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REVIEW

# Inflammation and cellular stress: a mechanistic link between immune-mediated and metabolically driven pathologies

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**Abstract**
*Background* Multiple cellular stress responses have been implicated in chronic diseases such as obesity, diabetes, cardiovascular, and inflammatory bowel diseases. Even though phenotypically different, chronic diseases share cellular stress signaling pathways, in particular endoplasmic reticulum (ER) unfolded protein response (UPR).
*Results and methods* The purpose of the ER UPR is to restore ER homeostasis after challenges of the ER function. Among the triggers of ER UPR are changes in the redox status, elevated protein synthesis, accumulation of unfolded or misfolded proteins, energy deficiency and glucose deprivation, cholesterol depletion, and microbial signals. Numerous mouse models have been used to characterize the contribution of ER UPR to several pathologies, and ER UPR-associated signaling has also been demonstrated to be relevant in humans. Additionally, recent evidence suggests that the ER UPR is interrelated with metabolic and inflammatory pathways, autophagy, apoptosis, and mitochondrial stress signaling. Furthermore, microbial as well as nutrient sensing is integrated into the ER-associated signaling network.
*Conclusion* The data discussed in the present review highlight the interaction of ER UPR with inflammatory pathways, metabolic processes and mitochondrial function, and their interrelation in the context of chronic diseases.

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## Introduction

Chronic diseases comprise metabolically driven pathologies such as obesity, insulin resistance, type 2 diabetes, and cardiovascular disease but also immunologically mediated disorders like allergies or inflammatory bowel diseases (IBD). The prevalence of chronic diseases has rapidly increased in the second half of the twentieth century [1–3], associated with the spread of the western lifestyle and now constitutes a global health problem [4]. Even though the phenotypes caused by chronic diseases are diverse, they share similarities at the molecular and cellular level [5]. Importantly, also metabolic diseases exhibit strong inflammatory underpinnings. For example, obesity, contributing to most metabolic diseases, evokes a broad array of inflammatory and metabolic responses leading to low-grade local inflammation and in turn to defective insulin receptor signaling and disruption of metabolic homeostasis [6]. Identifying common mechanisms underlying these pathologies will increase the understanding of chronic diseases and should lead to new treatment approaches.

One cellular condition present in various diseases is endoplasmic reticulum (ER) stress and the associated ER unfolded protein response (UPR) [7–9]. In mammalian cells, the endoplasmic reticulum is essential for cholesterol production, for calcium homeostasis, and for the transit of correctly folded proteins to the extracellular space, the plasma membrane, and the exo- and endocytic compartments. Among the conditions that challenge ER functions and elicit ER stress responses are changes in calcium homeostasis or

redox status, elevated protein synthesis, accumulation of unfolded or misfolded proteins, energy deficiency and glucose deprivation, altered protein glycosylation, cholesterol depletion, and microbial infections [10]. The purpose of the ER UPR is to restore ER homeostasis by enhancing protein degradation, reducing protein synthesis, and expanding the protein folding capacity by upregulation of chaperones that help proteins in the ER lumen to fold [11]. However, if the ER stress is prolonged or excessive, ER UPR can ultimately lead to cell death via mitochondria-dependent and mitochondria-independent apoptotic pathways [12, 13]. The ER UPR has been considered a cytoprotective mechanism as well as an autoregulatory system adjusting the ER capacity to cellular demand. Inflammation and ER stress are linked at many levels; inflammation is characterized by the production of large amounts of proteins such as cytokines or chemokines, and furthermore, recent work using mice deficient in ER UPR mediators link ER stress in the highly secretory subtypes of intestinal epithelial cell (IEC), anti-microbial peptides-producing Paneth cells and mucin-producing goblet cells, with anti-microbial defense and intestinal inflammation [14–16]. In addition, ER UPR signaling can directly intersect with inflammatory pathways including NF-$\kappa$B, JNK, and TLR-mediated signaling and production of reactive oxygen species (ROS) [17–20]. Yet, ER UPR is not only involved in inflammatory responses, but also in metabolic processes and during B cell and adipocyte differentiation [21, 22]. It has been suggested that the ER is essential in the coordination of metabolic responses through its ability to control the synthetic and catabolic pathways of various nutrients [23]. These features are reflected by the responsiveness of the ER UPR to the nutritional state of mammalian cells as well as the suggested contribution of the ER UPR to glucose sensing in pancreatic $\beta$-cells [24]. Since protein folding is an energy requiring process, the ER itself is dependent on a sufficient energy supply granted by mitochondria. ER and mitochondria fulfill distinct functions in cells, but they interact physically and functionally [25]. Mitochondrial dysfunction and alterations in energy metabolism in general have been implicated during the onset and the course of neoplasia, metabolic diseases, and inflammation [26–28]. Consistently, mitochondria have been shown to modulate ER UPR [26, 28, 29].

The data presented in this review highlight the interrelated role ER UPR, inflammatory pathways, metabolic processes, and mitochondrial function in the context of chronic diseases.

## ER UPR-associated signaling

In eukaryotic cells, the ER membrane-associated sensors IRE1 (inositol requiring enzyme 1), ATF6 (activation transcription factor 6), and PERK (PKR-like ER kinase) mediate three distinct branches of the ER UPR. In unstressed cells, these transmembrane proteins are bound by the ER chaperone glucose-regulated protein 78 (GRP78, also referred to as immunoglobulin heavy chain-binding protein, BIP) in their intraluminal domains and rendered inactive. Accumulation of mis- or unfolded proteins in the ER triggers recruitment of GRP78 away from these sensors. Liberation of PERK and IRE1 results in dimerization and activation of the two kinases and engages a complex downstream signaling pathway [10]. Activation of ATF6 requires release from the ER and migration to the Golgi apparatus where it is cleaved by site 1 protease (S1P) and site 2 protease (S2P) to generate an active transcription factor (nATF6) [30]. Together, the three branches of the ER UPR restore ER homeostasis by (I) enhancing the degradation of misfolded proteins by ER-associated degradation (ERAD), (II) translational attenuation through phosphorylation of the $\alpha$ subunit of eukaryotic translation initiation factor (eIF)2, and (III) expanding the protein folding capacity of the cell through upregulation of ER chaperones like the glucose-regulated protein (GRP)78 (Fig. 1).

