Endoplasmic Reticulum Stress in Immunity

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Abstract

Immune responses occur in the midst of a variety of cellular stresses that can severely perturb endoplasmic reticulum (ER) function. The unfolded protein response is a three-pronged signaling axis dedicated to preserving ER homeostasis. In this review, we highlight many important and emerging functional roles for ER stress in immunity, focusing on how the bidirectional cross talk between immunological processes and basic cell biology leads to pleiotropic signaling outcomes and enhanced sensitivity to inflammatory stimuli. We also discuss how dysregulated ER stress responses can provoke many diseases, including autoimmunity, firmly positioning the unfolded protein response as a major therapeutic target in human disease.

INTRODUCTION

Maintaining the fidelity of the host cell proteome is of the utmost importance for preserving cellular homeostasis, unequivocally illustrated by the ever-increasing number of diseases provoked by aberrant handling of misfolded proteins. An extensive network of over 1,000 components preserves basal protein homeostasis (also known as proteostasis; 1) by controlling protein synthesis and degradation rates, acting as folding chaperones, depositing stabilizing posttranslational modifications, identifying incorrectly folded proteins, and coordinating proper subcellular localization (1). Though multiple levels of surveillance and regulation have evolved to maintain the steady-state proteome, cells additionally require robust stress response networks in case the supply of nascent proteins exceeds the capacity of steady-state proteostasis networks.

These stress responses can be triggered exogenously, by microenvironmental cues such as hypoxia, nutrient deprivation, low pH, and exposure to oxidized lipids, as well as endogenously, via cellular differentiation or significant deviation from metabolic set points. Aggregation and misfolding of cytosolic proteins are detected via the heat shock protein system, a coordinated group of chaperones charged with facilitating substrate stabilization and/or proteasomal degradation. Transmembrane and secreted proteins, which make up a full third of the total cellular proteome, are cotranslationally translocated into the rough endoplasmic reticulum (ER) and therefore escape surveillance by the heat shock protein network. Instead, a comprehensive, three-pronged system known as the unfolded protein response (UPR) corrects pathological protein misfolding and aggregation within the ER.

We discuss in the following sections how individual UPR-signaling pathways are comprehensively integrated within the immune response at multiple levels. Though initial studies were centered on UPR roles in plasma cell differentiation, recent studies have found greatly extended functions of ER stress mediators in immunity, now known to encompass direct defense from microbial pathogens, proinflammatory cytokine production, antigen presentation to T cells, immunogenic cell death, metabolic homeostasis, and maintenance of immunological tolerance. Many of these recently discovered functions have sparked thoughtful reconsideration of the role of protein unfolding stress in the activation of canonical UPR mediators. The combined insights from recent studies highlight the close interplay between basic cell biological processes and inflammatory signaling and suggest potential strategies for therapeutically titrating the balance between tolerance and inflammation.

UPR SIGNAL TRANSDUCTION: THREE MAIN PATHWAYS

The ER requires a unique subcellular environment to simultaneously enable intra- and intermolecular disulfide bond formation, protein N-linked glycosylation, calcium storage, and lipid biosynthesis. These ER functions are highly interconnected, and perturbations in one directly affect the others. For instance, calcium is required for chaperone activity of many ER-resident proteins, and thus calcium store depletion induces ER stress by reducing the ER proteostasis network capacity. Similarly, genetic or chemical inhibition of either N-linked glycosylation or lipid biosynthesis activates ER-stress-response modules, and the UPR correspondingly upregulates genes required for protein folding, protein degradation, lipid production, and glycosylation.

To combat excessive accumulation of malfolded proteins, multicellular organisms mount a coordinated response driven primarily by three ER-localized transmembrane proteins—the dual kinase/endoribonuclease inositol-requiring enzyme 1α (IRE1α/*Ern1*), the kinase PKR-like ER-resident kinase (PERK/*Eif2ak3*), and activating transcription factor 6α (ATF6α/*Atf6*) (**Figure 1**). Under homeostatic conditions the luminal domains of each of these proteins are physically bound

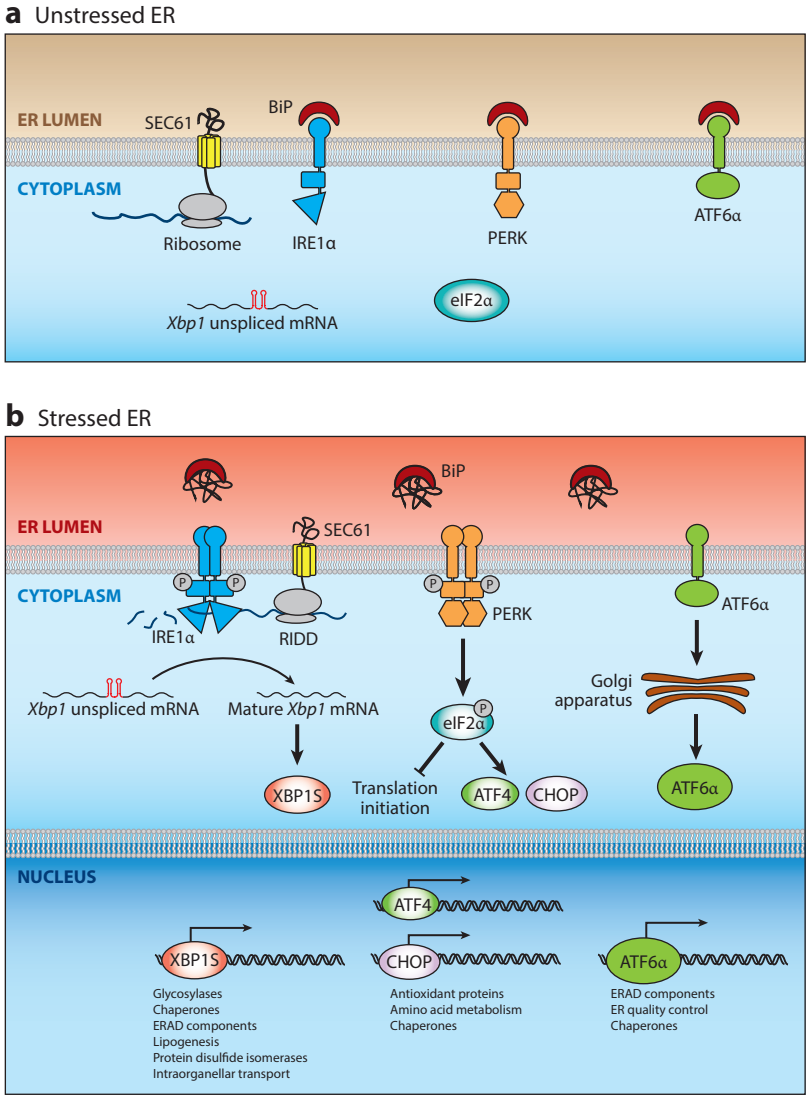

Figure 1

(*a*) During steady state, secretory and transmembrane proteins are translated directly into the ER via the SEC61 translocon, while the three main unfolded protein response (UPR) mediators are held inactive by the chaperone protein BiP. (*b*) Upon ER stress, BiP dissociates from all three UPR mediators, leading to their activation. Inositol-requiring enzyme 1α (IRE1α) splices the *Xbp1* mRNA and can also degrade ER-localized mRNAs via the regulated IRE1α-dependent decay (RIDD) pathway. PKR-like ER-resident kinase (PERK) phosphorylates eIF2α, which shuts down cap-dependent translation and facilitates the production of activating transcription factor 4 (ATF4) and CHOP. ATF6α translocates to the Golgi apparatus, where membrane proteases liberate the N-terminal transcription factor. All three branches work cohesively to correct the stress but can also drive apoptosis under unresolvable ER stress. Abbreviation: ERAD, ER-associated degradation.

and held inactive by the HSP70-type chaperone BiP/*Hspa5* (2, 3). However, BiP has higher affinity for misfolded proteins than for UPR mediators, and thus the accumulation of misfolded substrates titrates away this steady-state inhibition. Release from BiP leads to the activation of all three UPR branches, coupling PERK-mediated global translational suppression with robust transcriptional induction of proteostasis modulators.

IRE1α

The IRE1α-signaling axis is the most highly conserved of the three major UPR branches, present across species from yeasts to humans. BiP dissociation from the luminal domain of IRE1α facilitates its homodimerization and autophosphorylation, a process that, at least in *Saccharomyces cerevisiae*, may be additionally aided by direct detection of misfolded proteins (3a). IRE1α activation is also carefully tuned by a number of interacting proteins, such as BAK, BAX, BI-1, and AIP-1 (reviewed in 4). IRE1α phosphorylation then triggers a conformational shift that activates its C-terminal endoribonuclease activity. In an unconventional cytoplasmic-splicing reaction, the endoribonuclease then excises 26 base pairs from the *Xbp1* mRNA, and subsequent mRNA religation causes a translational reading frame shift yielding the highly active transcription factor known as XBP1S (5, 6). The translated product of unspliced *Xbp1* is apparently highly labile and is difficult to detect without the use of proteasome inhibitors, corroborating the importance of the IRE1α/XBP1-signaling chain (7). This unique isoform-switch mechanism enables rapid, finely tuned responses to perturbations in ER homeostasis.

XBP1 is a member of the CREB/ATF basic leucine zipper family of transcription factors and was originally identified over 20 years ago in our laboratory as a regulator of MHC-II expression (8). Since then, over two decades of work has clearly demonstrated that the canonical XBP1 transcriptional targets include protein chaperones, disulfide isomerases, ER translocases, glycosylases, members of the ER-associated degradation (ERAD) system, and components of the COP-II endomembrane transport system (9). Cumulatively, XBP1 promotes physical ER expansion and elaboration of the secretory protein apparatus (10, 11). The more recent application of global mRNA profiling techniques has greatly expanded the universe of known XBP1 direct transcriptional targets, which now encompasses lipid metabolism (12), proinflammatory cytokines (13), the HIF-1α hypoxia response pathway (14), cellular differentiation (15), and the hexosamine biosynthetic pathway (16). The IRE1α/XBP1-signaling axis therefore influences many signaling pathways previously thought to lie outside the scope of the traditional UPR program.

Under conditions of profound ER stress, the IRE1α RNAse domain robustly degrades non-*Xbp1* mRNA substrates, a phenomenon known as regulated IRE1α-dependent decay (RIDD) (17). Though *Xbp1* is the preferred IRE1α substrate, RIDD can be driven by the formation of higher-order IRE1α oligomers, possibly owing to enhanced avidity for mRNA substrates (18). ER localization is another major factor regulating sensitivity to this "promiscuous" RNAse behavior (19), suggesting that IRE1α hyperactivation acts as an adaptive mechanism to limit the influx of nascent proteins until extreme ER stress is mitigated. Intriguingly, the fission yeast *Schizosaccharomyces pombe* relies solely on this mechanism for maintaining ER homeostasis, as it lacks any identifiable homologues for XBP1 and a UPR transcriptional program (20). Despite its ability to reduce ER stress, RIDD initiation in mammalian cells is also costly, tipping cell fate toward apoptosis rather than survival (18). Furthermore, for reasons that have yet to be elucidated, tissue-specific genetic ablation of *Xbp1* can lead to constitutive IRE1α phosphorylation and RIDD activation (21), severely complicating interpretations of the in vivo function of XBP1. Indeed, the severity of some seemingly XBP1-dependent phenotypes has turned out to be partially driven by RIDD (21–23). Thus, future studies on the in vivo roles of XBP1 should be matched with

similar IRE1α genetic models for more accurate mechanistic insight, especially because evidence for physiologically relevant RIDD induction remains scarce.

PERK

PERK is an ER-resident type I transmembrane protein, and one of four known eIF2α protein kinases. Like IRE1α, BiP dissociation from PERK promotes autophosphorylation and dimerization. After PERK is phosphorylated, it directly phosphorylates the translation initiation factor eIF2α, greatly inhibiting general translation by interfering with 5′-cap assembly (24, 25). This translational inhibition is critical for maintaining pancreatic β cell survival and metabolic homeostasis, as *Eif2ak3*$^{-/-}$ mice progressively develop insulin resistance due to insufficient insulin production (26). General translational inhibition results in an increase in cap-independent translation, facilitating the accumulation of the transcription factor ATF4 through an alternative translation initiation site (27). ATF4 then transcriptionally upregulates the transcription factor *Ddit3*/CHOP (28), which has been shown to regulate apoptosis in a variety of cellular stress conditions. CHOP and ATF4 upregulate antioxidant defenses in parallel but are also responsible for translation reinitiation during the late-stage UPR through the induction of *Ppp1r15a*/GADD34 (29).

ATF6α

ATF6α is an ER-resident type II transmembrane protein featuring a cytoplasmic N-terminal bZIP transcription factor. Unlike PERK and IRE1α, BiP disengagement drives ATF6α mobilization to the Golgi apparatus, where it subsequently undergoes intramembrane proteolysis by site 1 and site 2 proteases to yield the active transcription factor (30, 31). Multiple members of the CREB3 family of transcription factors, including LUMAN and OASIS, are similarly activated by proteolytic cleavage and perform auxiliary functions in preserving secretory pathway health (32). ATF6α controls a limited set of ER quality control proteins, many of which are coregulated by XBP1 (33). Consistent with the more minor role of ATF6α in maintaining ER homeostasis, *Atf6*$^{-/-}$ mice are viable and have no apparent phenotype at baseline. This is in stark contrast with *Ern1*$^{-/-}$ and *Xbp1*$^{-/-}$ mice, both of which are embryonic lethal (34, 35). However, *Atf6* deficiency compromises cell survival during chemically induced ER stress both in vitro and in vivo, indicating that this factor optimizes the UPR along with IRE1α and PERK.

Coordinating a UPR

Under conditions of acute, pharmacological ER stress, all three UPR branches are carefully choreographed to maximize cellular adaptation. Finely coordinated regulation is critical, as decontextualizing individual UPR signaling pathways leads to fundamentally different proteostasis environments (36). XBP1 and ATF6α bolster the ER protein folding capacity by upregulating chaperones, glycosylases, ERAD components, intracellular transport machinery, and protein disulfide isomerases. In addition to splicing *Xbp1*, IRE1α may restrict protein influx into the ER by degrading ER-localized mRNAs. In parallel, PERK shuts down protein synthesis to allow time for the ER to correct existing misfolded proteins, while its downstream target genes induce a potent antioxidant response to counter the production of reactive oxygen species (ROS) generated during iterative protein folding cycles. Under lethal ER stress prosurvival IRE1α is gradually shut off while PERK remains activated, demonstrating that temporal and branch-specific UPR control is also critical for determining adaptation versus survival (37). Successful neutralization of the instigating stress results in cell survival, whereas the outcome for failure is cell death.

CONSTRUCTING AN IMMUNE SYSTEM: ER STRESS IN DIFFERENTIATION

Cellular differentiation is one of the most well established in vivo functions for the UPR. Indeed, the embryonic lethality of *Xbp1*$^{-/-}$ mice derives from failed liver development, whereas mice rescued by liver-specific *Xbp1* transgene expression die postpartum from defective development of the exocrine pancreas. Similarly, loss of *Ern1*, *Xbp1*, or *Eif2ak3* in the adult animal leads to significant histological aberrations, hypomorphic and disorganized subcellular secretory structures, secretory failure, and/or increased cell death in pancreatic β cells.

