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The unfolded protein response in immunity and inflammation

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Abstract

The unfolded protein response (UPR) is a highly conserved pathway that allows the cell to manage endoplasmic reticulum (ER) stress that is imposed by the secretory demands associated with environmental forces. In this role, the UPR has increasingly been shown to have crucial functions in immunity and inflammation. In this Review, we discuss the importance of the UPR in the development, differentiation, function and survival of immune cells in meeting the needs of an immune response. In addition, we review current insights into how the UPR is involved in complex chronic inflammatory diseases and, through its role in immune regulation, antitumour responses.

The endoplasmic reticulum (ER) is an extensive tubular-reticular network that is separated from the surrounding cytosol by a single lipid bilayer — the ER membrane. It is a crucial site involved in maintaining Ca^{2+} homeostasis and its major function is the synthesis and folding of secreted and transmembrane proteins, which constitute approximately one-third of all the proteins that are made in the cell[1,2]. Following translation on ER membrane-associated ribosomes, proteins enter the ER lumen where chaperone-based folding occurs, together with complex protein modifications. These include *N*-linked glycosylation, disulfide bond formation and proline *cis–trans* isomerization, which are mediated by glycosyltransferases, oxidoreductases and peptidyl-prolyl *cis–trans* isomerases, respectively[3–6].

Adequate folding and post-translational modifications of proteins are crucial for proper function; furthermore, in a dominant manner, misfolded and aggregated proteins can cause cellular stress and cell death, as exemplified by neurodegeneration and other protein-misfolding diseases[7,8]. Therefore, it is of crucial importance that protein folding is subject to stringent quality control systems to allow a cell to carry out its necessary secretory functions. For example, `ER-associated degradation` (ERAD) ensures that misfolded

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and unfolded proteins are removed from the ER lumen to the cytosol for subsequent degradation by the ubiquitin-proteasome system[9].

Numerous environmental conditions, both endogenous and exogenous, can disrupt the ER protein-folding environment, and when protein-folding requirements exceed the processing capacity of the ER, misfolded and unfolded proteins accumulate in the ER lumen, which triggers the `unfolded protein response` (UPR). The UPR is a sophisticated collection of intracellular signalling pathways that have evolved to respond to protein misfolding in the ER. In addition, it has become increasingly clear that UPR signalling has an important role in immunity and inflammation. In this Review, we discuss the role of UPR activation in the development of immune cells and discuss how the UPR is involved in mounting efficient immune responses. In addition, we highlight causes of UPR activation that are directly linked to inflammation and review current insights into the downstream pathways by which UPR activation induces inflammation. Last, we discuss how the UPR is involved in various prevalent diseases, including inflammatory bowel disease, metabolic disease and cancer. Owing to the breadth of this Review, we do not provide substantial detail for individual sections but have given an overview of the most relevant and recent findings.

The UPR pathways

In metazoans, the UPR is activated by the coordinated action of three ER transmembrane stress sensors: inositol-requiring enzyme 1α (IRE1α; also known as ERN1), PKR-like ER kinase (PERK; also known as EIF2AK3) and activating transcription factor 6α (ATF6α). Under homeostatic conditions, the luminal domains of these ER stress sensors are retained in an inactive state through association with binding immunoglobulin protein (BiP; also known as GRP78 and HSPA5). However, owing to the higher affinity of BiP for misfolded proteins, BiP dissociates from the ER stress sensors as misfolded proteins accumulate in the ER lumen, thereby releasing the stress sensors to permit downstream signalling[10] (FIG. 1). In addition, it has been elegantly shown that, at least in *Saccharomyces cerevisiae*, basic and hydro phobic residues on unfolded proteins can directly bind to a putative peptide groove of IRE1α, and direct binding of unfolded proteins is sufficient to induce the UPR[11]. It is currently unclear whether direct binding of unfolded proteins as a second mechanism of UPR activation is limited to IRE1α or whether it can also be observed with PERK and ATF6α. These mechanisms require further characterization.

The downstream transcriptional programmes of the UPR are primarily directed towards restoring proteostasis, which is achieved through at least four different strategies. First, mRNA translation is transiently attenuated through PERK-dependent phosphorylation of the α-subunit of eukaryotic translation initiation factor 2 (eIF2α), which inhibits the assembly of the eIF2-GTP–Met-tRNA ternary complex (eIF2–TC), and thereby reduces the quantity of proteins that enter the ER. Second, the entry of newly translated proteins into the ER is decreased by the degradation of ER membrane-associated mRNAs by regulated IRE1α-dependent decay (RIDD)[12–14]. Third, processes that eliminate unfolded proteins from the ER are induced by increasing the transcription of ERAD-related and autophagy-related proteins (BOX 1). Finally, genes are induced that increase the protein-folding capacity of the

ER and mediate its expansion through increasing the biogenesis of ER and lipid components[1,15].