## IRE1

The most evolutionary conserved branch of the ER UPR is mediated by IRE1 [31], a Ser/Thr protein kinase and endoribonuclease. Upon activation of IRE1$\alpha$, a 26 nucleotide intron is spliced out of the mRNA encoding the transcription factor XBP1 [10]. This shift in the reading frame results in the translation of the active, spliced form of the transcription factor, XBP1s, that comprises an N-terminal DNA-binding domain and a potent transactivation domain at the C-terminus [32]. XBP1s, alone or as heterodimer in conjugation with ATF6$\alpha$, controls the upregulation of a broad spectrum of ER UPR-related genes such as chaperones (e.g., GRP78), and proteins involved in ERAD and protein quality control [33, 34]. Since XBP1s also controls the expansion of secretory pathways by ER/Golgi biogenesis [35, 36], it is crucial for survival and function of secretory cells which are particularly susceptible to ER stress [16]. Recently, other mRNAs have been identified as substrates for IRE1 under stress conditions. IRE1 degrades these mRNAs to prevent their translation, a mechanism suggested to additionally alleviate ER stress [37]. Furthermore, the cytosolic domain of activated IRE1 can bind to the adaptor protein TNFR-associated factor (TRAF) 2 to activate the apoptosis signal-regulating kinase (ASK) 1 and cJun-N-terminal kinase (JNK) [38, 39].

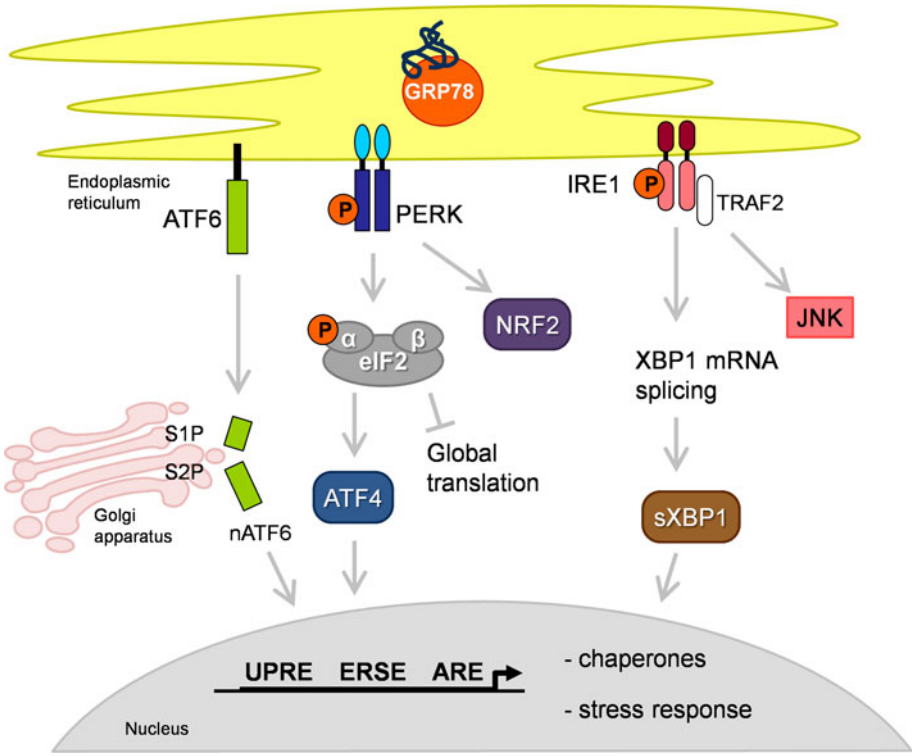


**Fig. 1** Endoplasmic reticulum unfolded protein response and associated signaling. The recruitment of the chaperone GRP78 to mis- or unfolded proteins in the ER lumen induces signaling cascades mediated by the transmembrane proteins ATF6, PERK, and IRE-1. Subsequently, this causes activation of kinases, attenuation of global protein translation, and recruitment of transcription factors to UPRE, ERSE, and ARE to evoke cellular stress responses. *ARE* antioxidant responsive element, *ATF* activating transcription factor, *eIF2* eukaryotic translation initiation factor 2, *ER* endoplasmic reticulum, *ERSE* ER stress response element, *GRP* glucose-regulated protein, *IRE* inositol requiring enzyme, *JNK* cJun-N-terminal kinase, *NRF* NF-E2-related factor, *PERK* PKR-like ER-associated kinase, *S1P* and *S2P* site 1 and site 2 proteases, *TRAF* TNF-receptor-associated factor, *UPRE* unfolded protein response element, *XBP* x-box-binding protein

## ATF6

A second ER UPR pathway is initiated by the type II ER transmembrane proteins ATF6$\alpha$ and ATF6$\beta$, whose cytosolic domain encodes a bZIP transcription factor [10]. The active, cleaved form translocates to the nucleus, binds to promoters containing ER stress elements (ERSE), UPR elements (UPRE) and cAMP response elements (CRE) and enhances gene transcription of xbp1 and many other ER UPR genes related to ERAD and protein folding [34, 40, 41]. In addition, ATF6$\alpha$ may also modulate lipid biosynthesis and ER expansion under stress conditions [42]. A number of recently identified ATF6 homologues add complexity to this branch of the ER UPR. OASIS, CREBH, LUMAN/CREB3, CREB4, and BBF2H7 are ER-anchored bZIP transcription factors that are processed at the Golgi in a similar way as ATF6 [10]. All these factors respond to ER stress and can activate UPR target genes [43]; however, differences in activating stimuli, response element binding, and distinct tissue distributions are proposed. For example, OASIS might play a role in osteoblast activity and bone formation [44], whereas CREBH is suggested to stimulate the acute phase response in the liver in response to lipopolysaccharide and cytokines [45]. Notably, ATF6$\alpha$- and ATF6$\beta$-single knockout mice develop normally, in contrast to double-knockout mice which are embryonic lethal [34, 46]. In summary, these data hint toward redundancies in the ER UPR as well as to a fine-tuned ER UPR in mammals that allows distinct responses depending on the affected tissue, the cause and duration of stress.