Plasma Cells

Plasma cells are terminally differentiated B cells specialized for secreting large amounts of immunoglobulin, and consequently they require an extensive, highly elaborated ER network. *Rag1*$^{-/-}$ blastocysts reconstituted with *Xbp1*$^{-/-}$ fetal liver cells failed to yield mature plasma cells and exhibited a drastic reduction in serum antibody levels (38), a finding replicated via selective deletion of *Xbp1* in the B cell compartment (39). However, XBP1 had no effect on B cell commitment or maturation, isotype switching, or memory cell development (39), thereby establishing XBP1 as an indispensable transcription factor for plasma cell development. After XBP1 was linked with the UPR, its function in plasma cells was further refined, placing it downstream of the plasma cell transcription factor BLIMP-1 and cementing the connection between protein folding, ER expansion, and plasma cell homeostasis (10, 40). More recent studies utilizing conditional *Ern1*$^{-/-}$ mice demonstrated that RIDD only partially accounts for the observed defects in antibody production (22, 41), confirming the importance of XBP1 in supporting optimal plasma cell function. These findings likely explain why proteasome inhibitors, which interfere with XBP1 activation through multiple mechanisms (42), exhibit high clinical efficacy against the plasma cell malignancy multiple myeloma.

Though it is generally assumed that UPR induction during plasma cell differentiation is caused by the differentiation-induced increase in immunoglobulin protein synthesis, genetic abrogation of IgM secretion has no effect on *Xbp1* splicing (43). Therefore, increased protein synthesis and misfolding per se are unlikely to directly trigger the UPR, though the responsible signaling cascade remains poorly understood. Furthermore, plasma cell differentiation triggered by LPS and IL-4 treatment selectively activates IRE1α and ATF6α, but not PERK, demonstrating that UPR branches can be individually modulated instead of simply activated or suppressed en masse (44). However, IRE1α is the only UPR branch required for robust antibody secretory production (45). Appreciating these intricacies of plasma cell differentiation will require a more nuanced understanding of the mechanisms regulating utilization of specific UPR branches, as well as a careful reconsideration of the relevance of unfolded protein accumulation to the activation of UPR mediators.

Paneth Cells

Paneth cells are specialized intestinal epithelial cells found at the base of intestinal crypts, histologically identifiable by prominent eosinophilic secretory granules. Paneth cells synthesize a wide array of antimicrobial proteins to control inflammatory responses in the gastrointestinal host-microbiota interface. The first indication that the UPR might help maintain intestinal homeostasis came from studies on *Ern2*$^{-/-}$ mice, which lack the protein IRE1β. Whereas IRE1α is expressed ubiquitously, expression of the closely related isoform IRE1β is restricted to the

intestinal and lung epithelia. *Ern2*$^{-/-}$ mice were hypersensitive to dextran sodium sulfate–induced colitis, and Bertolotti et al. (46) posited that UPR-associated pathways likely help maintain tolerance in the face of frequent environmental microbial and chemical challenges.

Several years later, the specific role of the UPR in Paneth cell homeostasis and survival and intestinal inflammation was directly addressed with mice lacking *Xbp1* specifically in the intestinal epithelium. Paneth cells were almost completely absent in these mice, with the few surviving cells demonstrating dramatic disorganization of subcellular secretory architecture and hypomorphic granule formation. *Xbp1* deficiency also reduced the number of secretory goblet cells to half. Interestingly, the combined defects in the intestinal epithelium led to spontaneous, microbiota-dependent enteritis and hyperreactivity to colitogenic stimuli, demonstrating that severe UPR dysfunction can directly contribute to breakdown in immunological tolerance by crippling Paneth cell development (47). Though later studies showing that mice conditionally deficient in *Ern1* lack intestinal inflammation, the combined deletion of *Xbp1* and *Ern1* resulted in an intermediate inflammatory phenotype, validating the importance of fine UPR control in Paneth cell differentiation and gastrointestinal homeostasis (48).

Dendritic Cells

It is generally believed that the UPR is only involved in the development and differentiation of professional secretory cells, where the persistent demand for robust protein synthesis may overwhelm a frequently strained proteostasis network. However, XBP1-deficient bone marrow cells also exhibit impaired dendritic cell (DC) viability. Freshly isolated splenic DCs constitutively splice *Xbp1* at steady state, and multiple DC subsets were reduced in *Xbp1*$^{-/-}$ lymphoid chimeras. *Xbp1* splicing was most dramatic in CD8α^+ DCs and plasmacytoid DCs (pDCs), and PERK was activated in both CD8α^+ DCs and CD11b$^+$ DCs (23). pDCs, which produce tremendous amounts of type I interferons in response to TLR activation, were most severely affected, being reduced to 25% of wild-type levels (49). More recent studies utilizing conditional knockout mice revealed that *Xbp1*$^{-/-}$ CD8α^+ DCs also have a defect in antigen cross presentation, though this appears to be driven entirely by RIDD and its physiological relevance remains unclear (23). Direct viral infection of DCs (50) may induce the necessary RIDD to deactivate cross presentation, but the in vivo consequences of such a selective antigen-presentation defect have yet to be determined. Identifying the mechanism(s) responsible for XBP1-dependent DC survival, as well as physiologically relevant microenvironmental RIDD inducers, is of critical importance. Furthermore, determining the signals responsible for such steady-state, physiological *Xbp1* splicing, as well as thorough documentation of the activation state of each UPR branch in DCs, will likely provide a more nuanced understanding of UPR compartmentalization and contextual specificity.

Hematopoietic Stem Cells

Long-term maintenance of a functioning hematopoietic system relies on dormant, long-term hematopoietic stem cells (HSCs) with robust self-renewal capabilities. Various stimuli such as DNA damage and oxidative injury induce cell death or entry into the cell cycle and progressive loss of self-renewal capacity, ostensibly to guard against loss of function or leukemogenesis (51). Recent reports indicate that various stem cell populations are similarly hypersensitive to ER stress and alterations in proteostasis. Intestinal epithelial stem cells undergo a PERK-dependent protective differentiation response to ER stress (52). Microarray analyses comparing human HSCs with more differentiated progeny revealed an HSC-selective upregulation of PERK target genes.

By contrast, the XBP1 branch of the UPR was most highly induced in the more downstream progenitors. HSCs were more sensitive to chemical ER-stress-induced cell death, and experimentally manipulating PERK-mediated signaling or ER chaperone function through genetic and pharmacological measures augmented survival and enhanced engraftment, perhaps by insulating hypersensitive HSCs from proteotoxic stresses (53).

In a separate study, FACS-mediated profiling of single-cell translation rates among different hematopoietic populations revealed that HSCs had the lowest rate of translation, whereas the common myeloid progenitor and its immediate downstream progeny were most translationally active. This correlated well with eIF2α phosphorylation, suggesting that physiological ER stress is induced during hematopoiesis. Critically, fine translational control was essential for maintaining HSC functionality, as genetic measures to enhance or suppress translation rates reduced reconstitution capacity (54). However, whether ER stress directly contributes to these phenotypes remains unknown. Hypersensitivity to ER stress may be a mechanism of protecting stem cells from cellular and/or DNA damage. Additionally, stem cell UPR hypersensitivity may act as a fail-safe against the deregulated protein synthesis rates characteristic of cells with oncogenic mutations. If true, this would also imply that enhancing protein-folding capabilities could potentially obscure oncogenic surveillance mechanisms, as previously postulated in a separate report (55). Collectively, these recent studies suggest that tight control over the UPR is critical for proper HSC function, and exploring the contribution of ER stress to stem cell function at steady state and in physiologically relevant disease models may yield important clinical insights.

Differentiation is therefore the foundational level on which the UPR regulates immunity. By controlling the development and health of plasma cells, DCs, Paneth cells, and HSCs, a fully functional UPR supports the full complement of immune effectors required for self-tolerance and defense from extracellular pathogens. Additionally, it appears to regulate stem cell homeostasis, potentially guarding against oncogenic cellular damage. The various UPR effectors differentially support development and function in cell type–specific patterns, providing unique insight into the physiological utilization of ER-stress-signaling modules and demanding thorough interrogation of how this selectivity is regulated and the relevance of protein misfolding.

THE UPR AND CELL BIOLOGICAL FOUNDATIONS OF IMMUNITY

Beyond differentiation, effective immunity depends on ER homeostatic processes such as calcium signaling, glycosylation, lipid metabolism, and oxidative protein folding. Consequently, ER stress and inflammation are fundamentally and comprehensively intertwined. In the following sections, we explore how the UPR preserves critically important ER-derived signaling to sustain a variety of immunological properties, as well as how inflammatory signaling feeds back onto ER homeostasis (**Figure 2**).

Calcium

One of the primary ER functions is to sequester millimolar quantities of calcium. This calcium is principally required for adequate chaperone-mediated protein folding and ERAD function, but its regulated mobilization to the cytoplasm additionally controls a host of biological activities. Activation of the T cell receptor (TCR), the B cell receptor (BCR), the Fc-γ receptor, and various cytokine receptors causes ER calcium efflux through the ER-localized calcium channel IP3R, which subsequently triggers further calcium influx through the activation of plasma membrane–localized CRAC channels (56). Increased intracellular calcium then activates many important signaling molecules, such as NFAT, calcium-dependent protein kinases (CAMKs), and calpains, influencing

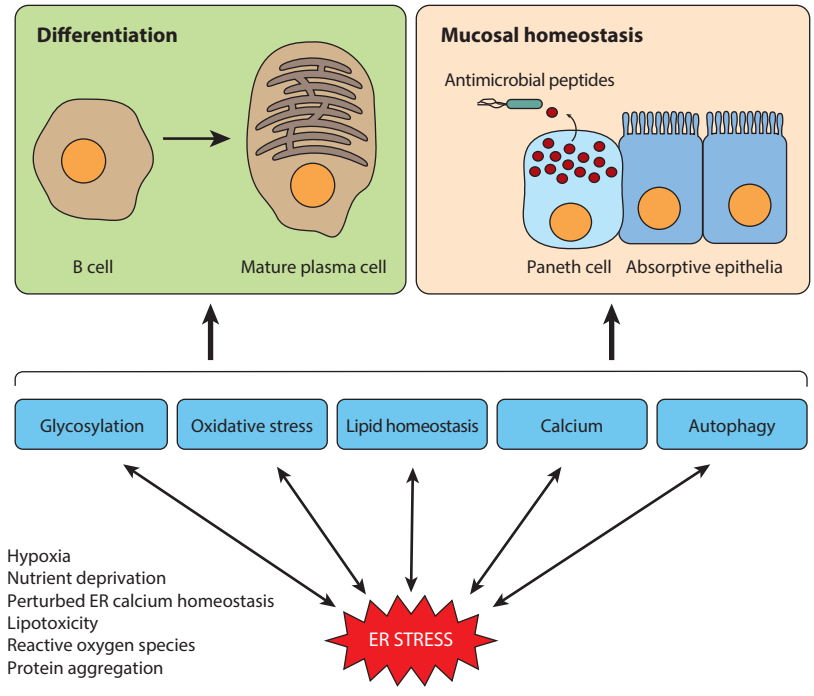

Figure 2

ER stress can be triggered by a variety of genetic and extracellular stimuli. The unfolded protein response triggers cellular changes in glycosylation, oxidative stress, lipogenesis, calcium signaling, and autophagy in an effort to correct the offending agent. These same foundational biological pathways are required to support a functioning immune system, particularly through cellular differentiation and the subsequent maintenance of immunological tolerance at mucosal barrier regions. ER homeostasis and stress may therefore influence the set points required for basal immunological function.

a highly complex set of biological phenomena, including T cell activation and anergy, myeloid cell functional maturation, cellular differentiation, migratory capacity, adhesion, and cell death (57).

Additionally, proinflammatory cytokines such as IL-1β and IFN-γ can directly reduce calcium in the ER through *Atp2a2* downregulation, thereby inducing ER stress (58). Critically, the induction of ER stress (59), BiP-mediated regulation of IP3R1 (59), UPR target genes including *Erp44* (60), and steady-state loss of key UPR transducers like *Eif2ak3* (61, 62) and possibly *Ern1* (63) have been shown to alter basal calcium signaling dynamics. Defects in ER stress response pathways may therefore influence immunological signaling even in the absence of severe microenvironmental stress. Furthermore, separate reports have shown that ER stress can activate calcium-dependent signaling axes, including calpains (64) and CAMKII (65). However, despite the frequent utilization of known ER stressors, such as thapsigargin, to study immune cell calcium signaling, to date no studies have carefully examined the immunological consequences of UPR involvement in calcium signaling and sequestration.

Protein Folding and Reactive Oxygen Species

The best-known function of ROS in the immune system involves the phagocyte-mediated antimicrobial oxidative burst. However, an impressive variety of immunological signals, including antigen

receptor signaling, TLRs, and cytokine receptors, can induce ROS production via NADPH oxidases (NOX), DUOX enzymes, and mitochondria-derived ROS (mtROS) (66), indicating that ROS are widely utilized for intracellular signaling. In turn, ROS carry out pleiotropic roles, including but not limited to inflammasome activation; cell migration; regulation of the intensity of antigen receptor signaling; phagosome pH control; and fine-tuning of the activation of growth factor receptors, NF-κB, and various mitogen-activated protein kinases (MAPKs) (66).

Disulfide bond formation within the ER, a prerequisite for correct folding of many transmembrane and secretory proteins, relies on an oxidative relay between the disulfide isomerase PDI and the oxidoreductase ERO1. This homeostatic system produces an estimated 25% of steady-state intracellular ROS (67), with significantly enhanced output under conditions of ER stress (68). Extracellular sources of ROS can also directly induce ER stress, possibly by interfering with ER calcium retention. This ER calcium leak can then directly drive mitochondrial ROS production, affecting downstream signaling pathways and sensitizing cells to apoptosis (69). Loss of *Ern1* (70) or *Ddit3* (71) dramatically reduced ROS production, whereas loss of *Xbp1* (48, 72) and *Eif2ak3* (73) significantly enhanced stress-induced intracellular ROS levels, likely due to the loss of PERK-mediated NRF2 activation. RIDD may account for the discrepancy between *Ern1*$^{-/-}$ and *Xbp1* knockdown ROS phenotypes, though cell type specificity cannot be ruled out. Therefore, through the UPR and coordination with mitochondria and other ROS control centers, the ER both maintains and amplifies ROS production, often engaging in feed-forward amplification loops.