However, when these attempts to restore proteostasis fail and ER stress is unabated, UPR signalling typically switches to a pro-apoptotic mode, a process that is known as the terminal UPR (reviewed in REF. 16). The terminal UPR may have evolved to eliminate, for example, excessively damaged or pathogen-infected cells.

IRE1α

The cytoplasmic tail of the type I transmembrane protein IRE1α possesses two enzymatic activities: a serine/threonine kinase domain and an endoribonuclease (RNase) domain[17]. On release from BiP, dimerization of IRE1α elicits RNase activity to initiate the non-conventional splicing of a single mRNA that encodes X-box binding protein 1 (XBP1). This produces a translational frameshift and creates a potent transcriptional activator known as XBP1s ('s' represents 'spliced')[18,19]. XBP1s translocates to the nucleus where it induces the transcription of a wide variety of ER-resident molecular chaperones and protein-folding enzymes that together increase ER size and function[15,20] (FIG. 1a). In addition to the specific endoribonuclease activity that splices *XBP1*, IRE1α-dependent activation of RIDD degrades ER-membrane-associated mRNAs to reduce the amount of protein that enters the secretory pathway[21] (FIG. 1a). In addition, emerging evidence has indicated that RIDD substrates encode proteins of a diverse nature, which modulate cellular processes that are distinct from the control of ER homeostasis, including the generation of inflammatory double-stranded RNA species through the activation of intracellular nucleic acid sensors[22,23].

During prolonged ER stress, the beneficial effects of IRE1α activation through the activity of XBP1s may be temporally and quantitatively impeded, and the PERK pathway can become dominant[24,25]. In addition, chronic ER stress increases the oligomerization state of IRE1α to hyperactivate its cytosolic RNase domains, which leads to the cleavage of many other RNAs in addition to *XBP1*, including precursors of apoptosis-inhibitory micro-RNAs, which thus promotes apoptosis[26–28]. Therefore, prolonged ER stress may tip the properties of IRE1α from being adaptive to promoting inflammation and cell death.

PERK

Similarly to IRE1α, dissociation of BiP from the ER luminal domain of PERK permits PERK homo-dimerization and autophosphorylation to activate the cytoplasmic kinase domain. In addition, it was shown that the lipid composition of the ER membrane can activate PERK, which highlights the importance of lipid metabolism as a direct trigger of UPR activation[29,30]. Activated PERK phosphorylates eIF2α, which inhibits eIF2-TC formation and thereby transiently attenuates global mRNA translation, enabling the cell to manage temporary ER stress (FIG. 1b). Notably, eIF2α can be phosphorylated in mammals independently of ER stress by three additional kinases: general control nonderepressible 2 (GCN2; also known as EIF2AK4), which is induced by amino acid deprivation; the haem-regulated inhibitor kinase (HRI; also known as EIF2AK1), which is induced by oxidative stress and haem deprivation; and protein kinase R (PKR; also known as EIF2AK2), which is

activated by double-stranded RNA as part of the interferon antiviral response[31]. Together, these additional mechanisms of eIF2α phosphorylation form the integrated stress response (ISR) system, which allows the cell to integrate multiple stress stimuli into one common node, that being the general control of protein synthesis through the phosphorylation of eIF2α[31]. For example, both epithelial cells and dendritic cells (DCs) activate GCN2 to phosphorylate eIF2α in response to amino acid deprivation, to induce autophagy, to reduce oxidative stress and to inhibit inflammasome activation[32].