## PERK

The third branch of ER UPR is mediated by PERK and results in the inhibition of global protein synthesis by phosphorylation of the eukaryotic translation initiation factor (eIF) 2$\alpha$ [47]. Downstream, this leads to the induction of activating transcription factor (ATF) 4 through alternative translation. Target genes of ATF4 comprise genes involved in ER redox control (ER oxidoreductin (ERO) 1) and apoptosis [C/EBP homologous protein (Chop)] as well as regulators of glucose metabolism [48, 49]. In addition, ATF4 induces genes related to a negative

feedback of eIF2α phosphorylation, such as growth arrest and DNA damage-inducible protein (Gadd) 34, which targets protein phosphatase (PP) 1 to the ER and promotes dephosphorylation of eIF2α, thereby reversing the shutoff of protein synthesis and facilitating recovery of cells from stress [50, 51]. PERK-dependent phosphorylation also triggers dissociation of Nrf2/Keap1 complexes, subsequent nuclear translocation of Nrf2 and transcription of genes harboring antioxidant response elements (ARE) in their promoters, a process thought to counteract oxidative stress evoked by ER stress [52, 53]. Besides PERK, three other kinases are known to have eIF2α as a substrate, double-stranded RNA-activated protein kinase (PKR), general control non-derepressible kinase 2 (GCN2), and heme-regulated inhibitor kinase (HRI). Of those, only PKR is described to participate in ER stress signaling [54], whereas GCN2 and HRI might be activated under oxidative stress and amino acid starvation, respectively.

## ER UPR and inflammation

Inflammatory pathways and the ER UPR are tightly interrelated through all three branches of the ER UPR. IRE1 can activate JNK and thereby the transcription factor activator protein (AP) 1 [11] and is able to modulate the inflammation-related MAP kinases p38 and ERK, possibly by binding of the adaptor protein Nck [55]. Moreover, IRE signaling might be interrelated to the inflammatory NF-κB pathway through interaction with an inhibitor κB kinase (IKK)/TRAF2 protein complex [20]. Downstream of IRE1, XBP1, and xbp1 splicing are required to elicit adequate antibody secretion in response to antigenic challenge in B cells [56, 57] and are essential for the production of antimicrobial peptides in Paneth cells [16]. ATF6 itself, in addition to the suggested role of its homologue CREBH as regulator of acute phase proteins such as serum amyloid and C-reactive protein in the liver [45], was recently shown to activate the transcription factor NF-κB via Akt phosphorylation [58]. In contrast, PERK-mediated translational suppression targets inhibitory kappa B (IκB), the inhibitor of NF-κB, thereby triggering NF-κB nuclear translocation and expression of inflammatory cytokines like interleukin (IL) 6 and tumor necrosis factor (TNF) α [18, 59]. Other proinflammatory molecules including IL-8 and MCP-1 have been reported to be responsive to experimental induction of UPR in vitro as well [60]. Specific inflammatory triggers may activate different branches of the ER UPR, but there is evidence that not only ER UPR can induce inflammatory changes, but also that inflammation in terms of activated inhibitor of NF-κB kinase (IKK)-β can induce ER UPR [61]. In addition to the mechanisms mentioned above, ER UPR and inflammatory pathways are interrelated by the generation of reactive oxygen species (ROS) and nitric oxide (NO) [52, 62]. Increased protein folding due to ER UPR activation and formation of disulfide bonds results in the accumulation of ROS and oxidative stress [63], whereas ROS generated by inflammation could aggravate ER stress. Similarly, NO production triggered by inflammation can induce ER UPR through NO-induced inhibition of protein disulfide isomerase (PDI) and subsequent accumulation of polyubiquitinated proteins [62].

A prerequisite to effective immune responses is the sensing of danger signals such as microbial-associated molecular pattern (MAMP) motifs. Distinct families of pattern-recognition receptors, particularly cell- or endosomal membrane bound Toll-like receptors (TLR), cytoplasmic retinoic acid-inducible gene (RIG) I-like receptors, and cytoplasmic Nod-like receptors (NLR) carry out this function and activate transcriptional programs to orchestrate adaptive immune responses. Interestingly, recent data suggest that TLR signaling can modulate ER UPR signaling and activate ER UPR-associated transcription factors [17, 64, 65]. Treatment of mice with low dose of the TLR4 ligand lipopolysaccharide (LPS) prior to induction of systemic ER stress prevented pro-apoptotic CHOP expression and tissue damage. This effect was shown to be mediated in a TRIF-dependant manner by selective attenuation of ATF4 translation and its downstream target CHOP. The authors suggest that this mechanism protects TLR-expressing cells from prolonged ER stress evoked during host responses to pathogens [64]. Using TLR2 and TLR4-deficient mice, we could demonstrate TLR signaling to modulate ER UPR in IEC [65] and another study showed that TLR2 and TLR4 specifically activated IRE1 and XBP1 in macrophages [17]. The latter study implies a distinct function for XBP1 in host defense, since TLR-mediated XBP1s induction did not induce ER UPR-associated target genes but was required for optimal and sustained production of proinflammatory cytokines in macrophages [17]. Regarding ROS, it is noteworthy that in a model of ischemia/reperfusion injury in which ROS participate, mice deficient in TLR2 showed increased levels of interferon (IFN) γ and IL-4 accompanied by aggravated tissue damage [66] hinting toward an additional protective, TLR-mediated mechanism in the context of ER UPR.