A small but growing number of studies have linked ER stress pathways, ROS, and the immune response. ER-stress-mediated cell death induced by free cholesterol loading in macrophages, characteristic of atherosclerotic plaques, was found to drive ROS production through NOX2-dependent ER calcium efflux and subsequent activation of CAMKII and CHOP (71). Interestingly, free cholesterol loading of macrophages also led to modest induction of TNF-α and IL-6 dependent on cholesterol trafficking to the ER, though the involvement of ROS in this system was not tested (74). NOX2 also appears to be important for mediating *Xbp1* splicing in response to TLR ligation (13). Furthermore, two recently published studies found that pancreatic β cells upregulate thioredoxin-interacting protein (*Txnip*) during ER-stress-induced cell death, leading directly to activation of the NLRP3 inflammasome and release of proinflammatory IL-1β. Interestingly, the two studies reported different conclusions about the underlying molecular mechanism, with one arguing for direct PERK-mediated transcriptional *Txnip* induction (75) and the other contending that the IRE1α RNAse domain directly degrades a *Txnip*-targeting miRNA (70). In macrophages, however, ER stress apparently can activate the NLRP3 inflammasome independently of major UPR signal transducers (76). Several important points emerge from synthesizing these studies. First, both chemically induced and physiologically relevant forms of ER stress generate ROS that facilitate proinflammatory signaling. Second, ER-stress-induced ROS can activate the inflammasome, suggesting that lethal ER stress itself may be immunogenic. Finally, different cell types apparently vary in their dependence on UPR-signaling transducers despite activating similar downstream ROS-dependent proinflammatory signaling programs. How this dramatic specificity is obtained is completely unknown at this point, but activation requirements may be woven into cell type–specific secretory loads to enhance sensitivity to tissue damage and dysfunction.

Lipid Metabolism

Lipid metabolism and biosynthesis are crucial for normal immune cell function. Membrane fluidity regulates lipid raft formation, receptor clustering, and signaling dynamics. Many immune

cell types stock hydrophobic molecules in massive intracellular depots known as lipid droplets for synthesizing prostaglandins and other eicosanoids (77). Lipid biosynthesis mediated by the transcription factor sterol regulatory element–binding protein (SREBP) sustains macrophage inflammasome activation (78) and T effector cell expansion and metabolism (79), whereas the lipid-activated nuclear receptors PPARγ and LXR drive anti-inflammatory transcriptional programs (80). Not surprisingly, immunological and metabolic homeostasis are inextricably intertwined, and their complex relationship is largely beyond the scope of this review (81, 82). Obesity and hyperglycemia influence a large number of immunological parameters, such as adipose tissue macrophage polarization (83), myelopoiesis (84), and proinflammatory cytokine production (85), resulting in persistent low-grade inflammation. This inflammation can, in turn, directly interfere with insulin receptor signaling, thereby forming a vicious cycle driving deteriorating glycemic control (79).

Certain metabolic by-products and conditions, including extracellular hyperglycemia (86) and scavenger receptor-mediated uptake of oxidized lipid species (87) and saturated fatty acids (88), can trigger all three UPR branches by depleting ER calcium stores (89, 90). Similarly, perturbations in intracellular unsaturated fatty acid biosynthesis and membrane composition, as occurs during macrophage-free cholesterol accumulation (91); a high-fat diet (89); or aberrant polyunsaturated fatty acid and phospholipid synthesis due to loss of *Scd* (92) or the LXR target gene *Lpcat3* (93) can drive ER stress, inflammation, and cell death. Several studies suggest that extracellular lipid stress is translated into intracellular pathological dyslipidemia, though it remains unclear whether this is a generalizable feature of metabolic ER stress. In yeast, chemical ER stress or disruption of proteostasis regulators involved with glycosylation and ERAD directly induces triglyceride synthesis and lipid droplet formation, revealing close cross talk between protein folding homeostasis and lipid biosynthesis (94). Furthermore, IRE1α and PERK can directly induce fatty acid, phospholipid, and cholesterol biosynthetic pathways (21, 95), likely to safeguard intracellular membrane homeostasis. Intriguingly, it was recently reported that the IRE1α and PERK transmembrane regions can sense saturated fatty acid accumulation and stiffening of the ER membrane (96), though surprisingly without concomitant IRE1α foci formation (97). UPR activation, and RIDD in particular, is therefore likely highly attuned to the intensity and nature of the extracellular stressor. Though much has been learned over the past 10 years about the relationship between ER stress and metabolism, studies on how metabolically demanding immune processes directly interface with the ER stress response lag far behind. Such studies will be instrumental for developing more accurate and holistic models to explain the cross talk between these three major cellular pathways.

Glycosylation

Protein glycosylation plays a critical role in the immune system, mediating diverse responses such as cellular trafficking, surface receptor signaling dynamics, and apoptosis. Sialyltransferases mediate the sialyl-Lewis-X glycosylation patterns required for selectin-mediated rolling and adhesion (98). Antibody effector functions are largely controlled by glycosylation (99), as is the critical T cell developmental regulator NOTCH (100, 101). Golgi apparatus–mediated complex N-glycan branching can acutely tune responses to differentiation and proliferation cues (102), and seemingly subtle changes in glycan patterning can yield dramatic in vivo phenotypes. For instance, slight alterations in N-glycan branching observed in *Mgat5*$^{-/-}$ mice enhance TCR clustering and signaling, generating hyperreactive T cells and autoimmunity (103). Though a large number of glycosylation-related genes, such as *Stt3a*, *Ostc*, *Uggt1*, *Serp1*, *Ddost*, *P4hb*, and *Gale*, are induced in vivo by chemical ER stress (21), ER-stress-mediated alterations

in global glycosylation patterns have been minimally explored. One study found that *Xbp1*$^{-/-}$ B cells were grossly defective in Golgi apparatus–mediated complex N-glycosylation, though the exact glycan alterations or responsible downstream signaling pathways were not identified (104). More recently, XBP1 was found to directly control the hexosamine biosynthesis pathway rate-limiting enzyme GFAT1 under conditions of physiological ischemia/reperfusion stress (16). The hexosamine biosynthesis pathway generates UDP-*N*-acetylglucosamine, critical for both N-linked and O-linked glycosylation, and therefore likely plays a significant role in determining glycan complexity during stressful conditions. Exploring the relationship of physiological ER stress and various UPR mediators to immunologically important glycosylation patterns will likely lead to novel, highly nuanced insights regarding the interplay between the UPR and inflammation. Therefore, defining how various types of ER stress meaningfully alter glycosylation patterns and delineating how the different UPR branches coordinate these changes are of critical importance for future study.

Autophagy

Autophagy is a cellular recycling pathway charged with degrading protein aggregates, damaged organelles, and intracellular pathogens. Entities marked for disposal are encapsulated into characteristic double-membraned cytoplasmic vacuoles, which then fuse with lysosomes, leading to cargo destruction. Autophagy is a key immunological process facilitating antigen processing and presentation on both MHC-I and MHC-II, capture and killing of intracellular microbes, efferocytosis, production of type I interferons, and differentiation and survival of multiple cell types (105). ER stress and autophagy are intimately intertwined proteostasis pathways. IFN-γ-induced antimicrobial autophagy relies on ATF6α-mediated induction of *Dapk1*, though the contribution of misfolded proteins remains unknown (106). Chemical ER stress can induce autophagy through both IRE1α (107) and PERK (108), and this induction greatly enhances survival during ER stress. Defects in either autophagy or ER stress drive compensatory upregulation of the alternative pathway in an effort to maintain liver function (109), immunoglobulin production (110), membrane lipid availability (111), gastrointestinal immune system homeostasis (48), and survival (107). Such reciprocity in proteostasis mechanisms likely operates as a fail-safe to guard against pathological proinflammatory signaling and provides a possible explanation for why genome-wide association studies (GWAS) have identified single nucleotide polymorphisms in numerous proteostasis components as risk factors for immunological disorders.

INFLAMMATION AND INFECTION CAN ACTIVATE ER STRESS

Intracellular pathogens, particularly viruses, frequently hijack organelles such as the ER to facilitate survival and replication. Cellular defense mechanisms have consequently evolved to detect biological perturbations frequently associated with infection, such as plasma membrane fusion and a rapid increase in glycoprotein production, activating the ER-localized antiviral pattern recognition receptor STING (112) and the UPR (113), respectively. Virus-mediated UPR activation varies widely by strain, carefully balancing species-specific replication requirements with immune-evasive virulence mechanisms. For instance, herpes simplex virus 1 selectively blocks PERK activation through viral glycoprotein gB (114), whereas the African swine fever virus and lymphocytic choriomeningitis virus (LCMV) solely activate the ATF6α branch (115, 116). Pathogen-derived inhibitory mechanisms may have evolved from mechanisms directed against structurally homologous antiviral effector proteins such as PKR and RNASE L (117). Intriguingly, recent data suggest that the precise virus-mediated alterations in UPR signaling directly suppress antiviral immune

responses (118) and antiviral UPR mediators (119), thereby balancing efficient viral replication with evasion of the interferon response. The UPR is also directly activated by certain secreted bacterial virulence factors, such as pore-forming toxins (120), subtilase cytotoxin (121), and cholera toxin (122). These toxins utilize distinct molecular mechanisms, potentially involving increased demand for membrane biosynthesis, induced protein misfolding, and direct UPR mediator activation, respectively. Microorganism-mediated UPR alterations therefore tune the quality and magnitude of immune responses.

Numerous studies have documented UPR activation in both acute and chronic infections, though the direct molecular mechanisms are poorly understood. Direct TLR ligation specifically activates the IRE1α/XBP1-signaling axis while suppressing the PERK-signaling branch, thereby enhancing proinflammatory cytokine production at the expense of canonical UPR target genes such as *P4hb* and *Dnajb9* (13). However, macrophages isolated from *Mycobacterium tuberculosis* granulomas resemble the lipid-laden foam cells often found in atherosclerotic lesions and exhibit activation of IRE1α, eIF2α, and CHOP and a transcriptional signature of an ongoing ER stress response (123). It is possible that specific virulence mechanisms or secondary environmental ER stressors deactivate the recently identified adaptive PERK suppression, with unknown consequences for inflammatory signaling.

Indeed, such alternative UPR triggers are abundant during infections and other inflammatory insults. Infection-triggered release of proinflammatory cytokines such as TNF-α, IL-1β, IL-6, and IFN-γ may feed back to amplify or perpetuate ER stress in multiple cell types, including pancreatic β cells, hepatocytes, macrophages, and oligodendrocytes. Furthermore, infections and tissue damage are often characterized by hypoxic conditions, driven at least partially by inflammation-induced alterations in microvascular blood supply (124). Concomitantly, antimicrobial neutrophil and macrophage functions at sites of infection heavily rely on anaerobic glycolysis (125), leading to both microenvironmental acidification due to lactic acid accumulation and local glucose deprivation (124). Monocyte- and neutrophil-derived respiratory bursts can additionally oxidize microenvironmental lipids (126), potentially generating ER-stress-inducing ligands. Intriguingly, most UPR-inducing stressors found in inflammatory microenvironments are also identifiable in immunosuppressive tumor microenvironments. Indeed, it was recently shown that the proangiogenic cytokine VEGF can also activate a full UPR in endothelial cells without interfering with protein folding or secretion (127). Given the abundance of UPR-inducing signals present during multiple phases of the immune response, future studies should address whether and how subtle contextual differences can repurpose UPR signaling during the initiation and resolution of inflammation.

ER STRESS CAN INITIATE INFLAMMATION

NF-κB

The NF-κB transcription factor family regulates many facets of innate and adaptive immune responses, from the differentiation and survival of multiple hematopoietic cell types to proinflammatory cytokine production and antibody isotype switching. Nearly 20 years ago, before the individual UPR mediators were even identified, multiple forms of ER stress were shown to activate NF-κB through a calcium- and ROS-dependent mechanism (128, 129). Since that time it has been shown that IRE1α activation specifically recruits IκB kinase (IKK) to the ER through the intermediate TRAF2. This IRE1α-TRAF2-IKK interaction activates NF-κB, leading to the production of proinflammatory TNF-α and facilitating stress-induced cell death (130). More recent studies have demonstrated that the IRE1α kinase activity, but not the RNAse activity, is

specifically required to nucleate this complex formation and also sustains basal IKK activity (131). Translational inhibition alone can activate NF-κB by strongly reducing IκBα translation (132), supporting an integrated model whereby PERK-mediated translational suppression cooperates with IRE1α-mediated complex formation to maximize NF-κB activation. Furthermore, IRE1α was recently shown to mediate the stress-mediated upregulation of the antiviral IKK-related kinase *Ikbke* via XBP1 (21), though the direct immunological consequences remain to be determined.

Importantly, ER stress does not always amplify NF-κB signaling. Low-dose ER stress preconditioning actually attenuates TNF-α-induced NF-κB activation in endothelial cells, thereby reducing the inflammatory upregulation of cell adhesion molecules (133). Cellular adaptation to chronic ER stress has been shown to suppress subsequent UPR activation (134), an effect perhaps attributable to enhanced proteostasis capacity. How cells decide between proinflammatory and anti-inflammatory UPR signaling is poorly understood, but the intensity of UPR activation may be a critical mediator of ER-stress- and cytokine-driven NF-κB activation. Whether this pattern is specific to certain cell types and/or NF-κB-activating signals or is more generalizable remains to be determined.

MAPKs

MAPKs are a family of stress-inducible kinases including JNK, p38, and ERK. Once phosphorylated, these kinases mediate diverse responses encompassing proliferation, autophagy, differentiation, glycemic regulation, inflammation, and adaptation to stress. In primary murine embryonic fibroblasts, ER stress activates all three MAPK pathways, though the precise upstream regulators for p38 and ERK remain controversial (64). PI3K mediates ER-stress-triggered ERK activation to enhance cellular survival (135). In parallel, phosphorylated IRE1α can directly activate JNK via the sequential recruitment of TRAF2 and ASK1 (35, 136). Under conditions of persistent IRE1α activation, such as inefficient XBP1 signaling, unremitting JNK activation drives tissue inflammation and proinflammatory cytokine and chemokine production (47). Feeding chemical chaperones to mice on high-fat diets reduced JNK activation and improved insulin sensitivity, suggesting that metabolic-stress-mediated loss of ER protein folding homeostasis drives JNK activation in vivo (137). Conversely, certain MAPKs can modulate UPR-signaling outputs. In *Caenorhabditis elegans*, p38 activates XBP1 to protect the host from an otherwise lethal inflammatory response to pathogenic bacterial infection (138). p38 activation also greatly enhances XBP1 nuclear import (139), maintaining insulin sensitivity and likely reinforcing the intimate link between ER-stress-response pathways and inflammatory signaling pathways. Collectively, the ER stress and MAPK cross talk tunes cell survival and inflammatory signaling pathways and may contribute to the dysregulated inflammatory responses characterizing inflammatory bowel disease (IBD) and metabolic disorders.

BROADCASTING ER STRESS

Most mechanistic understanding of ER stress and inflammation is derived from in vitro and in vivo experimental systems that rely on chronic or otherwise irremediable ER stress. Based on these studies, the ER-stress-mediated induction of secreted factors (nearly entirely proinflammatory cytokines) is generally interpreted as a prelude for pathological inflammatory processes. Yet these extreme experimental conditions likely obscure a far more complex reality given that, as elegantly outlined by Chovatiya & Medzhitov (140), extrinsic communication of perturbations in intracellular homeostasis is likely a critical component of stress adaptation, resolution, and preservation of overall tissue function. For example, cell extrinsic communication is critical for the

angiogenic response to various sources of hypoxia and is also responsible for interferon-mediated paracrine protection of uninfected cells during viral infection (140). Though our understanding of this facet of ER stress biology is in its infancy, a number of recent reports have uncovered such communicative mechanisms.

