the cytosol and translocates from the ER to the Golgi apparatus under ER stress. ATF6 is then cleaved by the proteases S1P and S2P to produce the amino-terminus of ATF6-N, which then migrates to the nucleus and upregulates target genes encoding ER chaperones, ERAD components, and XBP1. RNase, endoribonuclease: XBP1, X-box binding protein 1; eIF2α, α-subunit of eukaryotic translation initiation factor 4; CHOP, C/EBP homologous protein; GADD34, growth arrest and DNA damage-inducible protein 34; S1P, site-1 protease.
tein (CHOP) and growth arrest and DNA damage-inducible protein 34 (GADD34) (Fawcett et al., 1999; Ma and Hendershot, 2003; Ma et al., 2002). As a negative feedback mechanism, GADD34 then associates with protein phosphatase 1 (PP1) and promotes dephosphorylation of eIF2α to restore protein synthesis upon stress relief (Harding et al., 2009; Novoa et al., 2003). When ER stress remains unmitigated, CHOP induces apoptosis via the genes encoding death receptor 5 (DR5) and Bim (Puthalakath et al., 2007; Raffaella and Cristina, 2015; Yamaguchi and Wang, 2004; Zinszner et al., 1998). DR5 induces extrinsic apoptosis pathways by recruiting the adaptor protein FADD, which activates caspase-8 (Raffaella and Cristina, 2015). Concomitantly, the pro-apoptotic protein Bim activates Bax and Bak and induces permeabilization of the mitochondrial membrane to release cytochrome c (Urra et al., 2013).

ATF6 is a type-II ER transmembrane protein that contains a bZIP domain in the cytosol and a stress-sensing domain in ER lumen (Adachi et al., 2008)(Fig. 2C). Under conditions of protein homeostasis, ATF6 is maintained in the ER through interactions with Grp78, but is translocated from the ER to the Golgi apparatus under conditions of ER stress, where it is sequentially cleaved at two sites by S1P and S2P proteases (Ye et al., 2000). The released amino-terminal of ATF6 (ATF6-N) then migrates to the nucleus and binds to the ER stress response element (ERSE) containing the consensus sequence CCAAT-N9-CCACG to activate genes encoding ER chaperones, ERAD components, and XBP1 (Chen et al., 2010; Yamamoto et al., 2004; Yoshida et al., 2001).

CROSSTALK BETWEEN ER STRESS AND IMMUNE RESPONSES

ER stress profoundly affects innate and adaptive immune responses and is associated with autoimmune and inflammatory disorders such as diabetes, atherosclerosis, myositis,
and inflammatory bowel disease (Heazlewood et al., 2008; Kaser et al., 2008; Vattemi et al., 2004; Zhang and Kaufman, 2008). Many recent studies show immune roles of the UPR via direct crosstalk between ER stress-induced signaling pathways and immune responses (Bettigole and Glimcher, 2015; Cao et al., 2016; Garg et al., 2012; Janssens et al., 2014; Zhang and Kaufman, 2008).

Increased expression of pro-inflammatory cytokines during ER stress suggests roles of the UPR in inflammatory disorders (Smith, 2018; Wheeler et al., 2008) (Fig. 3A). In agreement, several studies suggest that ER stress induces inflammatory responses by activating UPR transcription factors such as XBP1s, ATF6, and CAMP response element-binding protein H (CREBH) (Kaser et al., 2008; Shkoda et al., 2007; Zhang et al., 2006). A missense mutation in the Muc2 gene, which encodes the major constituent of intestinal mucus mucin, led to the accumulation of the MUC2 precursor in mouse goblet cells, thereby increasing ER stress and Grp78 and XBP1s expression (Heazlewood et al., 2008). These mice were susceptible to intestinal inflammation and had increased levels of inflammatory cytokines IL-1β, TNF-α, and IFN-γ in the colon. UPR activation was also demonstrated during chronic inflammation, with increased Grp78 expression in intestinal epithelial cells of IL-10-deficient mice and in patients suffering inflammatory bowel disease (Shkoda et al., 2007). In this study, treatments with the anti-inflammatory cytokine IL-10 reduced Grp78 expression in MODE-K epithelial cells, reflecting suppressed recruitment of ATF6 to the Grp78 promoter following inhibition of nuclear translocation of ATF6. In contrast, XBP1s-deletion in mouse intestinal epithelial cells led to ER stress and increased pro-inflammatory responses to flagellin (Kaser et al., 2008). These mice also had impaired antimicrobial peptide secretory activities of Paneth cells, and thereby developed spontaneous enteritis. In another study, hepatocyte-specific transcription factor CREBH was cleaved by S1P and S2P in response to ER stress, and the amino-terminal fragment of CREBH upregulated several pro-inflammatory cytokines during ER stress, which induces translational suppression of IκBα and C-reactive protein (CRP), contributing to the inflammatory response (Zhang et al., 2006).