## ER UPR and autophagy

Autophagy is a highly regulated lysosomal pathway involved in the turnover of long-lived proteins and organelles. It is involved in cellular homeostasis, maintenance of immunologic tolerance and host defense against pathogens [67–69]. Autophagy starts with the envelopment of cytosol

and/or organelles in an isolating membrane, forming an autophagosome. Contrarily to phagosomes that posses a single membrane, autophagosomes feature double membranes [68]. Undergoing progressive maturation by fusion with endolysosomal vesicles, an autolysosome is created in which the cargo is degraded [67, 68]. Next to the autophagic–lysosomal pathway, the ubiquitin-proteasomal system is the second major degradation route in mammalian cells. During ER UPR and the associated degradation of mis- or unfolded proteins, the ER employs both proteasomal (ERAD) as well as autophagic pathways [11, 70]. ER UPR-induced autophagy might represent an alternative mechanism to dispose misfolded proteins in the ER lumen that cannot be removed by ERAD, but is also implied in the degradation of damaged ER and the counterbalance of the ER expansion during ER UPR [71]. Several canonical ER UPR pathways have been implicated in the induction of autophagy [72] including conflicting data about the necessity of different signaling components. The PERK/eIF2$\alpha$ pathway has been linked to the induction of autophagy [72, 73] as well as the IRE1 pathway [70]. Using mouse embryonic fibroblasts (MEF) deficient in IRE1 or ATF6 as well as embryonic stem cells deficient in PERK, Ogata et al. [70] presented evidence that accumulation of microtubule-associated protein 1 light chain (LC) 3-positive autophagic vesicles upon treatment with tunicamycin or thapsigargin, two chemical inducers of ER UPR, was dependent on IRE1, but not on PERK or ATF6. In accordance with these data, also in MEF deficient in TRAF2, the thapsigargin-induced accumulation of LC3-positive vesicles was inhibited, linking IRE1 to autophagy via JNK [39]. Subsequent pharmacological inhibition of JNK in this model system abrogated LC3 translocation suggesting the IRE1-TRAF2-JNK pathway to be essential for ER UPR-induced autophagy in MEF [67, 70]. Independently of innate UPR signaling, autophagy might also be triggered and/or amplified by ROS produced under stress conditions [74].

## ER UPR and apoptosis

The purpose of ER UPR is to adapt the ER to cellular demands and to overcome the stress induced by mis- or unfolded proteins. However, the activation of ER UPR is not always sufficient to cope with ER stress and prolonged or excessive ER stress ultimately lead to cell death. Under ER stress, cell death is induced by apoptosis, but the precise molecular mechanisms that mediate the switch from adaptive pathways to the induction apoptosis are still unclear. The first protease identified to mediate ER UPR-induced apoptosis was caspase-12. Although cells from mice deficient in caspase-12 undergo apoptosis in response to other death-inducing signals, they show partially resistance to ER UPR-induced apoptosis [75, 76]. Consistent with the function of the ER in regulating cellular free calcium levels, caspase-12 is activated by calpains [75, 77], cytoplasmic proteases that are activated by calcium. Subsequent to its activation at the ER, caspase-12 is thought to cleave procaspase-9, finally leading to the activation of caspase-3 via caspase-9 [78]. The ER stress-induced activation of procaspase-9 seems to be independent of the mitochondrial cytochrome c/Apaf-1 pathway since the processing of procaspase-9 can occur in the absence of cytochrome c release [79]. In humans, caspase-4 is implicated in ER UPR-induced cell death whereas the contribution of caspase-12 is arguable as the human gene contains several mutations impairing its function [80, 81].

Activation of PERK and downstream ATF4-mediated CHOP expression plays a distinguished role in ER UPR-induced apoptosis [82–84] since the deletion of CHOP in mouse cells reduces apoptosis upon ER stress [85] whereas CHOP overexpression is sufficient to induce apoptosis in cell lines [86]. Several mechanisms by which CHOP elicits apoptosis are proposed. CHOP has been shown to sensitize cells to ER stress-induced apoptosis through induction of Bim, a pro-apoptotic BH3-only member of the B cell lymphoma (Bcl) 2 family, and concurrent downregulation of the anti-apoptotic factor Bcl2 [86, 87]. Furthermore, CHOP-mediated upregulation of Ero1, a thiol oxidase required for disulfide bond formation during protein folding in the ER but also known to produce ROS as byproduct of its activity, might contribute to the induction of apoptosis. Supporting this hypothesis, reduced levels of Ero1 have been shown to strongly suppress ER UPR-induced apoptosis [63, 88]. In addition, the PERK/ATF4 pathway contributes to mitochondria-dependent apoptotic mechanisms under ER UPR. It induces a truncated form of the sarcoendoplasmic reticulum $Ca^{2+}$-ATPase1 (S1T) that promotes transfer of calcium from the ER to mitochondria, mitochondrial calcium overload finally leading to activation of the mitochondrial apoptotic pathway [89].