Stromal Cell Damage and the Extracellular Milieu

Efficient leukocyte infiltration into damaged tissues requires chemokine-mediated recruitment and upregulation of adhesion molecules on inflamed endothelia. Stromal endothelial cells exposed to the oxidized lipid 1-palmitoyl-2-arachidonoyl-*sn*-3-glycero-phosphorylcholine, often found in atherosclerotic lesions, upregulate the monocyte chemoattractant CXCL3 in an XBP1-dependent manner (141). Similarly, in response to proatherogenic triglyceride-rich lipoprotein, endothelial cells induce *Vcam1* via CHOP, potentially enhancing adhesion and diapedesis of lymphocytes, myeloid cells, and granulocytes (142). Furthermore, both muscle cells and airway epithelial cells secrete a functional leukocyte-adhesive hyaluronan matrix after exposure to various forms of ER stress (143). This may at least in part contribute to the development of autoimmune myositis in mice with muscle-specific transgenic overexpressing MHC-I heavy chains (144), as well as in human patients with inclusion-body myositis (145). ER-stress-mediated epithelial cell damage results in selective and potent release of the alarmin IL-1α, triggering massive IL-6 production from lung-resident fibroblasts (146). Therefore, in addition to being able to bias immune cell behavior via the secretion of polarizing cytokines, such as TNF-α and IL-6, broadcasting ER stress through extracellular cues likely enhances leukocyte recruitment, remodeling of the immunological microenvironment, and tissue homeostasis (**Figure 3**).

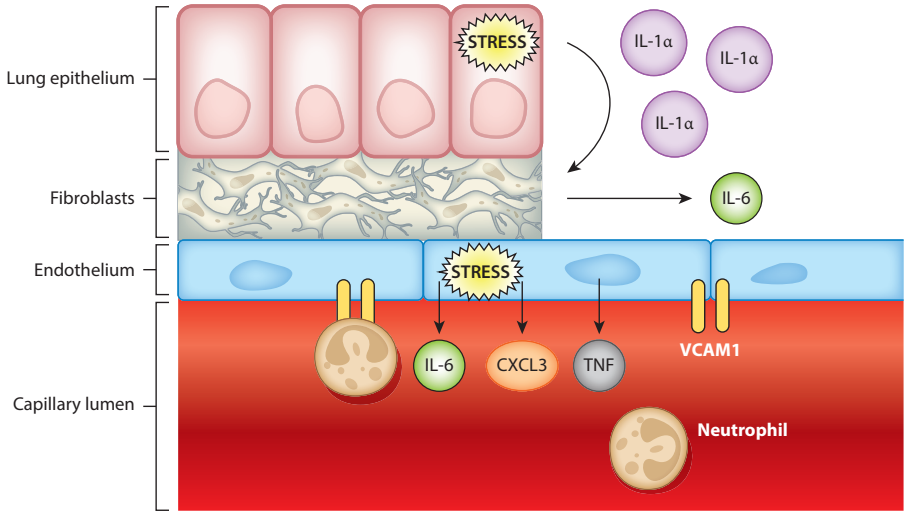

Figure 3

ER stress is sensed and interpreted differently depending on cell type and drives specific extracellular signals tailored to restore specific tissue homeostasis. Lung epithelial cells undergoing ER stress release IL-1α, which acts on neighboring fibroblasts to induce IL-6 production. Separately, endothelial cells undergoing ER stress, perhaps triggered by toxic lipid species, produce multiple chemokines and cytokines such as IL-6, TNF, and CXCL3 to recruit and polarize immune cells. ER stress can also drive surface expression of the integrin VCAM1, mediating granulocyte and myeloid cell adhesion at sites of injury.

Transmissible ER Stress in the Tumor Microenvironment

UPR activation has been documented in many cancers and is likely induced by a combination of hypoxia stemming from inefficient vascularization, glycolysis-mediated local acidification and glucose deprivation, and various sources of local oxidative stress (147). Numerous reports over the past decade have demonstrated the critical importance of various UPR pathways for sustaining tumor cell survival in vivo (148, 149). In addition, recent work has suggested that ER-stressed tumor cells secrete a heat-resistant factor that can propagate their internal ER stress to surrounding leukocytes via TLR4, thereby altering local immunological properties to favor tumor growth through the production of IL-6, IL-23, and TNF-α (150). Conditioned medium from ER-stressed tumor cells, but not tumor cells exposed to the cytotoxin staurosporine, also induced the upregulation of the proinflammatory cytokines MIP-1α, MIP-1β, and MCP-1 (150). Similar studies from an independent group demonstrated that macrophages additionally secrete VEGF in response to tumor-cell-conditioned media (151), thereby enhancing microenvironmental angiogenesis. DCs cultured in ER-stressed tumor-conditioned media induced the immunosuppressive molecule arginase-I, were defective at cross presenting high-affinity antigens to cytotoxic $CD8^+$ T cells, and enhanced tumor growth in vivo (152). This transmission of ER stress from tumor cells to myeloid cells may serve as an immunosuppressive strategy to dampen antitumor immunity while simultaneously promoting tumor growth via the secretion of proangiogenic and proinflammatory factors.

Immunogenic Cell Death

Understanding how the UPR dictates cellular adaptation versus apoptosis remains critically important to the field of ER stress biology. But we can also reframe this idea into a crucially important immunological question—how does the immune system interpret ER-stress-induced cell death? Dying cells communicate with tissue-resident leukocytes through context-specific induction of cell surface receptors and secreted factors, and this dialogue is crucial for maintaining the balance between tolerance, tissue homeostasis, and autoimmunity (153). During homeostatic cell death such as T cell negative selection in the thymus, dead cell clearance by tissue-resident leukocytes is immunologically silent or even tolerogenic. In contrast, cells killed by extrinsic or intrinsic stress such as infection or tissue damage broadcast endogenous alarmins and danger-associated molecular patterns (DAMPs), such as HMGB1, IL-1α, ATP, and plasma membrane exposure of the ER-resident protein calreticulin, that elicit potent inflammatory responses (153–155). This so-called immunogenic cell death (ICD) generates requisite physiological cues for tissue stress responses and has also been clinically harnessed to create more effective oncology therapeutics.

Though tissue ER stress, apoptosis, and immune cell infiltration are frequently observed together, the relationship between ER stress and ICD remains poorly understood. ICD-mediated HMGB1 release can activate all three major UPR branches in bystander cells through the receptor RAGE (156). It was later shown that HMGB1 triggers *Xbp1* splicing in DCs to maximize T cell activation (157). Therefore, the UPR may be able to sense nearby immunogenic cell death, potentially important for tuning subsequent adaptive responses. Recent evidence from cancer cell studies indicates that the relationship between ER stress and ICD is likely bidirectional. Chemical ER stress alone fails to induce DAMPs or ICD, yet PERK-mediated translational suppression appears critical for cytotoxin-induced ICD (154, 158, 159). Many mechanistic details remain to be elucidated, but calcium flux seems to be important (160), and other UPR mediators are apparently dispensable. These findings were recently extended to show that tumor-associated chromosomal tetraploidy activates all three UPR branches and drives strong ICD responses

dependent on PERK-mediated surface calreticulin exposure, greatly reducing tumor outgrowth in immunocompetent mice (161). How the tetraploid state drives ER stress remains unclear, but this study presents the intriguing possibility that extreme ER stress is a functionally relevant tumor immunosurveillance mechanism. Because the UPR is also critical for surviving numerous tumor microenvironmental challenges, additional studies are needed to dissect the trade-offs between adaptation and immunoevasion. Though this facet of ER stress biology is in its infancy, it is clear that the UPR both is activated by DAMPs and can regulate DAMP exposure in a highly selective, context-specific manner. Moving forward, it will be critical to dissect how PERK-mediated translational control sustains ICD, and whether PERK contributes similarly to other physiologically relevant ICD-mediated pathologies.

NETWORK CROSS TALK AND SIGNAL AMPLIFICATION

Though chemically induced ER stress can activate NF-κB and proinflammatory MAPKs, it does not activate a particularly strong inflammatory response. The recent revelation that ER stress potently synergizes with various innate immune signaling pathways, particularly the TLRs (13, 162), was therefore quite unexpected. Initial studies showed that cotreating macrophages with chemical ER stressors and intracellular dsRNA or ligands for TLR3/TLR4 enhanced *Ifnb* induction by more than tenfold in an XBP1-dependent manner (162). This augmentation was traced to direct XBP1 binding to a *cis*-acting *Ifnb* enhancer, indicating that signal integration between ER stress and inflammatory signaling might repurpose UPR mediators (163). Both chemical ER stress and nutrient deprivation can drive IRF3 phosphorylation, thereby priming synergistic IFN-β induction (164). Comparable synergistic cytokine induction has now been observed for *Il23*, *Il6*, *Tnf*, *Isg15*, *Cxcl1*, and *Cxcl2*, though the specific molecular mechanisms vary depending on cytokine and cell type, with demonstrated functions for CHOP and RIPK1 (13, 164–166). It is tempting to speculate that these synergistic mechanisms exist to amplify the ability to identify and correct potentially dangerous cellular perturbations before they deteriorate beyond control (**Figure 4**). However, such excessive synergy may also contribute to the augmented basal inflammation observed in patients with genetically encoded structurally destabilized proteins, including chymotrypsinogen C (167), α-1 antitrypsin (168), and HLA-B27 (169).

Perhaps most interestingly, TLR ligation suppresses PERK signaling while simultaneously activating and rerouting XBP1 signaling away from its canonical UPR targets and instead toward proinflammatory genes (13, 170). Innate immune signaling therefore appears to be prioritized above protein-folding homeostasis and can differentially tune UPR outputs, though the consequences of the latter on the quality of the immune response remain unclear (**Figure 4**). This may have clinically relevant implications for protein misfolding–driven neurodegenerative diseases, many of which include signs of inflammation (171). Determining the range of inflammatory signals capable of synergizing with ER stress, whether adaptive suppression occurs in nonmacrophage cell types, and the functional consequences of adaptive UPR suppression will greatly enhance our understanding of the cross talk between ER stress and immunity.

TRANSCRIPTION FACTOR COOPERATIVITY

One of the most fascinating yet vastly understudied areas in ER stress biology involves the context-specific, dimerization-mediated activities of UPR transcription factors. XBP1, ATF6α, ATF4, and CHOP are all bZIP transcription factors whose canonical DNA-transactivating capabilities require homo- or heterodimerization with structurally related bZIP family members. Heterodimerization between bZIP factors is dictated by precise structural constraints (172). However, bZIP proteins

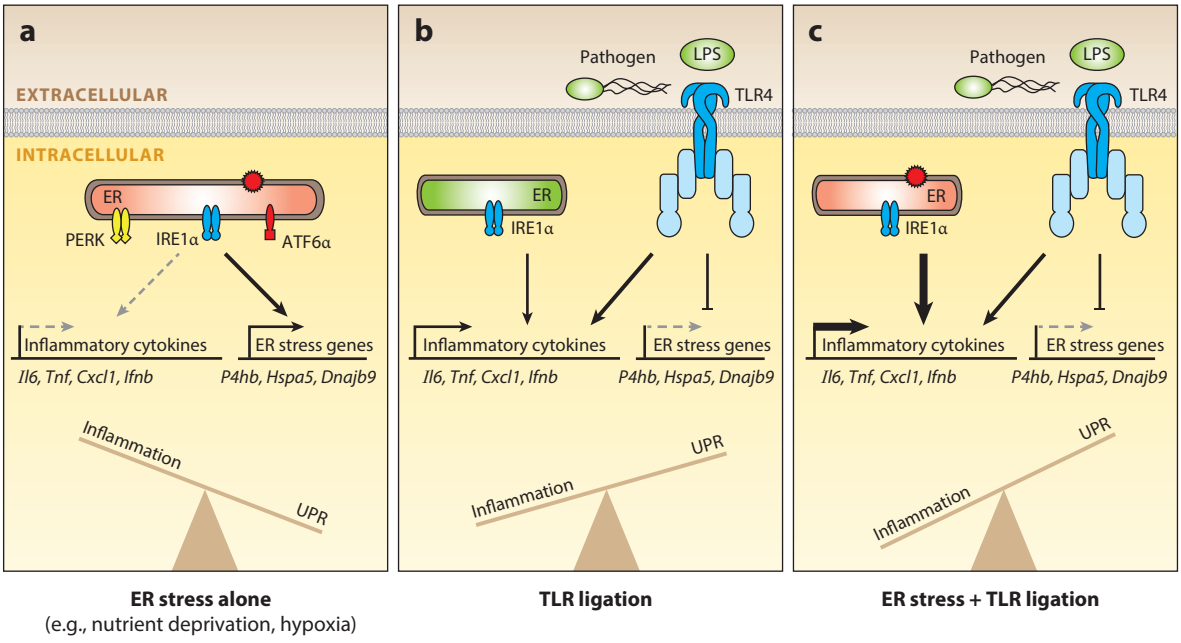

Figure 4

(*a*) Cells undergoing ER stress upregulate a host of proteostasis factors to correct misfolded protein accumulation but also weakly produce proinflammatory cytokines owing to the activation of NF-κB and various mitogen-activated protein kinases. (*b*) TLR ligation, by contrast, drives potent proinflammatory cytokine production, partially mediated by selective activation of IRE1α and suppression of PKR-like ER resident kinase (PERK). (*c*) When combined, TLR ligation and ER stress lead to synergistic cytokine production while actively suppressing select unfolded protein response (UPR) branch outputs. Protein-folding transcriptional programs are therefore suppressed in favor of innate immune signaling, while cellular stress lowers the detection threshold for pathogen-associated molecular patterns.

can also heterodimerize with transcription factors outside the bZIP family, greatly expanding the scope of potential target genes. Dimerization partner choice can either enhance or repress target gene induction, providing even further transcriptional complexity. Large-scale yeast two-hybrid and FRET-based screens have broadly highlighted the great potential diversity in UPR transcription factor heterodimerization partners, many of which have critical functions in the immune system (173, 174). Indeed, this versatile dimerization capacity is likely where many noncanonical UPR behaviors derive from. For instance, both ATF4 and the C/EBP family member CHOP can directly interact with multiple members of the ATF, BATF, and C/EBP families, which are critical for myeloid and granulocyte lineage commitment, development, and function (173–175). Interactions with C/EBPα and C/EBPε have been shown to facilitate ATF4-mediated control of myeloid gene expression (176). Similarly, in myeloid cell lines CHOP can repress myeloid gene expression during retinoic acid–mediated differentiation, possibly through suppressing the activity of other C/EBP family members (177). It is tempting to speculate that myeloid leukemias might co-opt this CHOP-mediated interference system to sustain their partially dedifferentiated state.

Several years ago an important study demonstrated that XBP1 directly activates unique transcriptional targets depending on cell type (15). XBP1 ChIP-on-chip experiments revealed a striking enrichment of the ETS motif in addition to more canonical UPR-like binding motifs, though direct interaction with ETS transcription factors was not demonstrated (15). Whether ETS family factors dictate XBP1 cell type transcriptional networks therefore remains to be determined (15).