Accumulating evidence suggests that ER stress activates inflammatory signaling cascades through the interaction between UPR components and canonical cytokine-regulatory transcription factors (Smith et al., 2008)(Fig. 3B). ER stress reportedly activates NF-κB signaling, and this was considered a mechanism for inducing inflammatory responses (Deng et al., 2004; Hu et al., 2006). ER stress induced the formation of a complex between IRE1α and IκB kinase (IKK) through the adaptor protein TNF-α receptor associated factor 2 (TRAF2), thus promoting TNF-α production by enhancing IκBα degradation and NF-κB activation (Hu et al., 2006). In addition, NF-κB was activated by eIF2α phosphorylation, which induces translational suppression of IκBα (Deng et al., 2004). Following binding of TRAF2 to IRE1 cytoplasmic regions, IRE1α and IRE1β activated c-Jun N-terminal kinase (JNK) (Urano et al., 2000). These data were also confirmed in XBP1-deficient small intestines, with IRE1α hyperactivation and increased phosphorylation of JNK (Kaser et al., 2008). Although these studies collectively indicate immunological roles of the UPR, further studies are required to characterize and identify the related regulatory mechanisms and signaling molecules.

Several studies show that inflammation augments ER stress responses (Fig. 3C). In particular, injections of pro-inflammatory cytokines such as IL-1β and IL-6, induced ER stress and activated the UPR in the livers of mice (Zhang et al., 2006). The inflammatory cytokine TNF-α also increased eIF2α phosphorylation and XBP1s expression by elevating reactive oxygen species (ROS) levels in L929 murine fibrosarcoma cells (Xue et al., 2005). The immunostimulant lipopolysaccharide (LPS) increases the production of inflammatory cytokines, and intraperitoneal injections of LPS into mice activated the transcription of ER stress-related genes, including Xbp1s, Atf4, and Chop (Endo et al., 2005). Among encoded proteins, CHOP plays a key role in the apoptosis of lung cells. LPS injection also increased protein levels of XBP1s, Grp78, CHOP, and ER degradation-enhancing α-mannosidase-like protein (EDEM) in the livers of mice (Zhang et al., 2006). However, the mechanisms by which LPS activates the UPR pathway have not been precisely demonstrated and are likely key factors in the link between inflammatory responses and ER stress.

**ROLES OF THE UPR IN IMMUNE CELLS**

Because the UPR is required for ER expansion and protein secretion, it is essential for development, differentiation, and the precise function of highly secretory cells, including pancreatic β cells, exocrine acinar cells, hepatocytes, and salivary gland epithelial cells (Bettigole and Glimcher, 2015; Harding et al., 2001; Lee et al., 2005; Lipson et al., 2006; Marisa et al., 2017; Reimold et al., 2000; Rutkowski and Hegde, 2010)(Fig. 4A). The UPR also has crucial roles in the development of immune cells, such as plasma cells, dendritic cells (DCs), and eosinophils (Bettigole et al., 2015; Iwakoshi et al., 2007; Lee et al., 2003; Reimold et al., 2001)(Fig. 4B). Many recent studies of various immune cell types show roles of ER stress in immune processes, including differentiation, immune activation, and cytokine expression.