IRE1 plays a dual role in ER UPR-induced apoptosis. Splicing of xbp1 is supposed to mediate anti-apoptotic signals whereas the activation of JNK is assumed to be a rather pro-apoptotic event. At late stages of ER UPR when apoptosis is induced, xbp1 splicing seems to be attenuated and forced expression of XBP1s during these stages protects human cells from apoptosis [90]. Interestingly, the pro-apoptotic Bcl2 family members Bak and Bax which are required for the induction of apoptosis under ER stress and regulate the release of pro-apoptotic factors from the mitochondria and calcium from the ER [91–93] also bind to IRE1. This interaction seems to be important for efficient xbp1 splicing during ER stress and is independent

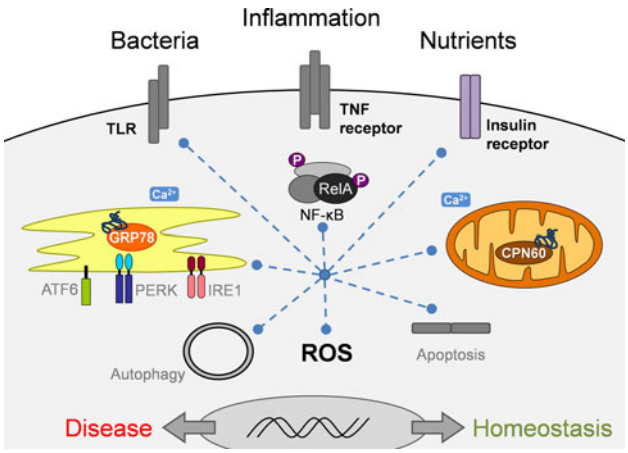


**Fig. 2** Cellular stress responses form a tightly interrelated network. Stress responses including metabolic, inflammatory, mitochondrial, and ER UPR pathways are interrelated and connected to bacterial and nutrient sensing. Polymorphisms in genes associated with these cellular processes have been identified as disease susceptibility factors and underlie several chronic diseases. *ATF* activating transcription factor, *CPN* chaperonin, *GRP* glucose-regulated protein, *IRE* inositol requiring enzyme, *NF-κB* nuclear factor κB, *PERK* PKR-like ER-associated kinase, *ROS* reactive oxygen species, *TLR* Toll-like receptor, *TNF* tumor necrosis factor

from the pro-apoptotic activity of Bak and Bax at the mitochondria [94].

It has been suggested that during mild and strong ER stress all UPR sensors are activated and evoke anti- as well as pro-apoptotic responses. The decision between adaptation vs apoptosis might primarily depend on the intensity of the signal which needs to overcome the low stability of pro-apoptotic mRNAs and proteins in order to prevail the activation of the apoptotic program [12] (Fig. 2).

## ER UPR and metabolism

Protein folding and glycosylation in the ER are energy requiring processes, and thus, the ER is very sensitive to energy fluctuations and depends on glucose availability. During ER UPR, all three branches of ER UPR impact glucose metabolism as well as lipogenesis.

Pathways involved in glucose synthesis and breakdown are both transcriptionally regulated by ER UPR, for example using genome wide approaches, XBP1 has been linked to glycolysis as well as glycogen synthesis [95]. Through interaction with CREB-regulated transcription coactivator (CRTC) 2, also ATF6 has been linked to the regulation of glucose synthesis in the liver [96], though the best characterized branch of the ER UPR in context of glucose metabolism is the PERK pathway. PERK-deficient mice and mice harboring a mutation that prevents phosphorylation of eIF2α at serine 51 display defective gluconeogenesis in the liver [24, 84], linked to pancreatic islet cell dysfunction and death triggered by ER failure [97]. Further addressing the role of eIF2α phosphorylation, Oyadomari et al. [98] showed that mice expressing a fragment of Gadd34 in the liver, resulting in forced eIF2α dephosphorylation, encounter hypoglycemia during fasting due to impaired gluconeogenesis and low liver glycogen levels. However, on high-fat diet, these mice show improved glucose tolerance and diminished hepatosteatosis, probably as a result of reduced lipogenesis.

The family of SREBP transcription factors is resident in the ER and is crucial for the regulation of genes involved in cholesterol metabolism or lipid synthesis [99]. SREBP transcription factors are classically activated in response to insulin or low sterol levels, but they might also integrate lipid metabolism into ER UPR. Indeed, lipid-lowering HMG-CoA reductase inhibitors (statins) have been shown to activate ER UPR [100]. The ER is the site of triglyceride formation in liver cells as well as adipocytes [101], and XBP1s regulates the transcription of genes involved in fatty acid synthesis [95]. Accordingly, XBP1 expression is required for normal fatty acid and cholesterol synthesis in the liver [102] and both XBP1 as well as eIF2α have been shown to participate in basal and/or diet-induced regulation of lipid metabolism [98, 102]. PERK has also been implicated in the regulation of fatty acid synthesis in mammary epithelial cells [103]. Moreover, using loss-of-function mouse models of multiple ER UPR proteins, all three branches of ER UPR have been shown to cooperate in protecting the organism from ER stress-induced deregulation of lipid metabolism [104]. Mice with genetic ablations of either ER stress-sensing pathways (ATF6α, eIF2α, IRE1α) or of ER quality control ($p58^{IPK}$) have been shown to have a dysregulated response to tunicamycin-induced ER stress. This included the suppression of metabolic transcription factors regulating lipid homeostasis but at the same time development of hepatic steatosis, probably due to a loss of liver lipoprotein production. Liver tissue from these mice exhibited signs of unresolved ER stress, partially associated with perpetuated expression of CHOP. Underscoring the role of CHOP in this setup, livers from CHOP-deficient mice sustained metabolic gene expression under tunicamycin challenge [104]. CHOP can act as dominant-negative inhibitor of C/EBP family members including CEBPα, a key mediator of lipid homeostasis. Interestingly, mice with a postnatal, but not with a constitutive embryonic deletion of CEBPα also show a phenotype including fatty liver, hypoglycemia, and changes in gene expression profiles [105–107]. Contrarily to the observations mentioned above, that tunicamycin challenge increased ectopic lipid accumulation in mice with a functional knockout of eIF2α, Oyadomari et al. found reduced hepatic lipid accumulation in mice overexpressing Gadd34

in the liver (silencing eIF2α phosphorylation) exposed to a high-fat diet [98, 104]. These conflicting outcomes might be explained by the level of ER stress induced by the different stimuli. While a more physiological dietary stress might allow for gradual adaptation of eIF2α-signaling depleted cells, a strong death-inducing UPR evoked by tunicamycin might not, significantly impacting the resultant phenotype. In summary, these findings suggest that ER UPR might be seen as an adaptive response to handle high metabolic loads [23] and raise the possibility that severe ER stress, by leading to profound metabolic disruption, is a contributing factor to the development of hepatic steatosis.