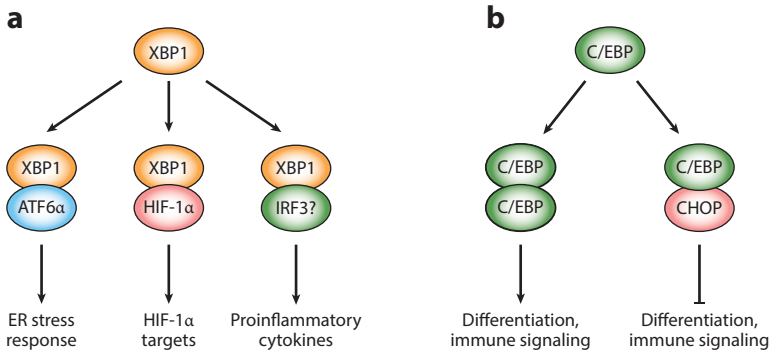

Figure 5

(*a*) In cells undergoing strong ER stress, XBP1 primarily homodimerizes or heterodimerizes with ATF6α. XBP1 can also interact with alternative binding partners under select circumstances, such as hypoxia or inflammation, leading to the formation of novel transcriptional complexes that repurpose unfolded protein response (UPR) mediators to drive noncanonical outputs. (*b*) Such heterodimeric binding can also suppress certain transcriptional programs by competing against the formation of cell-type-specific transcription factor homodimers and heterodimers, as observed with the protein CHOP in combination with other C/EBP family members.

More recently, our laboratory showed that XBP1 can directly interact with HIF-1α in triple-negative breast cancer cells, and this interaction is critical for maximal induction of HIF-1α target genes (14). Similarly, XBP1 can cooperate directly or indirectly with IRF3 to facilitate *Ifnb* transcription at an upstream enhancer site (163), whereas ATF6α directly potentiates C/EBPβ activity to drive *Dapk1* expression (106). The cell type–specific transcription factor landscape therefore dictates the available noncanonical functions of UPR transcription factors through cooperative binding behavior (**Figure 5**). Given the extensive number of reported dimerization partners, surprisingly little is known about how immunological function can be affected by ER-stress-mediated alterations in hematopoietic transcription factor complexes.

ER STRESS IN AUTOIMMUNITY

UPR activation has been documented in a vast number of human diseases, particularly neurodegenerative and immune system disorders (178). Though precise UPR signaling is critical for managing pathogen infection and tissue stress, unremitting activation may directly contribute to failures in immunological tolerance observed in diseases including IBD, rheumatoid arthritis (RA), and airway disease by dangerously lowering the threshold for proinflammatory signaling and cell death. Sources of potential homeostatic UPR disruptions include structurally destabilizing genetic mutations leading to ER protein retention, genetically reduced proteostasis capacity, and environmental toxicants. In turn, these perturbations may alter tolerance thresholds by promoting excessive proinflammatory signaling or stress-mediated exposure of novel immunogenic or misfolded autoantigens (179). Unraveling how ER stress and proteostasis defects alter the threshold for proinflammatory signaling remains an area of keen interest and may ultimately help explain how genetic susceptibilities collaborate with environmental stimuli to collectively corrupt homeostatic tolerance mechanisms. Continued research in this area will be instrumental for the development of anti-inflammatory UPR-targeted therapeutics.

Inflammatory Bowel Disease

IBD and associated disorders are believed to arise from a complex interplay between genetic, microbial, and environmental susceptibility factors that ultimately break tolerance at the mucosal boundary. Interestingly, multiple genome-wide association studies identified the *XBP1*-containing chromosomal location 22q12 as an IBD risk factor (180), and deep sequencing of 1,200 IBD patients independently identified several hypomorphic *XBP1* variants (47). As previously mentioned, genetic studies on *Ern2*$^{-/-}$ mice (46) and mice with targeted deletions of either *Xbp1* or *Ern1* in the intestinal epithelium have experimentally validated defective UPR signaling as a bona fide driver of IBD (47, 48). Additionally, multiple genome-wide association studies have implicated autophagy-related proteins such as ATG16L1 (181) and IRGM (182) as susceptibility loci for IBD. The *ATG16L1* risk allele has been shown to selectively trigger ER stress in Paneth cells at steady state, though it is unclear why this polymorphism exhibits such cell type–specific effects (183). Intriguingly, selective ablation of *Atg*7 in the intestinal epithelium induced compensatory upregulation of ER stress pathways and a mild but statistically significant increase in inflammatory pathology (48). Similarly, loss of *Xbp1* led to a compensatory increase in autophagy, which partially insulated the intestine from excessive inflammatory damage.

Numerous other perturbations in UPR signaling also alter susceptibility to IBD, potentially through similar effects on intestinal epithelial cell differentiation and homeostasis. Genetic inhibition of eIF2α phosphorylation (184) and knockouts for the mucin *Muc2* (185) and the protein disulfide isomerase anterior gradient 2 (*Agr2*) (186) lead to defects in Paneth cell homeostasis and basal intestinal inflammation, whereas mice lacking *Creb3l1* (OASIS) (187) or ATF6α (188) are hyperresponsive to DSS-induced colitis. Administration of compounds with chemical chaperone properties, such as taurodeoxycholic acid (TUDCA) or 4-phenylbutyrate (4-PBA), can ameliorate the severity of DSS-induced colitis (188), possibly by reducing ER stress. Similarly, recent studies have argued that the anti-inflammatory properties of both glucocorticoids (189) and IL-10 (190) may partially stem from their ability to reduce protein misfolding.

In line with the recent renaissance of immune-microbiome interaction studies, gastrointestinal bacterial colonization was found to be a major factor for translating pathological UPR perturbations into intestinal inflammation (48). This raises the tantalizing question of whether microbes or microbial by-products may directly modulate UPR behavior and consequent Paneth cell–derived intestinal inflammation. It has already been shown that the bacterial virulence factor subtilase cytotoxin induces the UPR by cleaving and inactivating BiP, possibly enhancing inflammatory signaling (191, 192). Intriguingly, the bile acid and chemical chaperone TUDCA is found naturally at low levels in the gastrointestinal tract (193), though it remains unknown whether the composition of microbial communities can affect its production.

Fully functioning proteostasis networks are therefore critical for the preservation of tolerance at the intestinal epithelium by maintaining the highest possible threshold against steady-state inflammatory signaling. Though much remains to be learned, deciphering the complex cross talk between the UPR, autophagy, the microbiome, and inflammation is of vital importance for disentangling how genetic susceptibility and environmental factors cooperatively drive inflammatory disease.

Arthritis

RA is an autoimmune disease characterized by inflammation of joint synovial linings and progressive bone erosion. UPR activation has been documented in macrophages isolated from the synovial fluid of active RA patients. A major risk factor for RA and various spondyloarthropathies

is the *HLA-B27* MHC class I allele (194). In contrast with other MHC proteins, HLA-B27 is prone to misfolding due to structural instability and can trigger an ER stress response (195, 196). Furthermore, transgenic rats overexpressing human *HLA-B27* spontaneously develop multiple autoimmune phenotypes, including arthritis, IBD, and psoriasis (197), and exhibit enhanced IL-23 production in response to TLR ligands (198). Critically, a recent report demonstrated that IRE1α functionally contributes to inflammatory pathology in the K/BxN serum transfer murine model of arthritis, as both myeloid-specific genetic ablation and pharmacological IRE1α inhibition greatly improved clinical scores (199). How RA mediates UPR activation remains poorly understood, but it may be the result of chronic inflammation-mediated proinflammatory cytokine production and microenvironmental stresses. At this time the involvement of other UPR branches in the pathogenesis of arthritis is unknown, but preliminary reports suggest that inhibiting the IRE1α/XBP1-signaling axis would confer significant clinical benefits.

Lung Disease

The airway epithelium represents a second mucosal boundary region that must maintain tolerance in the face of highly variable and largely unpredictable environmental challenges. Like gastrointestinal epithelial cells, the airway mucosa constitutively produces mucus and antimicrobial compounds to minimize steady-state inflammation. Research on the function of the UPR in inflammatory lung disorders has greatly accelerated in the past several years, bolstered by clinical documentation of ongoing ER stress during cystic fibrosis, tissue fibrosis, and certain forms of asthma (200). The most direct links between ER stress, protein misfolding, and lung inflammation stem from studies on cystic fibrosis. Genetic loss of function of the chloride channel CFTR results in improper mucus secretion, frequent bacterial infections, and progressive deterioration of lung function. Though defective mucus production directly facilitates bacterial colonization and immune stimulation, several lines of evidence suggest that CFTR deficiency can prime inflammatory responses by perturbing ER stress and other proteostasis functions. Certain mutated *CFTR* variants, such as F508del-CFTR, accumulate in the ER and induce NF-κB (201) and p38 (202) activation through ER stress, thereby inducing chronic, low-grade inflammation and potentiating TLR-mediated immune activation. Intriguingly, PERK was selectively suppressed in both patient samples and multiple experimental models, and artificial induction of eIF2α phosphorylation dampened inflammatory responses (202). Furthermore, CFTR loss of function directly impedes autophagic processes, potentially inducing inflammation by lowering the UPR activation threshold (203, 204). Cystic fibrosis therefore provides an intriguing opportunity for dissecting how genetically imposed proteostasis constraints can stimulate inflammation via ER stress.

Asthma is a chronic Th2-driven inflammatory airway disorder that can lead to fibrosis and airway remodeling over time. Several years ago genome-wide association studies identified the sphingolipid biosynthetic enzyme ORMDL3 as an asthma susceptibility factor (205). Interestingly, ORMDL3 contributes to calcium homeostasis (206) and can induce ATF6α activation in airway epithelial cells, though whether ATF6α contributes to asthma pathology remains to be determined (207). Similarly, insufficient SERCA activity, a known driver of ER stress, has been implicated in allergic airway remodeling (208). IRE1α- or IRE1β-mediated *Xbp1* splicing may sustain the enhanced ER calcium stores frequently observed in inflamed airway mucosa (209), as well as the IL-13-driven excessive airway epithelial mucus production observed in allergic airway disease. However, a recent study demonstrated that chemical chaperones dose-dependently reduce UPR gene expression and inflammatory markers (210). Robust genetic studies will be critical to confidently determine whether and how the observed UPR activation contributes to inflammatory

airway disease. Until then, it is tempting to speculate that ER stress may at least partially explain why viral infection often instigates or exacerbates inflammatory airway pathology (211).

CONCLUSIONS AND PERSPECTIVES

New data from the past several years have greatly enhanced our understanding of the complex interplay between ER stress, inflammation, and organismal homeostasis. In addition to the well-established roles in cellular differentiation, there are now clear links between a vast array of disparate immunological processes including inflammatory cytokine secretion, antigen presentation, and stem cell renewal. UPR coordination defines critical set points for inflammatory signaling, and a robust proteostasis network forms a foundation for immunological tolerance. Major UPR-signaling axes can be independently modulated and repurposed for a variety of noncanonical functions, indicating that we are only just beginning to grasp the nuanced, context-dependent functions for ER stress. Inflammation is both a cause and consequence of ER stress, and identifying additional signaling convergence points will guide the development of powerful therapeutics for autoimmune diseases and other UPR-mediated disorders with inflammatory components.

FUTURE ISSUES

1. How does UPR control over basic cell biological functions influence immunologically relevant signaling mechanisms?
2. Do different cell types vary in their sensitivity to environmental ER stressors?
3. How does ER adaptation to chronic stress influence the inflammatory response?
4. Does ER stress have a function in the resolution of inflammation?
5. What is the physiological relevance of the inflammatory synergism between TLR signaling and ER stress?
6. How are UPR mediators co-opted and repurposed by cell type–specific transcription factor milieus?
7. What factors are responsible for cell type–specific sensitivities to perturbed proteostasis?

DISCLOSURE STATEMENT

The authors are not aware of any affiliations, memberships, funding, or financial holdings that might be perceived as affecting the objectivity of this review.

LITERATURE CITED

1. Powers ET, Morimoto RI, Dillin A, Kelly JW, Balch WE. 2009. Biological and chemical approaches to diseases of proteostasis deficiency. *Annu. Rev. Biochem.* 78:959–91
2. Ye J, Rawson RB, Komuro R, Chen X, Dave UP, et al. 2000. ER stress induces cleavage of membrane-bound ATF6 by the same proteases that process SREBPs. *Mol. Cell* 6:1355–64
3. Bertolotti A, Zhang Y, Hendershot LM, Harding HP, Ron D. 2000. Dynamic interaction of BiP and ER stress transducers in the unfolded-protein response. *Nat. Cell Biol.* 2:326–32

3a. Gardner BM, Walter P. 2011. Unfolded proteins are Ire1-activating ligands that directly induce the unfolded protein response. *Science* 333:1891–94

4. Hetz C, Glimcher LH. 2009. Fine-tuning of the unfolded protein response: Assembling the IRE1α interactome. *Mol. Cell* 35:551–61