**CD4+ T cells**

Depending on microenvironments, naive CD4+ T cells differentiate into one of several lineages of helper T (Th) cells, including T helper type 1 (Th1), Th2, Th9, Th17, and regulatory T cells (Tregs) (Stadhouders et al., 2018). Effector T cell subsets secrete distinguishing cytokines and coordinate regulation of different aspects of immune responses. Potentially, the UPR plays fundamental roles in T cell differentiation upon antigen recognition. This hypothesis is supported by observations of activated ER stress responses during differentiation of Th2 cells, and the PERK-eIF2α axis has been implicated in this process (Scheu et al., 2006). Specifically, primed Th2 cells showed increased phosphorylation of eIF2α and upregulation of ATF4 and its target genes Gadd34, Herp, Chop, and Grp78. Moreover, restimulation of Th2 cells resulted in rapid dephosphorylation of eIF2α, thereby activating translation and production of IL-4. XBP1 is important for the differentiation of Th17 cells, which are associated with...
Fig. 4. Roles of the UPR in immune cells. (A) Roles of the UPR in secretory cells: the UPR regulates ER expansion and protein secretion, and is therefore essential for development, differentiation, and specialized functions of highly secretory cells, such as pancreatic β cells, exocrine acinar cells, hepatocytes, and salivary gland epithelial cells. (B) Roles of the UPR in immune cells: the UPR plays crucial roles in the development of immune cells, such as plasma cells, DCs, and eosinophils. ER stress also regulates immune cell differentiation, activation, and cytokine expression. In CD4+ T cells, the UPR regulates differentiation to Th2 cells, Th17 cells, and Tregs, and has an important function in TCR-mediated activation. The IRE1–XBP1 pathway is important for differentiation of CD8+ T cells into effector cells. The UPR is also activated during B cell differentiation, and XBP1s is essential for antibody secretion from plasma cells. ER stress strongly influences innate and adaptive immune responses by modulating the production of pro-inflammatory cytokines in B cells, macrophages, and DCs. In macrophages, XBP1s and ATF6 function as positive regulators of inflammatory cytokine expression following TLR stimulation. XBP1s also regulates developmental and inflammatory responses of DCs. However, in DCs of tumor microenvironments, XBP1s induces abnormal lipid accumulation and inhibits anti-tumor immunity. TCR, T cell receptor; Th2, T helper type 2; Tregs, regulatory T cells; TLR, Toll-like receptor.

various inflammatory and autoimmune diseases (Brucklacher-Waldert et al., 2017; Stadhouders et al., 2018). In this study, cellular stress, such as low oxygen or glucose levels and ionic pressure, enhanced the generation of Th17 cells by increasing cytoplasmic calcium levels and XBP1 activity (Brucklacher-Waldert et al., 2017). In contrast, inhibition of cellular stress and conditional deletion of XBP1 in lymphocytes suppressed Th17 cell-dependent autoimmunity in a mouse model of experimental autoimmune encephalomyelitis (EAE). Moreover, adoptive transfer of Th17 cells generated by ER stress inducer increased the disease severity of EAE.

A recent study showed that ER stress responses are important for CD4+ T cell activation (Thaxton et al., 2017). In their study, T cell receptor (TCR) ligation-mediated ER stress increased Grp94 expression in CD4+ T cells, whereas deletion of Grp94 resulted in a critical activation defect. In addition, Grp94-deficient T cells showed impaired Ca2+ mobilization upon TCR engagement and failed to accomplish activation-induced glycolysis. ER molecular chaperone Grp94, upregulated by ER stress, has diverse immunological activities (Ansa-Addo et al., 2016).

Regulatory T cells (Tregs)
The effects of ER stress on differentiation have been investigated in Tregs that maintain tolerance to self-antigens and prevent autoimmune disease (Franco et al., 2010). Specifically, T cells from patients with Kawasaki disease produced high levels of the anti-inflammatory cytokines IL-10 and TGF-β, and Foxp3, which is a critical transcription factor for Tregs (Franco et al., 2010). Treatments of these cells with thapsigargin induced the expression of the ER stress-response genes Grp78, Chop, and Gadd34, and the Il-10. Conversely, inhibition of eIF2α phosphorylation by the agent salubrinal limited Il-10 transcription, suggesting that eIF2α phosphorylation suppresses the differentiation of IL-10-producing Tregs.

CD8+ T cells
In the presence of pathogens, CD8+ cytotoxic T cells secrete various cytokines and cytotoxic molecules to eliminate infected cells. In a study of CD8+ T cells by Kamimura and Bevan, the IRE1-XBP1 pathway was activated by acute infection and was required for differentiation into effector T cells.
stimulated IFN-β expression of XPB1s or thapsigargin treatments increased LPS-phagosome, and the bacterial burden was increased in mice in absence of XBP1-deficiency, IL-6 production was reduced in macrophages, and TLR2 and TLR4 activated the IRE1α-mediated splicing and increases XBP1s mRNA expression in Ag-specific CD8+ T cells (Kamimura and Bevan, 2008). Finally, splicing of XBP1 mRNA was enriched in terminally differentiated effector cells expressing killer cell lectin-like receptor G1 (KLRG1), whereas XBP1-deficiencies in CD8+ T cells decreased the proportion of KLRG1high effector cells.