## ER UPR and mitochondria

The mechanisms described above already present several possibilities for the intersection of ER UPR and mitochondrial signals. Beyond the connection via ATP and energy supply, mitochondria and ER interact, e.g., through generation of ROS and during apoptosis. The interplay of the different organelles and signaling pathways might not be one-sided as for example the generation of ROS can be both a cause as well as a consequence of ER UPR, mitochondrial dysfunction, and inflammatory responses. On a more sophisticated level, mitochondria and ER directly interact under cellular stress conditions. Recent data present evidence that dysfunctional mitochondria contain endogenous high-affinity human Toll-like receptor 4 (TLR4) ligands and induce TLR4-mediated inflammatory reactions [108], suggesting a model in which mitochondria could impact TLR signaling and associated ER UPR. Furthermore, it has been reported that nuclear genes encoding mitochondrial proteins such as the mitochondrial matrix proteases Lon, mtHsp70, and Yme1 are induced by ER stress [109]. Likewise, the ER-mitochondria interconnection plays a prominent role in the caspase-mediated induction of neuronal cell death [29], and mitochondria modulate the ER UPR under glucose deprivation conditions [28]. Conversely, it has been suggested that mitochondria support ER function via adenylate kinase (AK) 2 [21] and mitochondrial dysfunction triggers the ER stress response and aggravates hepatic insulin resistance [26].

Recently, a mitochondrial-specific unfolded protein response (mtUPR) similar to that of the ER has been described [110–112]. The mitochondrial matrix contains its own set of molecular chaperones involved in the folding of newly synthesized or imported proteins [111, 113]. Upon accumulation of unfolded protein within the mitochondrial matrix, the transcription of nuclear genes encoding mitochondrial stress proteins is upregulated. In *C. elegans*, it has been shown that this retrograde stress signal is dependent on the efflux of peptides generated by the mitochondrial protease ClpP into the cytosol [114, 115]. Most of these mtUPR responsive genes are activated through CHOP and include mitochondrial proteases and chaperones such as chaperonin (CPN) 60 which promotes the refolding and proper assembly of unfolded polypeptides generated under stress conditions in the mitochondria [111, 116]. The ER and mtUPR seem to be two distinct signaling pathways as genes encoding stress proteins of the ER or cytosol are not upregulated during mtUPR [111] even though both pathways share the transcription factor CHOP [112]. It is likely that mitochondrial stress, as well as ER stress, participates in the pathology of chronic diseases, but the contribution of mtUPR and its possible interrelation with ER stress are virtually unknown.

Interestingly, we showed that the cytosolic kinase PKR is specifically induced under mtUPR and integrates mtUPR into ER UPR signaling (Rath and Haller, unpublished data). PKR was previously described to be activated by various triggers including ER UPR, TLRs, growth receptor signaling, cytokines, and palmitic acid [54, 117, 118]. In turn, PKR is able to phosphorylate eIF2α, modulate tumor necrosis factor (TNF)-induced signaling [119], IkB kinase (IKK) [54, 119] activity and can induce insulin receptor substrate (IRS) phosphorylation at serine 307 thereby blocking insulin action [118]. These broad functions of PKR are reflected by the observation that $Pkr^{-/-}$ mice, in response to high-fat diet, exhibited significantly reduced levels of several inflammatory cytokines [118] and showed almost complete resistance to DSS-induced colitis (Rath and Haller, unpublished data). Significantly, Nakamura et al. [118] suggest that PKR-coordinated sensing and signaling may represent a central mechanism for the integration of innate immunity with metabolic pathways that are critical in metabolic diseases. In combination with our finding that mtUPR employs PKR to integrate into ER UPR signaling, this implicates that PKR integrates metabolic, inflammatory, mitochondrial, and ER pathways.

## ER stress and chronic diseases

Considering the before mentioned properties of ER UPR, it is obvious that ER UPR is associated with a variety of chronic diseases (Fig. 3).

## ER stress and metabolically driven pathologies

Accumulation of misfolded proteins is observed in several metabolic diseases such as neurodegenerative disorders, diabetes, and atherosclerosis. In some cases of Parkinson's, Alzheimer's, and Huntington's disease, which are characterized by misfolded proteins and protein aggregates in the

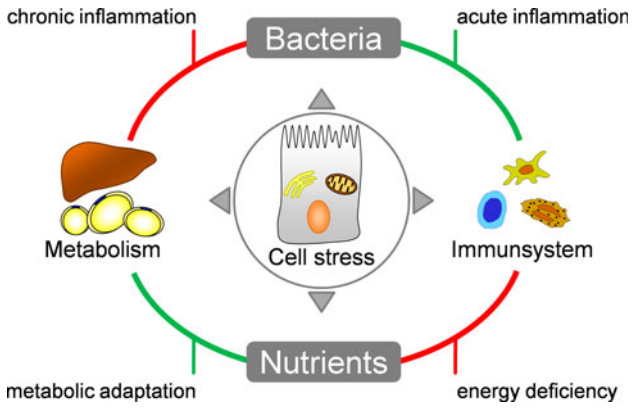


**Fig. 3** The central role of cellular stress responses. The development of chronic diseases is a complex process involving host genetic background and environmental factors. Cellular stress responses integrate bacterial and nutrient sensing with metabolism as well as immune responses and play a central role in chronic diseases

cytoplasm, also an accumulation of misfolded proteins in the ER and activation of ER UPR was observed [38, 120]. Likewise, for some mutations leading to type III autosomal dominant retinitis pigmentosa (ADRP) and retinal degradation, accumulation of misfolded Rhodopsin in the ER and associated activation of ER UPR and apoptosis have been described [121].