5. Calfon M, Zeng H, Urano F, Till JH, Hubbard SR, et al. 2002. IRE1 couples endoplasmic reticulum load to secretory capacity by processing the XBP-1 mRNA. *Nature* 415:92–96
6. Yoshida H, Matsui T, Yamamoto A, Okada T, Mori K. 2001. XBP1 mRNA is induced by ATF6 and spliced by IRE1 in response to ER stress to produce a highly active transcription factor. *Cell* 107:881–91
7. Tirosh B, Iwakoshi NN, Glimcher LH, Ploegh HL. 2006. Rapid turnover of unspliced Xbp-1 as a factor that modulates the unfolded protein response. *J. Biol. Chem.* 281:5852–60
8. Liou HC, Boothby MR, Finn PW, Davidon R, Nabavi N, et al. 1990. A new member of the leucine zipper class of proteins that binds to the HLA DR alpha promoter. *Science* 247:1581–84
9. Lee AH, Iwakoshi NN, Glimcher LH. 2003. XBP-1 regulates a subset of endoplasmic reticulum resident chaperone genes in the unfolded protein response. *Mol. Cell. Biol.* 23:7448–59
10. Shaffer AL, Shapiro-Shelef M, Iwakoshi NN, Lee AH, Qian SB, et al. 2004. XBP1, downstream of Blimp-1, expands the secretory apparatus and other organelles, and increases protein synthesis in plasma cell differentiation. *Immunity* 21:81–93
11. Lee AH, Chu GC, Iwakoshi NN, Glimcher LH. 2005. XBP-1 is required for biogenesis of cellular secretory machinery of exocrine glands. *EMBO J.* 24:4368–80
12. Lee AH, Scapa EF, Cohen DE, Glimcher LH. 2008. Regulation of hepatic lipogenesis by the transcription factor XBP1. *Science* 320:1492–96
13. Martinon F, Chen X, Lee AH, Glimcher LH. 2010. TLR activation of the transcription factor XBP1 regulates innate immune responses in macrophages. *Nat. Immunol.* 11:411–18
14. Chen X, Iliopoulos D, Zhang Q, Tang Q, Greenblatt MB, et al. 2014. XBP1 promotes triple-negative breast cancer by controlling the HIF1alpha pathway. *Nature* 508:103–7
15. Acosta-Alvear D, Zhou Y, Blais A, Tsikitis M, Lents NH, et al. 2007. XBP1 controls diverse cell type- and condition-specific transcriptional regulatory networks. *Mol. Cell* 27:53–66
16. Wang ZV, Deng Y, Gao N, Pedrozo Z, Li DL, et al. 2014. Spliced X-box binding protein 1 couples the unfolded protein response to hexosamine biosynthetic pathway. *Cell* 156:1179–92
17. Hollien J, Weissman JS. 2006. Decay of endoplasmic reticulum-localized mRNAs during the unfolded protein response. *Science* 313:104–7
18. Han D, Lerner AG, Vande Walle L, Upton JP, Xu W, et al. 2009. IRE1α kinase activation modes control alternate endoribonuclease outputs to determine divergent cell fates. *Cell* 138:562–75
19. Gaddam D, Stevens N, Hollien J. 2013. Comparison of mRNA localization and regulation during endoplasmic reticulum stress in *Drosophila* cells. *Mol. Biol. Cell* 24:14–20
20. Kimmig P, Diaz M, Zheng J, Williams CC, Lang A, et al. 2012. The unfolded protein response in fission yeast modulates stability of select mRNAs to maintain protein homeostasis. *Elife* 1:e00048
21. So JS, Hur KY, Tarrio M, Ruda V, Frank-Kamenetsky M, et al. 2012. Silencing of lipid metabolism genes through IRE1α-mediated mRNA decay lowers plasma lipids in mice. *Cell Metab.* 16:487–99
22. Benhamron S, Hadar R, Iwawaky T, So JS, Lee AH, Tirosh B. 2014. Regulated IRE1-dependent decay participates in curtailing immunoglobulin secretion from plasma cells. *Eur. J. Immunol.* 44:867–76
23. Osorio F, Tavernier SJ, Hoffmann E, Saeys Y, Martens L, et al. 2014. The unfolded-protein-response sensor IRE-1α regulates the function of CD8α^+ dendritic cells. *Nat. Immunol.* 15:248–57
24. Harding HP, Zhang Y, Ron D. 1999. Protein translation and folding are coupled by an endoplasmic-reticulum-resident kinase. *Nature* 397:271–74
25. Harding HP, Zhang Y, Bertolotti A, Zeng H, Ron D. 2000. *Perk* is essential for translational regulation and cell survival during the unfolded protein response. *Mol. Cell* 5:897–904
26. Harding HP, Zeng H, Zhang Y, Jungries R, Chung P, et al. 2001. Diabetes mellitus and exocrine pancreatic dysfunction in *Perk−/−* mice reveals a role for translational control in secretory cell survival. *Mol. Cell* 7:1153–63
27. Vattem KM, Wek RC. 2004. Reinitiation involving upstream ORFs regulates ATF4 mRNA translation in mammalian cells. *Proc. Natl. Acad. Sci. USA* 101:11269–74
28. Ma Y, Brewer JW, Diehl JA, Hendershot LM. 2002. Two distinct stress signaling pathways converge upon the CHOP promoter during the mammalian unfolded protein response. *J. Mol. Biol.* 318:1351–65
29. Marciniak SJ, Yun CY, Oyadomari S, Novoa I, Zhang Y, et al. 2004. CHOP induces death by promoting protein synthesis and oxidation in the stressed endoplasmic reticulum. *Genes Dev.* 18:3066–77

30. Haze K, Yoshida H, Yanagi H, Yura T, Mori K. 1999. Mammalian transcription factor ATF6 is synthesized as a transmembrane protein and activated by proteolysis in response to endoplasmic reticulum stress. *Mol. Biol. Cell* 10:3787–99
31. Shen J, Chen X, Hendershot L, Prywes R. 2002. ER stress regulation of ATF6 localization by dissociation of BiP/GRP78 binding and unmasking of Golgi localization signals. *Dev. Cell* 3:99–111
32. Bailey D, O'Hare P. 2007. Transmembrane bZIP transcription factors in ER stress signaling and the unfolded protein response. *Antioxid. Redox Signal.* 9:2305–21
33. Adachi Y, Yamamoto K, Okada T, Yoshida H, Harada A, Mori K. 2008. ATF6 is a transcription factor specializing in the regulation of quality control proteins in the endoplasmic reticulum. *Cell Struct. Funct.* 33:75–89
34. Reimold AM, Etkin A, Clauss I, Perkins A, Friend DS, et al. 2000. An essential role in liver development for transcription factor XBP-1. *Genes Dev.* 14:152–57
35. Urano F, Wang X, Bertolotti A, Zhang Y, Chung P, et al. 2000. Coupling of stress in the ER to activation of JNK protein kinases by transmembrane protein kinase IRE1. *Science* 287:664–66
36. Shoulders MD, Ryno LM, Genereux JC, Moresco JJ, Tu PG, et al. 2013. Stress-independent activation of XBP1s and/or ATF6 reveals three functionally diverse ER proteostasis environments. *Cell Rep.* 3:1279–92
37. Lin JH, Li H, Yasumura D, Cohen HR, Zhang C, et al. 2007. IRE1 signaling affects cell fate during the unfolded protein response. *Science* 318:944–49
38. Reimold AM, Iwakoshi NN, Manis J, Vallabhajosyula P, Szomolanyi-Tsuda E, et al. 2001. Plasma cell differentiation requires the transcription factor XBP-1. *Nature* 412:300–7
39. Todd DJ, McHeyzer-Williams LJ, Kowal C, Lee AH, Volpe BT, et al. 2009. XBP1 governs late events in plasma cell differentiation and is not required for antigen-specific memory B cell development. *J. Exp. Med.* 206:2151–59
40. Iwakoshi NN, Lee AH, Vallabhajosyula P, Otipoby KL, Rajewsky K, Glimcher LH. 2003. Plasma cell differentiation and the unfolded protein response intersect at the transcription factor XBP-1. *Nat. Immunol.* 4:321–29
41. Iwawaki T, Akai R, Kohno K. 2010. IRE1α disruption causes histological abnormality of exocrine tissues, increase of blood glucose level, and decrease of serum immunoglobulin level. *PLOS ONE* 5:e13052
42. Lee AH, Iwakoshi NN, Anderson KC, Glimcher LH. 2003. Proteasome inhibitors disrupt the unfolded protein response in myeloma cells. *PNAS* 100:9946–51
43. Hu CC, Dougan SK, McGehee AM, Love JC, Ploegh HL. 2009. XBP-1 regulates signal transduction, transcription factors and bone marrow colonization in B cells. *EMBO J.* 28:1624–36
44. Ma Y, Shimizu Y, Mann MJ, Jin Y, Hendershot LM. 2010. Plasma cell differentiation initiates a limited ER stress response by specifically suppressing the PERK-dependent branch of the unfolded protein response. *Cell Stress Chaperones* 15:281–93
45. Aragon IV, Barrington RA, Jackowski S, Mori K, Brewer JW. 2012. The specialized unfolded protein response of B lymphocytes: ATF6α-independent development of antibody-secreting B cells. *Mol. Immunol.* 51:347–55
46. Bertolotti A, Wang X, Novoa I, Jungreis R, Schlessinger K, et al. 2001. Increased sensitivity to dextran sodium sulfate colitis in IRE1β-deficient mice. *J. Clin. Invest.* 107:585–93
47. Kaser A, Lee AH, Franke A, Glickman JN, Zeissig S, et al. 2008. XBP1 links ER stress to intestinal inflammation and confers genetic risk for human inflammatory bowel disease. *Cell* 134:743–56
48. Adolph TE, Tomczak MF, Niederreiter L, Ko HJ, Bock J, et al. 2013. Paneth cells as a site of origin for intestinal inflammation. *Nature* 503:272–76
49. Iwakoshi NN, Pypaert M, Glimcher LH. 2007. The transcription factor XBP-1 is essential for the development and survival of dendritic cells. *J. Exp. Med.* 204:2267–75
50. Rinaldo CR Jr, Piazza P. 2004. Virus infection of dendritic cells: portal for host invasion and host defense. *Trends Microbiol.* 12:337–45
51. Rossi DJ, Jamieson CH, Weissman IL. 2008. Stems cells and the pathways to aging and cancer. *Cell* 132:681–96

52. Heijmans J, van Lidth de Jeude JF, Koo BK, Rosekrans SL, Wielenga MC, et al. 2013. ER stress causes rapid loss of intestinal epithelial stemness through activation of the unfolded protein response. *Cell Rep.* 3:1128–39
53. van Galen P, Kreso A, Mbong N, Kent DG, Fitzmaurice T, et al. 2014. The unfolded protein response governs integrity of the haematopoietic stem-cell pool during stress. *Nature* 510:268–72
54. Signer RA, Magee JA, Salic A, Morrison SJ. 2014. Haematopoietic stem cells require a highly regulated protein synthesis rate. *Nature* 509:49–54
55. Senovilla L, Vitale I, Martins I, Kepp O, Galluzzi L, et al. 2013. An anticancer therapy-elicited immunosurveillance system that eliminates tetraploid cells. *Oncoimmunology* 2:e22409
56. Feske S, Okamura H, Hogan PG, Rao A. 2003. Ca^{2+}/calcineurin signalling in cells of the immune system. *Biochem. Biophys. Res. Commun.* 311:1117–32
57. Vig M, Kinet JP. 2009. Calcium signaling in immune cells. *Nat. Immunol.* 10:21–27
58. Cardozo AK, Ortis F, Storling J, Feng YM, Rasschaert J, et al. 2005. Cytokines downregulate the sarcoendoplasmic reticulum pump Ca^{2+} ATPase 2b and deplete endoplasmic reticulum Ca^{2+}, leading to induction of endoplasmic reticulum stress in pancreatic β-cells. *Diabetes* 54:452–61
59. Higo T, Hamada K, Hisatsune C, Nukina N, Hashikawa T, et al. 2010. Mechanism of ER stress-induced brain damage by IP_3 receptor. *Neuron* 68:865–78
60. Higo T, Hattori M, Nakamura T, Natsume T, Michikawa T, Mikoshiba K. 2005. Subtype-specific and ER lumenal environment-dependent regulation of inositol 1,4,5-trisphosphate receptor type 1 by ERp44. *Cell* 120:85–98
61. Verfaillie T, Rubio N, Garg AD, Bultynck G, Rizzuto R, et al. 2012. PERK is required at the ER-mitochondrial contact sites to convey apoptosis after ROS-based ER stress. *Cell Death Differ.* 19:1880–91
62. Huang G, Yao J, Zeng W, Mizuno Y, Kamm KE, et al. 2006. ER stress disrupts Ca^{2+}-signaling complexes and Ca^{2+} regulation in secretory and muscle cells from PERK-knockout mice. *J. Cell Sci.* 119:153–61
63. Son SM, Byun J, Roh SE, Kim SJ, Mook-Jung I. 2014. Reduced IRE1α mediates apoptotic cell death by disrupting calcium homeostasis via the InsP3 receptor. *Cell Death Dis.* 5:e1188
64. Tan Y, Dourdin N, Wu C, De Veyra T, Elce JS, Greer PA. 2006. Ubiquitous calpains promote caspase-12 and JNK activation during endoplasmic reticulum stress-induced apoptosis. *J. Biol. Chem.* 281:16016–24
65. Timmins JM, Ozcan L, Seimon TA, Li G, Malagelada C, et al. 2009. Calcium/calmodulin-dependent protein kinase II links ER stress with Fas and mitochondrial apoptosis pathways. *J. Clin. Invest.* 119:2925–41
66. Nathan C, Cunningham-Bussel A. 2013. Beyond oxidative stress: an immunologist's guide to reactive oxygen species. *Nat. Rev. Immunol.* 13:349–61
67. Tu BP, Weissman JS. 2004. Oxidative protein folding in eukaryotes: mechanisms and consequences. *J. Cell Biol.* 164:341–46
68. Malhotra JD, Miao H, Zhang K, Wolfson A, Pennathur S, et al. 2008. Antioxidants reduce endoplasmic reticulum stress and improve protein secretion. *PNAS* 105:18525–30
69. Malhotra JD, Kaufman RJ. 2007. Endoplasmic reticulum stress and oxidative stress: a vicious cycle or a double-edged sword? *Antioxid. Redox Signal.* 9:2277–93
70. Lerner AG, Upton JP, Praveen PV, Ghosh R, Nakagawa Y, et al. 2012. IRE1α induces thioredoxin-interacting protein to activate the NLRP3 inflammasome and promote programmed cell death under irremediable ER stress. *Cell Metab.* 16:250–64
71. Li G, Scull C, Ozcan L, Tabas I. 2010. NADPH oxidase links endoplasmic reticulum stress, oxidative stress, and PKR activation to induce apoptosis. *J. Cell Biol.* 191:1113–25
72. Liu Y, Adachi M, Zhao S, Hareyama M, Koong AC, et al. 2009. Preventing oxidative stress: a new role for XBP1. *Cell Death Differ.* 16:847–57
73. Gupta S, Giricz Z, Natoni A, Donnelly N, Deegan S, et al. 2012. NOXA contributes to the sensitivity of PERK-deficient cells to ER stress. *FEBS Lett.* 586:4023–30