B cells
The physiological importance of the UPR was first described in B cells that were differentiating into plasma cells. In these studies, the UPR was activated during differentiation of B cells, and XPB1s was deemed essential for antibody production from plasma cells (Gass et al., 2002; Reimold et al., 2001; Shaffer et al., 2004; Todd et al., 2009). Accordingly, XPB1s induced ER expansion in plasma cells, therefore accommodating the synthesis of large amounts of immunoglobulin (Shaffer et al., 2004). Whereas XPB1-deficient B cells developed normally and formed germinal centers upon activation, they failed to secrete immunoglobulins (Reimold et al., 2001; Taubenheim et al., 2012). As a transcription factor, Blimp-1 necessary for plasma cell differentiation, and Blimp-1-deficient B cells failed to activate transcription of most plasma cell-related genes, including Xbp1 (Shaffer et al., 2004). In contrast, Blimp-1 was normally induced in XPB1-deficient B cells, indicating that XPB1 acts downstream of Blimp-1. Moreover, XPB1-deficiency prevented upregulation of genes encoding secretory pathway components. A recent study suggested that Blimp-1 also plays crucial roles in the UPR in plasma cells, reflecting direct transcriptional regulation of Atf6 and Em1 (encoding IRE1) (Tellier et al., 2016).

ER stress also upregulated the production of pro-inflammatory cytokines in B cells, and expression of Ag with the ER-retention motif KDEL in B cells induced the ER stress-responsive genes Gadd34, Grp78, and Chop (Wheeler et al., 2008). Thapsigargin treatment induced transcription of those UPR genes and pro-inflammatory cytokine genes, IL-23p19, IL-6, TNF-α, and IL-2 in B cells. It follows that these B cells induced the production of IFN-γ and TNF-α in CD4+ T cells.

Macrophages
Macrophages are crucial effector cells of the innate immune system that phagocytose pathogens and produce various inflammatory mediators (Hirayama et al., 2018). XPB1s is a positive regulator of toll-like receptor (TLR) responses in macrophages, and TLR2 and TLR4 activated the IRE1α-XBP1s axis, but not the PERK or ATF6α pathways (Martinson et al., 2010). Moreover, XPB1s was required to produce pro-inflammatory cytokines, such as IL-6, TNF, and INF-β. TLR-mediated splicing of XBP1 mRNA was dependent on signaling via TIRAP, MyDD8, TRIF, TRAF6, and NADPH oxidase 2 (NOX2) as a TRAF-bound enzyme complex. Under condition of XPB1-deficiency, IL-6 production was reduced in macrophages, and the bacterial burden was increased in mice infected with an intracellular pathogen. Conversely, overexpression of XPB1s or thapsigargin treatments increased LPS-stimulated IFN-β production in RAW267.4 cells (Smith et al., 2008).

Prolonged ischemia induces the expression of pro-inflammatory cytokines in liver Kupffer cells, primarily through ER stress-activated ATF6 (Rao et al., 2014). Accordingly, knockdown of ATF6 in macrophages suppressed the expression of TNF-α and IL-6 by limiting NF-κB activity. In agreement, alleviation of ER stress using the chemical chaperone 4-phenylbutyrate (4-PBA) or ATF6 siRNA led to decreased inflammatory responses in Kupffer cells against ischemia-reperfusion.

Dendritic cells (DCs)
DCs are professional antigen-presenting cells, and developmental and survival roles of XPB1s have been demonstrated in these cells (Iwakoshi et al., 2007). In agreement, XPB1s expression was greater in plasmacytoid DCs than in immature conventional DCs, and XPB1-deficient chimeric mice had decreased numbers of conventional and plasmacytoid DCs. Under conditions of ER stress, treatment with TLR agonists significantly enhanced IL-23p19 expression in DCs (Goodall et al., 2010). The gene Il-23 is a target of CHOP whereby both ER stress and TLR stimulation enhanced binding of CHOP to its promoter. Consequently, knockdown of CHOP reduced the expression of IL-23 in U937 cells and in Chlamydia trachomatis-infected myeloid cells. ER stress also significantly increased the levels of inflammatory cytokines and IFN-β in DCs stimulated by polyIC (Fanlei et al., 2011). Whereas silencing of XPB1 inhibited polyIC-induced IFN-β expression, overexpression of XPB1s synergistically augmented inflammatory responses in polyIC-stimulated DCs. In addition, XPB1s-induced IFN-β effectively inhibited vesicular stomatitis virus infections.

A recent study associated tumor microenvironments with ER stress in DCs, and showed that XPB1s is important for the suppression of anti-tumor immunity (Cubillos-Ruiz et al., 2015). Specifically, XPB1s promoted the triglyceride biosynthetic program in DCs, which led to abnormal lipid accumulation and impaired antigen presentation. Conversely, DC-specific deletion of XPB1 restored immunostimulatory activities and increased anti-tumor responses.