Activation of ER UPR is also prevalent in cancer and might protect the tumor cells from toxic effects of misfolded proteins caused by mutations and/or decreased supply of nutrients and oxygen [7, 122]. Hypoxia has profound effects on tumor growth and can activate the PERK/ATF4 pathway [123, 124] and XBP1, which is essential for tumor growth and survival under hypoxic conditions [125]. In addition, IRE1-mediated splicing of xbp1 has been observed in human tumors [122] and interestingly, expression of XBP1s is sufficient to induce a multiple myeloma-like pathology in mice [126].

In the case of atherosclerosis, ER stress is predominantly linked to toxic lipids like saturated fatty acids and oxidized lipoproteins, especially in macrophages. When exposed to lipotoxic signals, macrophages show endoplasmic reticulum (ER) stress that can lead to lipotoxic death. In this setting, lipid chaperones such as fatty acid-binding protein-4 (aP2) are the predominant regulators of lipid-induced macrophage ER stress and therefore have critical implications for atherosclerosis and obesity [127].

As described above, ER UPR impacts glucose as well as lipid metabolism. Consequently, there is strong evidence that ER UPR plays a critical role in pancreatic $\beta$-cell survival and is relevant in the pathology of diabetes, obesity, and insulin resistance. Pancreatic $\beta$-cells need to dramatically increase their insulin production to fit the demand under chronic insulin resistance and hence pancreatic islets from mice and humans with type 2 diabetes show signs of ER UPR [128]. Additionally, several factors associated with obesity and type 2 diabetes such as inflammatory cytokines and free fatty acids can induce ER UPR [129, 130]. On the other hand, IRE1 and PERK branches of ER UPR can trigger the activation of the NF-$\kappa$B pathway that results in the induction of inflammatory mediators and has been implicated in insulin resistance [18, 20, 131]. Furthermore, IRE1-mediated activation of JNK has been linked to the development of insulin resistance and diabetes by inhibition of insulin receptor signaling [9]. Various mouse models targeting signaling components as well as protein chaperones of the ER UPR have been used to elucidate the relationship between ER UPR and diabetes. For instance, PERK-deficient mice develop severe hyperglycemia due to defects in pancreatic islet proliferation and increased $\beta$-cells apoptosis [132] and similarly preventing eIF2$\alpha$ phosphorylation in pancreatic $\beta$-cells leads to the development of diabetes mice [97]. Importantly, a loss of function mutation in PERK causes severe defects in pancreatic $\beta$-cells and a form of type 1 diabetes, the Wallcot-Rallison syndrome, in humans [133]. Along this line, also XBP1 haploinsufficiency in mice results in ER stress, hyperinsulinemia, hyperglycemia, and impaired glucose tolerance [9]. Notably, recent data have revealed new aspects of XBP1 action in the context of glucose metabolism. It was shown that the regulatory subunits of phosphotidyl inositol 3-kinase (PI3 K), p85$\alpha$ and p85$\beta$, can interact with XBP1s increasing its nuclear translocation and accelerating ER stress resolution [134, 135]. Heterodimers formed by p85$\alpha$ and p85$\beta$ were found to be disrupted by insulin treatment, allowing the monomers of p85 to interact with XBP1s. Importantly, this interaction was lost in insulin-resistant ob/ob mice, resulting in the inability to adequately resolve ER stress in the liver during refeeding [134]. Furthermore, Zhou et al. [136] demonstrated XBP1s to interact with the transcription factor Forkhead box (Fox) O1, promoting its degradation by the 26S proteasome system. FoxO1 acts as a master regulator of whole-body energy homeostasis and enhances transcription of genes involved in gluconeogenesis. Upon activation of insulin receptor signaling, FoxO1 is phosphorylated and excluded from the nucleus. This mechanism is thought to prevent hypoglycemia during fasting states, but failure of FoxO1 regulation contributes to the development of hyperglycemia under insulin-resistant conditions. Since a DNA-binding–defective mutant of XBP1s, which does not have the ability to increase ER folding capacity, was still capable of reducing serum glucose concentrations and increasing glucose tolerance in the severely insulin-resistant *ob/ob* mouse strain, this action of XBP1s is thought to be independent of its role in ER UPR [136]. Both, increased nuclear translocation of XBP1s mediated by p85 as well as attenuation of FoxO1

transcriptional activity by XBP1s have also been suggested to reduce inflammatory responses [135, 136], implicating additional links between inflammation and metabolism. Also, overexpression of ATF6 in the liver of obese mice was shown to be beneficial on hepatic gluconeogenesis, in this case due to ATF6 interaction with CRTC2 [96].

Moreover, interfering with the targets of ER UPR signaling, represented by chaperones involved in protein folding, also impacts glucose metabolism. Deficiency in the ER chaperones p58 (IPK) or oxygen-regulated protein (ORP) 150 leads to $\beta$-cell failure [137] and results in impaired glucose tolerance and decreased insulin receptor signaling through phosphorylation of IRS1, respectively [138], whereas overexpression of GRP78 in the liver of obese mice increased insulin sensitivity [139]. The pathology of diabetes has also been linked to autophagy since mice deficient in p62, a protein important for autophagy, develop mature-onset obesity, leptin resistance, and other metabolic abnormalities [140], and a loss of autophagy leads to pancreatic islet degeneration and reduced insulin secretion [141, 142]. Also, mitochondrial dysfunction has been implied in type 2 diabetes and recent data links mtUPR and impaired mitochondrial function to DAF-28/insulin secretion in *C. elegans* [143].