74. Li Y, Schwabe RF, DeVries-Seimon T, Yao PM, Gerbod-Giannone MC, et al. 2005. Free cholesterol-loaded macrophages are an abundant source of tumor necrosis factor-α and interleukin-6: model of NF-κB- and map kinase-dependent inflammation in advanced atherosclerosis. *J. Biol. Chem.* 280:21763–72
75. Oslowski CM, Hara T, O'Sullivan-Murphy B, Kanekura K, Lu S, et al. 2012. Thioredoxin-interacting protein mediates ER stress-induced beta cell death through initiation of the inflammasome. *Cell Metab.* 16:265–73
76. Menu P, Mayor A, Zhou R, Tardivel A, Ichijo H, et al. 2012. ER stress activates the NLRP3 inflammasome via an UPR-independent pathway. *Cell Death Dis.* 3:e261
77. Melo RC, D'Avila H, Wan HC, Bozza PT, Dvorak AM, Weller PF. 2011. Lipid bodies in inflammatory cells: structure, function, and current imaging techniques. *J. Histochem. Cytochem.* 59:540–56
78. Im SS, Yousef L, Blaschitz C, Liu JZ, Edwards RA, et al. 2011. Linking lipid metabolism to the innate immune response in macrophages through sterol regulatory element binding protein-1a. *Cell Metab.* 13:540–49
79. Kidani Y, Elsaesser H, Hock MB, Vergnes L, Williams KJ, et al. 2013. Sterol regulatory element-binding proteins are essential for the metabolic programming of effector T cells and adaptive immunity. *Nat. Immunol.* 14:489–99
80. Kidani Y, Bensinger SJ. 2012. Liver X receptor and peroxisome proliferator-activated receptor as integrators of lipid homeostasis and immunity. *Immunol. Rev.* 249:72–83
81. Hotamisligil GS. 2010. Endoplasmic reticulum stress and the inflammatory basis of metabolic disease. *Cell* 140:900–17
82. Osborn O, Olefsky JM. 2012. The cellular and signaling networks linking the immune system and metabolism in disease. *Nat. Med.* 18:363–74
83. Lumeng CN, Bodzin JL, Saltiel AR. 2007. Obesity induces a phenotypic switch in adipose tissue macrophage polarization. *J. Clin. Invest.* 117:175–84
84. Nagareddy PR, Murphy AJ, Stirzaker RA, Hu Y, Yu S, et al. 2013. Hyperglycemia promotes myelopoiesis and impairs the resolution of atherosclerosis. *Cell Metab.* 17:695–708
85. Esposito K, Nappo F, Marfella R, Giugliano G, Giugliano F, et al. 2002. Inflammatory cytokine concentrations are acutely increased by hyperglycemia in humans: role of oxidative stress. *Circulation* 106:2067–72
86. Lipson KL, Fonseca SG, Ishigaki S, Nguyen LX, Foss E, et al. 2006. Regulation of insulin biosynthesis in pancreatic beta cells by an endoplasmic reticulum-resident protein kinase IRE1. *Cell Metab.* 4:245–54
87. Vladykovskaya E, Sithu SD, Haberzettl P, Wickramasinghe NS, Merchant ML, et al. 2012. Lipid peroxidation product 4-hydroxy-trans-2-nonenal causes endothelial activation by inducing endoplasmic reticulum stress. *J. Biol. Chem.* 287:11398–409
88. Seimon TA, Nadolski MJ, Liao X, Magallon J, Nguyen M, et al. 2010. Atherogenic lipids and lipoproteins trigger CD36-TLR2-dependent apoptosis in macrophages undergoing endoplasmic reticulum stress. *Cell Metab.* 12:467–82
89. Fu S, Yang L, Li P, Hofmann O, Dicker L, et al. 2011. Aberrant lipid metabolism disrupts calcium homeostasis causing liver endoplasmic reticulum stress in obesity. *Nature* 473:528–31
90. Cai L, Wang Z, Ji A, Meyer JM, van der Westhuyzen DR. 2012. Scavenger receptor CD36 expression contributes to adipose tissue inflammation and cell death in diet-induced obesity. *PLOS ONE* 7:e36785
91. Feng B, Yao PM, Li Y, Devlin CM, Zhang D, et al. 2003. The endoplasmic reticulum is the site of cholesterol-induced cytotoxicity in macrophages. *Nat. Cell Biol.* 5:781–92
92. Flowers MT, Keller MP, Choi Y, Lan H, Kendziorski C, et al. 2008. Liver gene expression analysis reveals endoplasmic reticulum stress and metabolic dysfunction in SCD1-deficient mice fed a very low-fat diet. *Physiol. Genomics* 33:361–72
93. Rong X, Albert CJ, Hong C, Duerr MA, Chamberlain BT, et al. 2013. LXRs regulate ER stress and inflammation through dynamic modulation of membrane phospholipid composition. *Cell Metab.* 18:685–97
94. Fei W, Wang H, Fu X, Bielby C, Yang H. 2009. Conditions of endoplasmic reticulum stress stimulate lipid droplet formation in *Saccharomyces cerevisiae*. *Biochem. J.* 424:61–67

95. Sriburi R, Bommiasamy H, Buldak GL, Robbins GR, Frank M, et al. 2007. Coordinate regulation of phospholipid biosynthesis and secretory pathway gene expression in XBP-1(S)-induced endoplasmic reticulum biogenesis. *J. Biol. Chem.* 282:7024–34
96. Volmer R, van der Ploeg K, Ron D. 2013. Membrane lipid saturation activates endoplasmic reticulum unfolded protein response transducers through their transmembrane domains. *PNAS* 110:4628–33
97. Kitai Y, Ariyama H, Kono N, Oikawa D, Iwawaki T, Arai H. 2013. Membrane lipid saturation activates IRE1α without inducing clustering. *Genes Cells* 18:798–809
98. Ellies LG, Sperandio M, Underhill GH, Yousif J, Smith M, et al. 2002. Sialyltransferase specificity in selectin ligand formation. *Blood* 100:3618–25
99. Raju TS. 2008. Terminal sugars of Fc glycans influence antibody effector functions of IgGs. *Curr. Opin. Immunol.* 20:471–78
100. Bruckner K, Perez L, Clausen H, Cohen S. 2000. Glycosyltransferase activity of Fringe modulates Notch-Delta interactions. *Nature* 406:411–15
101. Moloney DJ, Panin VM, Johnston SH, Chen J, Shao L, et al. 2000. Fringe is a glycosyltransferase that modifies Notch. *Nature* 406:369–75
102. Lau KS, Partridge EA, Grigorian A, Silvescu CI, Reinhold VN, et al. 2007. Complex N-glycan number and degree of branching cooperate to regulate cell proliferation and differentiation. *Cell* 129:123–34
103. Demetriou M, Granovsky M, Quaggin S, Dennis JW. 2001. Negative regulation of T-cell activation and autoimmunity by *Mgat5N*-glycosylation. *Nature* 409:733–39
104. McGehee AM, Dougan SK, Klemm EJ, Shui G, Park B, et al. 2009. XBP-1-deficient plasmablasts show normal protein folding but altered glycosylation and lipid synthesis. *J. Immunol.* 183:3690–99
105. Munz C. 2009. Enhancing immunity through autophagy. *Annu. Rev. Immunol.* 27:423–49
106. Gade P, Ramachandran G, Maachani UB, Rizzo MA, Okada T, et al. 2012. An IFN-γ-stimulated ATF6-C/EBP-β-signaling pathway critical for the expression of Death Associated Protein Kinase 1 and induction of autophagy. *PNAS* 109:10316–21
107. Ogata M, Hino S, Saito A, Morikawa K, Kondo S, et al. 2006. Autophagy is activated for cell survival after endoplasmic reticulum stress. *Mol. Cell. Biol.* 26:9220–31
108. Kouroku Y, Fujita E, Tanida I, Ueno T, Isoai A, et al. 2007. ER stress (PERK/eIF2α phosphorylation) mediates the polyglutamine-induced LC3 conversion, an essential step for autophagy formation. *Cell Death Differ.* 14:230–39
109. Yang L, Li P, Fu S, Calay ES, Hotamisligil GS. 2010. Defective hepatic autophagy in obesity promotes ER stress and causes insulin resistance. *Cell Metab.* 11:467–78
110. Pengo N, Scolari M, Oliva L, Milan E, Mainoldi F, et al. 2013. Plasma cells require autophagy for sustainable immunoglobulin production. *Nat. Immunol.* 14:298–305
111. Bernales S, McDonald KL, Walter P. 2006. Autophagy counterbalances endoplasmic reticulum expansion during the unfolded protein response. *PLOS Biol.* 4:e423
112. Holm CK, Jensen SB, Jakobsen MR, Cheshenko N, Horan KA, et al. 2012. Virus-cell fusion as a trigger of innate immunity dependent on the adaptor STING. *Nat. Immunol.* 13:737–43
113. Liberman E, Fong YL, Selby MJ, Choo QL, Cousens L, et al. 1999. Activation of the *grp78* and *grp94* promoters by hepatitis C virus E2 envelope protein. *J. Virol.* 73:3718–22
114. Mulvey M, Arias C, Mohr I. 2007. Maintenance of endoplasmic reticulum (ER) homeostasis in herpes simplex virus type 1-infected cells through the association of a viral glycoprotein with PERK, a cellular ER stress sensor. *J. Virol.* 81:3377–90
115. Galindo I, Hernaez B, Munoz-Moreno R, Cuesta-Geijo MA, Dalmau-Mena I, Alonso C. 2012. The ATF6 branch of unfolded protein response and apoptosis are activated to promote African swine fever virus infection. *Cell Death Dis.* 3:e341
116. Pasqual G, Burri DJ, Pasquato A, de la Torre JC, Kunz S. 2011. Role of the host cell's unfolded protein response in arenavirus infection. *J. Virol.* 85:1662–70
117. Martinon F, Glimcher LH. 2011. Regulation of innate immunity by signaling pathways emerging from the endoplasmic reticulum. *Curr. Opin. Immunol.* 23:35–40
118. Ke PY, Chen SS. 2011. Activation of the unfolded protein response and autophagy after hepatitis C virus infection suppresses innate antiviral immunity in vitro. *J. Clin. Invest.* 121:37–56

119. Ambrose RL, Mackenzie JM. 2013. ATF6 signaling is required for efficient West Nile virus replication by promoting cell survival and inhibition of innate immune responses. *J. Virol.* 87:2206–14
120. Bischof LJ, Kao CY, Los FC, Gonzalez MR, Shen Z, et al. 2008. Activation of the unfolded protein response is required for defenses against bacterial pore-forming toxin in vivo. *PLOS Pathog* 4:e1000176
121. Wolfson JJ, May KL, Thorpe CM, Jandhyala DM, Paton JC, Paton AW. 2008. Subtilase cytotoxin activates PERK, IRE1 and ATF6 endoplasmic reticulum stress-signalling pathways. *Cell Microbiol.* 10:1775–86
122. Cho JA, Lee AH, Platzer B, Cross BC, Gardner BM, et al. 2013. The unfolded protein response element IRE1α senses bacterial proteins invading the ER to activate RIG-I and innate immune signaling. *Cell Host Microbe* 13:558–69
123. Seimon TA, Kim MJ, Blumenthal A, Koo J, Ehrt S, et al. 2010. Induction of ER stress in macrophages of tuberculosis granulomas. *PLOS ONE* 5:e12772
124. Lardner A. 2001. The effects of extracellular pH on immune function. *J. Leukoc. Biol.* 69:522–30
125. Vats D, Mukundan L, Odegaard JI, Zhang L, Smith KL, et al. 2006. Oxidative metabolism and PGC-1β attenuate macrophage-mediated inflammation. *Cell Metab.* 4:13–24
126. Cathcart MK, Morel DW, Chisolm GM 3rd. 1985. Monocytes and neutrophils oxidize low density lipoprotein making it cytotoxic. *J. Leukoc. Biol.* 38:341–50
127. Karali E, Bellou S, Stellas D, Klinakis A, Murphy C, Fotsis T. 2014. VEGF signals through ATF6 and PERK to promote endothelial cell survival and angiogenesis in the absence of ER stress. *Mol. Cell* 54:559–72
128. Pahl HL, Baeuerle PA. 1996. Activation of NF-κB by ER stress requires both Ca^{2+} and reactive oxygen intermediates as messengers. *FEBS Lett.* 392:129–36
129. Pahl HL, Baeuerle PA. 1995. A novel signal transduction pathway from the endoplasmic reticulum to the nucleus is mediated by transcription factor NF-kappa B. *EMBO J.* 14:2580–88
130. Hu P, Han Z, Couvillon AD, Kaufman RJ, Exton JH. 2006. Autocrine tumor necrosis factor alpha links endoplasmic reticulum stress to the membrane death receptor pathway through IRE1α-mediated NF-κB activation and down-regulation of TRAF2 expression. *Mol. Cell. Biol.* 26:3071–84
131. Tam AB, Mercado EL, Hoffmann A, Niwa M. 2012. ER stress activates NF-κB by integrating functions of basal IKK activity, IRE1 and PERK. *PLOS ONE* 7:e45078
132. Deng J, Lu PD, Zhang Y, Scheuner D, Kaufman RJ, et al. 2004. Translational repression mediates activation of nuclear factor kappa B by phosphorylated translation initiation factor 2. *Mol. Cell. Biol.* 24:10161–68
133. Li J, Wang JJ, Zhang SX. 2011. Preconditioning with endoplasmic reticulum stress mitigates retinal endothelial inflammation via activation of X-box binding protein 1. *J. Biol. Chem.* 286:4912–21
134. Rutkowski DT, Arnold SM, Miller CN, Wu J, Li J, et al. 2006. Adaptation to ER stress is mediated by differential stabilities of pro-survival and pro-apoptotic mRNAs and proteins. *PLOS Biol.* 4:e374
135. Hu P, Han Z, Couvillon AD, Exton JH. 2004. Critical role of endogenous Akt/IAPs and MEK1/ERK pathways in counteracting endoplasmic reticulum stress-induced cell death. *J. Biol. Chem.* 279:49420–29
136. Nishitoh H, Matsuzawa A, Tobiume K, Saegusa K, Takeda K, et al. 2002. ASK1 is essential for endoplasmic reticulum stress-induced neuronal cell death triggered by expanded polyglutamine repeats. *Genes Dev.* 16:1345–55
137. Ozcan U, Yilmaz E, Ozcan L, Furuhashi M, Vaillancourt E, et al. 2006. Chemical chaperones reduce ER stress and restore glucose homeostasis in a mouse model of type 2 diabetes. *Science* 313:1137–40
138. Richardson CE, Kooistra T, Kim DH. 2010. An essential role for XBP-1 in host protection against immune activation in *C. elegans*. *Nature* 463:1092–95
139. Lee J, Sun C, Zhou Y, Lee J, Gokalp D, et al. 2011. p38 MAPK-mediated regulation of Xbp1s is crucial for glucose homeostasis. *Nat. Med.* 17:1251–60
140. Chovatiya R, Medzhitov R. 2014. Stress, inflammation, and defense of homeostasis. *Mol. Cell* 54:281–88
141. Gargalovic PS, Gharavi NM, Clark MJ, Pagnon J, Yang WP, et al. 2006. The unfolded protein response is an important regulator of inflammatory genes in endothelial cells. *Arterioscler. Thromb. Vasc. Biol.* 26:2490–96