ROLES OF REGULATED IRE1-DEPENDENT DECAY (RIDD) IN IMMUNE RESPONSES
Several recent studies show that IRE1 recognizes unspliced XBP1 mRNA and various other mRNAs as substrates to be degraded, and the associated process is called regulated IRE1-dependent decay (RIDD) (Coelho and Domingos, 2014; Hollien and Weissman, 2006; Hollien et al., 2009)(Fig. 5). Because IRE1 mediates the degradation of mRNAs encoding ER-targeted proteins, RIDD was originally thought to reduce ER protein loads during ER stress (Hollien and Weissman, 2006). In mammalian cells, RIDD targets have specific motifs with the consensus sequence CUGCAG and secondary structures that are similar to the stem-loop of XBP1 mRNA (Moore and Hollien, 2015; Oikawa et al., 2010; So et al., 2015)(Fig. 5A). Emerging evidence indicates that RIDD targets various mRNAs and therefore has diverse physiological functions, particularly in drug and lipid metabolism, and ER
A Unconventional splicing of XBP1 mRNA by IRE1: ER stress results in activation of the RNase domain of IRE1 by inducing IRE1 oligomerization and autophosphorylation of kinase domains. The RNase domain of activated IRE1 recognizes two stem-loop structures on XBP1 mRNA and splices motifs with the consensus sequence CUGCAG. The 26-nucleotides intron is cleaved from XBP1 mRNA, and the exons are joined by tRNA ligase to generate spliced XBP1 mRNA encoding XBP1s.

B Regulated IRE1-dependent decay (RIDD): in addition to XBP1 mRNA, IRE1 recognizes ER-bound mRNAs and promotes their degradation to reduce the protein folding load of ER. This process is known as regulated IRE1-dependent decay (RIDD). IRE1 recognition motifs of RIDD substrates carry the CUGCAG consensus sequence and a secondary structure that is similar to the stem-loop of XBP1 mRNA. XBP1 deficiency induces IRE1 hyperactivation in various cells by as yet unknown mechanisms. RIDD targets various mRNAs to achieve diverse physiological functions, such as reducing plasma lipid levels (Ces1, Angptl3), protecting against drug toxicity (Cyp1a2, Cyp2e1), maintaining ER homeostasis in goblet cells (MUC2), and causing dysfunction of pancreatic \( \beta \)-cells (Ins1, Ins2, PC1, PC2, CPE).

RIDD also regulates immune processes, such as antigen presentation by CD8\(^+\) DCs (Itgb2, Tapbp), synthesis of secretory IgM in B cells (\( \mu S \) heavy chain), and cytokine production from iNKT cells (T-bet, Gata-3). Ces1, carboxylesterase 1; Angptl3, angiopoietin-like protein 3; Cyp1a2, cytochrome P450 1A2; Cyp2e1, cytochrome P450 2E1; MUC2, mucin 2; Ins1, insulin 1; Ins2, insulin 2; PC1, prohormone convertase 1; CPE, carboxypeptidase E; Itgb2, integrin subunit beta 2; Tapbp, TAP binding protein; \( \mu S \), secretory \( \mu \) chain; iNKT, invariant natural killer T.
promoted by palmitic acid, leading to the inhibition of IL-4 and IFN-γ production in γδT cells and suppression of arthritis (Ko et al., 2017).

Several miRNAs have been identified as RIDD targets, and these reportedly increase the expression of other mRNAs during ER stress (Upton et al., 2012). IRE1α improved the stability of thioredoxin-interacting protein (TXNIP) mRNA by inducing cleavage of miR17, which destabilizes TXNIP (Lerner et al., 2012). Consequent augmentation of TXNIP likely activates the NLRP3 inflammasome, thus inducing caspase-1 cleavage and IL-1β secretion, and promoting inflammation and programmed cell death.

CONCLUSION

The ER is an essential organelle for protein homeostasis, and perturbations of ER homeostasis by physiological or pathological stressors cause accumulations of misfolded proteins in the ER. ER stress-induced UPR restores ER homeostasis through dynamic intracellular signaling pathways but gains its relationship with various diseases by regulating cell-specific functions. Much remains unknown regarding the impacts of ER stress on immune responses, although recent studies suggest that ER stress has specific immune regulatory activities in specialized cells and tissues. These studies collectively suggest that the UPR is a fundamental mediator of the pathogenesis of inflammatory disorders. In line with this suggestion, ER stress is known to induce inflammatory responses through UPR signaling, and immune cells are extensively dependent on the signaling branches of the UPR to perform their specific functions. Improved understanding of the molecular mechanisms underlying ER stress-regulated immune responses may lead to the discovery of new therapeutic targets for immune disorders. However, investigations of the UPR branches and their associated molecules in specific immune cells and under specific immune disorders remain challenging.

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