## ER stress and immune-mediated pathologies

IBD and its two main idiopathic pathologies ulcerative colitis (UC) and Crohn's disease (CD) are chronic, immunologically mediated disorders of the gastrointestinal tract and represent another aspect of chronic pathologies. UC as well as CD are multifactorial diseases and are characterized by alterations of the innate and adaptive immune system, luminal and mucosa-associated microbiota as well as epithelial function [3]. Intestinal epithelial cells (IEC) are crucial for maintaining intestinal homeostasis, constituting an interface between the two major factors influencing intestinal inflammation, the gut microbiota and the immune system [144]. Conversely, failure to control inflammatory processes at the IEC level may critically contribute to IBD pathogenesis. Recently, ER UPR at the epithelial cell level was implicated in promotion and perpetuation of intestinal inflammation [15, 16, 145]. Consistently, recent work using mice deficient in ER UPR mediators (IRE1$\beta$, XPB1, S1P) or mice with a mutation in the *Muc2* gene links ER stress in the highly secretory subtypes of IEC, anti-microbial peptides-producing Paneth cells, and mucin-producing goblet cells, with anti-microbial defense and intestinal inflammation [14–16]. Moreover, we provided first evidence that ER UPR in IEC is relevant to patients with IBD [145], and Kaser et al. [16] reported single-nucleotide polymorphisms within the *XBP1* locus in human IBD patients. The commensal microbiota is one of the key drivers of intestinal inflammation in IBD and pathways crucial for sensing and controlling the composition of bacteria, like TLR signaling and autophagy interact with ER UPR. Genome wide association studies (GWAS) have identified multiple polymorphisms as disease susceptibility factors in CD such as the autophagy-related *ATG16L1* [146, 147] and *IRGM* [148, 149], and bacterial sensing-related *NOD2* [150, 151], *TLR4* [152] genes. Interestingly, several of these polymorphisms affect Paneth cells. NOD2- as well as XBP1-deficient and ATG16L1-hypomorphic mice all display alterations in Paneth cell structure and function, consistently with CD patients harboring the *NOD2* or *ATG16L1* alleles [153–155]. Perpetuation of bacterial sensing and reduced ability to eliminate bacteria (via autophagy and anti-microbial peptides) might therefore be directly linked to ER UPR. Of note, also luminal iron was shown to impact the composition of the intestinal microbiota as well as epithelial ER UPR [156], and concomitant CREBH and CHOP have been implicated in iron metabolism through regulation of the peptide hormone hepcidin [157]. The central role of ER stress in intestinal inflammation is further emphasized by the suggestion that ER stress and particularly XBP1 not only limit the anti-microbial activity of the epithelium but also determine the sensitivity of the epithelium toward cytokines and bacterial signals [16, 144].

It has been repeatedly suggested that chronic intestinal inflammation represents an energy-deficiency disease involving the mitochondria and featuring alterations in epithelial cell oxidative metabolism [27, 158]. This hypothesis is supported by the fact that several pathogens and their toxins specifically target mitochondria to disrupt their function [159] and proinflammatory cytokine-evoked ROS generation is associated with a drop in mitochondrial membrane potential [160]. Contrarily, treating epithelial cells with the oxidative phosphorylation uncoupler dinitrophenol (DNP) to induce mitochondrial stress caused a decrease in transepithelial electrical resistance (TER) and increased translocation of *E. coli* [161]. Confirming the relevance of this data, enterocytes of IBD patients have been reported to display swollen mitochondria with irregular cristae indicative of impaired function [162, 163]. In accordance, reduced ATP levels have been found in the colon of some CD patients [164] and biopsies from patients with IBD can be more susceptible to uncouplers of oxidative phosphorylation [163]. Finally, in line with the hypothesis that ER and mtUPR are interrelated pathways, we found increased expression of the ER UPR surrogate marker GRP78 associated with augmented expression of the mitochondrial chaperone CPN60, an indicator of mtUPR, in two murine models of chronic, immune-mediated colitis as well as human patients with IBD (Rath and

Haller, unpublished data). The presence of ER and mtUPR was accompanied by induction PKR in humans and mice IEC, once more suggesting the integration of metabolic, inflammatory, mitochondrial, and ER pathways.

## Conclusion and perspective

Cellular stress responses including metabolic, inflammatory, mitochondrial, and ER UPR pathways are common features of many diseases. These signaling pathways have been extensively investigated regarding their contributions to numerous pathologies, leading to improved characterization of specific cellular responses. Yet, accumulating evidence suggests that these pathways cannot be regarded separately but are tightly interrelated. In multifactorial disorders especially like IBD, where several triggers may be need for the onset of pathology, it is indispensable to take various cellular processes such as protein folding, secretion, organelle biosynthesis, bacterial sensing, autophagy, apoptosis, and their interaction into account for a better understanding of disease pathogenesis (Fig. 3).

However, therapeutic approaches to improve ER function, targeting a stress pathways on which multiple signals converge, might have beneficial outcomes on various (cellular and organ) levels. Notably, several chemicals already used to treat type 2 diabetes like PPAR agonists or salicylates have been shown to affect ER UPR-associated pathways [165, 166]. Moreover, studies with chemical chaperones, phenyl butyric acid (PBA), and tauro-ursodeoxycholic acid (TUDCA), confirmed that the ER can be chemically targeted to enhance its functional capacity and that multiple diseases could be tackled by such strategies. In murine models of obesity and diabetes, administration of these chaperones increased systemic insulin sensitivity, established normoglycemia, reduced fatty liver disease, and suppressed inflammatory signaling [167]. PBA and TUDCA were furthermore shown to prevent ER stress-induced inhibition of apoB100 secretion, a feature contributing to hepatic steatosis [168] and to ameliorate atherosclerosis in mouse models [127]. Alongside, specific molecules of the ER UPR could be directly targeted. For example, Salubrinal, a small molecule that prevents dephosphorylation of eIF2a [169] has been shown to confer protection against ER stress-induced cell death both in vitro and in vivo [170]. Likewise, specifically increasing the activity of XBP1s (e.g., by p85) could improve the outcome of metabolically driven as well as inflammatory diseases. The use of mitochondria-specific antioxidants such as acetyl-L-carnitine and R-alphalipoic acid could complement such strategies by additionally diminishing causes/consequences of ER stress [171]. Whether the data obtained from animal models can be translated into treatments for human diseases is currently unknown, but they provide promising evidence for new therapeutic approaches.

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