142. Wang YI, Bettaieb A, Sun C, DeVerse JS, Radecke CE, et al. 2013. Triglyceride-rich lipoprotein modulates endothelial vascular cell adhesion molecule (VCAM)-1 expression via differential regulation of endoplasmic reticulum stress. *PLOS ONE* 8:e78322
143. Majors AK, Austin RC, de la Motte CA, Pyeritz RE, Hascall VC, et al. 2003. Endoplasmic reticulum stress induces hyaluronan deposition and leukocyte adhesion. *J. Biol. Chem.* 278:47223–31
144. Li CK, Knopp P, Moncrieffe H, Singh B, Shah S, et al. 2009. Overexpression of MHC class I heavy chain protein in young skeletal muscle leads to severe myositis: implications for juvenile myositis. *Am. J. Pathol.* 175:1030–40
145. Vattemi G, Engel WK, McFerrin J, Askanas V. 2004. Endoplasmic reticulum stress and unfolded protein response in inclusion body myositis muscle. *Am. J. Pathol.* 164:1–7
146. Suwara MI, Green NJ, Borthwick LA, Mann J, Mayer-Barber KD, et al. 2014. IL-1α released from damaged epithelial cells is sufficient and essential to trigger inflammatory responses in human lung fibroblasts. *Mucosal Immunol.* 7:684–93
147. Wang G, Yang ZQ, Zhang K. 2010. Endoplasmic reticulum stress response in cancer: molecular mechanism and therapeutic potential. *Am. J. Transl. Res.* 2:65–74
148. Drogat B, Auguste P, Nguyen DT, Bouchecareilh M, Pineau R, et al. 2007. IRE1 signaling is essential for ischemia-induced vascular endothelial growth factor-A expression and contributes to angiogenesis and tumor growth in vivo. *Cancer Res.* 67:6700–7
149. Bi M, Naczki C, Koritzinsky M, Fels D, Blais J, et al. 2005. ER stress-regulated translation increases tolerance to extreme hypoxia and promotes tumor growth. *EMBO J.* 24:3470–81
150. Mahadevan NR, Rodvold J, Sepulveda H, Rossi S, Drew AF, Zanetti M. 2011. Transmission of endoplasmic reticulum stress and pro-inflammation from tumor cells to myeloid cells. *PNAS* 108:6561–66
151. Cullen SJ, Fatemie S, Ladiges W. 2013. Breast tumor cells primed by endoplasmic reticulum stress remodel macrophage phenotype. *Am. J. Cancer Res.* 3:196–210
152. Mahadevan NR, Anufreichik V, Rodvold JJ, Chiu KT, Sepulveda H, Zanetti M. 2012. Cell-extrinsic effects of tumor ER stress imprint myeloid dendritic cells and impair $CD8^+$ T cell priming. *PLOS ONE* 7:e51845
153. Kono H, Rock KL. 2008. How dying cells alert the immune system to danger. *Nat. Rev. Immunol.* 8:279–89
154. Obeid M, Tesniere A, Ghiringhelli F, Fimia GM, Apetoh L, et al. 2007. Calreticulin exposure dictates the immunogenicity of cancer cell death. *Nat. Med.* 13:54–61
155. Scaffidi P, Misteli T, Bianchi ME. 2002. Release of chromatin protein HMGB1 by necrotic cells triggers inflammation. *Nature* 418:191–95
156. Luo Y, Li SJ, Yang J, Qiu YZ, Chen FP. 2013. HMGB1 induces an inflammatory response in endothelial cells via the RAGE-dependent endoplasmic reticulum stress pathway. *Biochem. Biophys. Res. Commun.* 438:732–38
157. Zhu XM, Yao FH, Yao YM, Dong N, Yu Y, Sheng ZY. 2012. Endoplasmic reticulum stress and its regulator XBP-1 contributes to dendritic cell maturation and activation induced by high mobility group box-1 protein. *Int. J. Biochem. Cell Biol.* 44:1097–105
158. Tufi R, Panaretakis T, Bianchi K, Criollo A, Fazi B, et al. 2008. Reduction of endoplasmic reticulum Ca^{2+} levels favors plasma membrane surface exposure of calreticulin. *Cell Death Differ.* 15:274–82
159. Garg AD, Krysko DV, Verfaillie T, Kaczmarek A, Ferreira GB, et al. 2012. A novel pathway combining calreticulin exposure and ATP secretion in immunogenic cancer cell death. *EMBO J.* 31:1062–79
160. Martins I, Kepp O, Schlemmer F, Adjemian S, Tailler M, et al. 2011. Restoration of the immunogenicity of cisplatin-induced cancer cell death by endoplasmic reticulum stress. *Oncogene* 30:1147–58
161. Senovilla L, Vitale I, Martins I, Tailler M, Pailleret C, et al. 2012. An immunosurveillance mechanism controls cancer cell ploidy. *Science* 337:1678–84
162. Smith JA, Turner MJ, DeLay ML, Klenk EI, Sowders DP, Colbert RA. 2008. Endoplasmic reticulum stress and the unfolded protein response are linked to synergistic IFN-beta induction via X-box binding protein 1. *Eur. J. Immunol.* 38:1194–203
163. Zeng L, Liu YP, Sha H, Chen H, Qi L, Smith JA. 2010. XBP-1 couples endoplasmic reticulum stress to augmented IFN-beta induction via a *cis*-acting enhancer in macrophages. *J. Immunol.* 185:2324–30

164. Liu YP, Zeng L, Tian A, Bomkamp A, Rivera D, et al. 2012. Endoplasmic reticulum stress regulates the innate immunity critical transcription factor IRF3. *J. Immunol.* 189:4630–39
165. Goodall JC, Wu C, Zhang Y, McNeill L, Ellis L, et al. 2010. Endoplasmic reticulum stress-induced transcription factor, CHOP, is crucial for dendritic cell IL-23 expression. *PNAS* 107:17698–703
166. Zhao C, Pavicic PG Jr, Datta S, Sun D, Novotny M, Hamilton TA. 2014. Cellular stress amplifies TLR3/4-induced CXCL1/2 gene transcription in mononuclear phagocytes via RIPK1. *J. Immunol.* 193:879–88
167. Szmola R, Sahin-Toth M. 2010. Pancreatitis-associated chymotrypsinogen C (CTRC) mutant elicits endoplasmic reticulum stress in pancreatic acinar cells. *Gut* 59:365–72
168. Carroll TP, Greene CM, O'Connor CA, Nolan AM, O'Neill SJ, McElvaney NG. 2010. Evidence for unfolded protein response activation in monocytes from individuals with alpha-1 antitrypsin deficiency. *J. Immunol.* 184:4538–46
169. Feng Y, Ding J, Fan CM, Zhu P. 2012. Interferon-gamma contributes to HLA-B27-associated unfolded protein response in spondyloarthropathies. *J. Rheumatol.* 39:574–82
170. Woo CW, Cui D, Arellano J, Dorweiler B, Harding H, et al. 2009. Adaptive suppression of the ATF4-CHOP branch of the unfolded protein response by Toll-like receptor signalling. *Nat. Cell Biol.* 11:1473–80
171. Amor S, Puentes F, Baker D, van der Valk P. 2010. Inflammation in neurodegenerative diseases. *Immunology* 129:154–69
172. Vinson CR, Hai T, Boyd SM. 1993. Dimerization specificity of the leucine zipper-containing bZIP motif on DNA binding: prediction and rational design. *Genes Dev.* 7:1047–58
173. Reinke AW, Baek J, Ashenberg O, Keating AE. 2013. Networks of bZIP protein-protein interactions diversified over a billion years of evolution. *Science* 340:730–34
174. Ron D, Habener JF. 1992. CHOP, a novel developmentally regulated nuclear protein that dimerizes with transcription factors C/EBP and LAP and functions as a dominant-negative inhibitor of gene transcription. *Genes Dev.* 6:439–53
175. Geissmann F, Manz MG, Jung S, Sieweke MH, Merad M, Ley K. 2010. Development of monocytes, macrophages, and dendritic cells. *Science* 327:656–61
176. Gombart AF, Grewal J, Koeffler HP. 2007. ATF4 differentially regulates transcriptional activation of myeloid-specific genes by C/EBPε and C/EBPα. *J. Leukoc. Biol.* 81:1535–47
177. Gery S, Park DJ, Vuong PT, Chih DY, Lemp N, Koeffler HP. 2004. Retinoic acid regulates C/EBP homologous protein expression (CHOP), which negatively regulates myeloid target genes. *Blood* 104:3911–17
178. Kim I, Xu W, Reed JC. 2008. Cell death and endoplasmic reticulum stress: disease relevance and therapeutic opportunities. *Nat. Rev. Drug Discov.* 7:1013–30
179. Todd DJ, Lee AH, Glimcher LH. 2008. The endoplasmic reticulum stress response in immunity and autoimmunity. *Nat. Rev. Immunol.* 8:663–74
180. Hampe J, Schreiber S, Shaw SH, Lau KF, Bridger S, et al. 1999. A genomewide analysis provides evidence for novel linkages in inflammatory bowel disease in a large European cohort. *Am. J. Hum. Genet.* 64:808–16
181. Hampe J, Franke A, Rosenstiel P, Till A, Teuber M, et al. 2007. A genome-wide association scan of nonsynonymous SNPs identifies a susceptibility variant for Crohn disease in *ATG16L1*. *Nat. Genet.* 39:207–11
182. Parkes M, Barrett JC, Prescott NJ, Tremelling M, Anderson CA, et al. 2007. Sequence variants in the autophagy gene *IRGM* and multiple other replicating loci contribute to Crohn's disease susceptibility. *Nat. Genet.* 39:830–32
183. Deuring JJ, Fuhler GM, Konstantinov SR, Peppelenbosch MP, Kuipers EJ, et al. 2014. Genomic ATG16L1 risk allele-restricted Paneth cell ER stress in quiescent Crohn's disease. *Gut* 63:1081–91
184. Cao SS, Wang M, Harrington JC, Chuang BM, Eckmann L, Kaufman RJ. 2014. Phosphorylation of eIF2α is dispensable for differentiation but required at a posttranscriptional level for Paneth cell function and intestinal homeostasis in mice. *Inflamm. Bowel Dis.* 20:712–22

185. Heazlewood CK, Cook MC, Eri R, Price GR, Tauro SB, et al. 2008. Aberrant mucin assembly in mice causes endoplasmic reticulum stress and spontaneous inflammation resembling ulcerative colitis. *PLOS Med.* 5:e54
186. Zhao F, Edwards R, Dizon D, Afrasiabi K, Mastroianni JR, et al. 2010. Disruption of Paneth and goblet cell homeostasis and increased endoplasmic reticulum stress in *Agr2−/−* mice. *Dev. Biol.* 338:270–79
187. Hino K, Saito A, Asada R, Kanemoto S, Imaizumi K. 2014. Increased susceptibility to dextran sulfate sodium-induced colitis in the endoplasmic reticulum stress transducer OASIS deficient mice. *PLOS ONE* 9:e88048
188. Cao SS, Zimmermann EM, Chuang BM, Song B, Nwokoye A, et al. 2013. The unfolded protein response and chemical chaperones reduce protein misfolding and colitis in mice. *Gastroenterology* 144:989–1000.e6
189. Das I, Png CW, Oancea I, Hasnain SZ, Lourie R, et al. 2013. Glucocorticoids alleviate intestinal ER stress by enhancing protein folding and degradation of misfolded proteins. *J. Exp. Med.* 210:1201–16
190. Hasnain SZ, Tauro S, Das I, Tong H, Chen AC, et al. 2013. IL-10 promotes production of intestinal mucus by suppressing protein misfolding and endoplasmic reticulum stress in goblet cells. *Gastroenterology* 144:357–68.e9
191. Paton AW, Beddoe T, Thorpe CM, Whisstock JC, Wilce MC, et al. 2006. AB5 subtilase cytotoxin inactivates the endoplasmic reticulum chaperone BiP. *Nature* 443:548–52
192. Yamazaki H, Hiramatsu N, Hayakawa K, Tagawa Y, Okamura M, et al. 2009. Activation of the Akt-NF-κB pathway by subtilase cytotoxin through the ATF6 branch of the unfolded protein response. *J. Immunol.* 183:1480–87
193. Martin FP, Dumas ME, Wang Y, Legido-Quigley C, Yap IK, et al. 2007. A top-down systems biology view of microbiome-mammalian metabolic interactions in a mouse model. *Mol. Syst. Biol.* 3:112
194. van der Linden SM, Valkenburg HA, de Jongh BM, Cats A. 1984. The risk of developing ankylosing spondylitis in HLA-B27 positive individuals. A comparison of relatives of spondylitis patients with the general population. *Arthritis Rheum.* 27:241–49
195. Turner MJ, Sowders DP, DeLay ML, Mohapatra R, Bai S, et al. 2005. HLA-B27 misfolding in transgenic rats is associated with activation of the unfolded protein response. *J. Immunol.* 175:2438–48
196. Turner MJ, Delay ML, Bai S, Klenk E, Colbert RA. 2007. HLA–B27 up-regulation causes accumulation of misfolded heavy chains and correlates with the magnitude of the unfolded protein response in transgenic rats: implications for the pathogenesis of spondylarthritis-like disease. *Arthritis Rheum.* 56:215–23
197. Hammer RE, Maika SD, Richardson JA, Tang JP, Taurog JD. 1990. Spontaneous inflammatory disease in transgenic rats expressing HLA-B27 and human β_2m: an animal model of HLA-B27-associated human disorders. *Cell* 63:1099–112
198. DeLay ML, Turner MJ, Klenk EI, Smith JA, Sowders DP, Colbert RA. 2009. HLA-B27 misfolding and the unfolded protein response augment interleukin-23 production and are associated with Th17 activation in transgenic rats. *Arthritis Rheum.* 60:2633–43
199. Qiu Q, Zheng Z, Chang L, Zhao YS, Tan C, et al. 2013. Toll-like receptor-mediated IRE1α activation as a therapeutic target for inflammatory arthritis. *EMBO J.* 32:2477–90
200. Osorio F, Lambrecht B, Janssens S. 2013. The UPR and lung disease. *Semin. Immunopathol.* 35:293–306
201. Bartoszewski R, Rab A, Jurkuvenaite A, Mazur M, Wakefield J, et al. 2008. Activation of the unfolded protein response by ΔF508 CFTR. *Am. J. Respir. Cell Mol. Biol.* 39:448–57
202. Blohmke CJ, Mayer ML, Tang AC, Hirschfeld AF, Fjell CD, et al. 2012. Atypical activation of the unfolded protein response in cystic fibrosis airway cells contributes to p38 MAPK-mediated innate immune responses. *J. Immunol.* 189:5467–75
203. Perez A, Issler AC, Cotton CU, Kelley TJ, Verkman AS, Davis PB. 2007. CFTR inhibition mimics the cystic fibrosis inflammatory profile. *Am. J. Physiol. Lung Cell. Mol. Physiol.* 292:L383–95
204. Luciani A, Villella VR, Esposito S, Brunetti-Pierri N, Medina D, et al. 2010. Defective CFTR induces aggresome formation and lung inflammation in cystic fibrosis through ROS-mediated autophagy inhibition. *Nat. Cell Biol.* 12:863–75
205. Moffatt MF, Kabesch M, Liang L, Dixon AL, Strachan D, et al. 2007. Genetic variants regulating *ORMDL3* expression contribute to the risk of childhood asthma. *Nature* 448:470–73

206. Cantero-Recasens G, Fandos C, Rubio-Moscardo F, Valverde MA, Vicente R. 2010. The asthma-associated *ORMDL3* gene product regulates endoplasmic reticulum-mediated calcium signaling and cellular stress. *Hum. Mol. Genet.* 19:111–21
207. Miller M, Tam AB, Cho JY, Doherty TA, Pham A, et al. 2012. *ORMDL3* is an inducible lung epithelial gene regulating metalloproteases, chemokines, OAS, and ATF6. *PNAS* 109:16648–53
208. Mahn K, Hirst SJ, Ying S, Holt MR, Lavender P, et al. 2009. Diminished sarco/endoplasmic reticulum Ca^{2+} ATPase (SERCA) expression contributes to airway remodelling in bronchial asthma. *PNAS* 106:10775–80
209. Martino ME, Olsen JC, Fulcher NB, Wolfgang MC, O'Neal WK, Ribeiro CM. 2009. Airway epithelial inflammation-induced endoplasmic reticulum Ca^{2+} store expansion is mediated by X-box binding protein-1. *J. Biol. Chem.* 284:14904–13
210. Makhija L, Krishnan V, Rehman R, Chakraborty S, Maity S, et al. 2013. Chemical chaperones mitigate experimental asthma by attenuating endoplasmic reticulum stress. *Am. J. Respir. Cell Mol. Biol.* 50:923–31
211. Lukacs NW, Tekkanat KK, Berlin A, Hogaboam CM, Miller A, et al. 2001. Respiratory syncytial virus predisposes mice to augmented allergic airway responses via IL-13-mediated mechanisms. *J. Immunol.* 167:1060–65