Although the translation of most mRNAs is inhibited in ER-stressed cells, the translation of some species of mRNA is favoured under ER stress conditions when eIF2α is phosphorylated and eIF2-TC availability is low (mechanisms reviewed in REF 33)[34]. One important example is the mRNA that encodes activating transcription factor 4 (ATF4; also known as CREB2), which is a crucial UPR mediator that transactivates genes that are involved in amino acid metabolism and oxidative stress resistance, as well as autophagy[12] (FIG. 1b). As a sustained translational block is not compatible with cell survival, ATF4 also induces *PPP1R15A* expression, which encodes GADD34, a regulatory subunit of protein phosphatase 1 (PP1) that directs the dephosphorylation of eIF2α to restore mRNA translation[185] (FIG. 1b). However, ATF4 also activates the transcription of C/EBP homologous protein (CHOP; also known as DDIT3)[12,35], which is involved in ER-stress-mediated apoptosis both *in vitro* and *in vivo*[36,37]. To allow the cell a chance to manage the ER stress, several mechanisms suppress CHOP at early time points after ER stress, such as PERK-dependent microRNA (miRNA) miR-211 expression, which represses *CHOP* transcription through histone methylation[38]. In addition, CHOP is suppressed by Toll-like receptor (TLR) signalling during immune responses in macrophages by protein phosphatase 2A (PP2A)-mediated serine dephosphorylation of the eIF2Bε sub-unit[39]. Indeed, only strong and chronic activation of PERK increases steady-state levels of CHOP, owing to the short half-lives of both ATF4 and CHOP mRNAs and proteins, so that only excessive ER stress will promote the terminal UPR[25]. Studies of ATF4 and CHOP in cells experiencing chronic ER stress indicate that these proteins function together as a heterodimer to induce apoptosis by increasing protein synthesis, thereby enhancing protein misfolding, oxidative stress and cell death[40].

ATF6

ATF6 is a type II transmembrane protein that contains a bZIP transcription factor within its cytosolic domain. Although there are two *ATF6* genes in the mammalian genome (*ATF6A* and *ATF6B*), only ATF6α is required to activate UPR gene expression[41]. On release from BiP, ATF6α transfers to the Golgi compartment where it is processed by the Golgi enzymes site 1 protease (S1P) and S2P to produce a cytosolic p50 fragment that migrates to the nucleus. The p50 fragment activates the expression of genes encoding proteins that function to increase ER capacity and folding (including, BiP, GRP94, p58IPK (also known as DNAJC3) and XBP1), as well as the ERAD pathway[19,41–43] (FIG. 1c).

The physiological UPR in immune cells

Cells that have a large secretory demand as part of their function are particularly dependent on a well-developed and large ER and, consequently, UPR signalling. Therefore, it is not surprising that highly secretory immune cells are exquisitely susceptible to environmental conditions that impose ER stress, either by directly targeting ER-folding capacity (for example, microbial toxins)[44] or by markedly increasing folding demand (for example, exposure to pathogens). Thus, inflammation per se is an important factor in the induction of ER stress, and UPR activation may be a sensitive hallmark of inflammation. In addition to the pathophysiological conditions that affect specific cell types, it is now well established that activation of the UPR has a role in a wide range of physiological events that are associated with immunologically important cell types[45]. Furthermore, although they have not been well studied, germline polymorphisms and, potentially, somatically generated mutations may affect the ability of the host to determine whether an appropriate UPR level has been achieved based on the demand. Understanding how the UPR affects specific functions at the cellular level and the host-related factors that affect this are thus of great importance, as considered below.

B cells and plasma cells

Over the past 15 years, the role of the transcription factor XBP1 in plasma cell differentiation has become increasingly clear and has served as a paradigm for numerous secretory systems and their relationships with immune function and inflammation. Plasma cell differentiation is regulated by the transcription factors interferon-regulatory factor 4 (IRF4) and B lymphocyte-induced maturation protein 1 (BLIMP1; also known as PRDM1)[46,47]. In addition, the induction of *Xbp1*, which is downstream of BLIMP1, is required for the marked expansion of the ER and the increased protein synthesis that are necessary for high levels of antibody production and secretion during both physiological and pathological immune responses[48,49] (FIG. 2a). Indeed, XBP1 deficiency in B cells leads to an absence of plasma cells and markedly reduces circulating antibody levels but has no effect on B cell maturation or isotype switching[50]. Although it was initially assumed that XBP1 induction was caused by increased immunoglobulin synthesis and the accumulation of unfolded immunoglobulin heavy chains[51], subsequent studies have shown that ER expansion is evident in B cells before the onset of immunoglobulin synthesis[52] and that *Xbp1* is similarly spliced when IgM secretion is genetically abrogated[53]. This suggests that XBP1 induction is a differentiation-dependent event in plasma cells, rather than a response to increased immunoglobulin secretion. The factors that drive UPR activation early in plasma cell development are incompletely understood. Notably, part of the decrease in immunoglobulin production in XBP1-deficient B cells was later explained by IRE1α hyperactivation leading to increased RIDD and the subsequent degradation of immunoglobulin-μ heavy-chain mRNAs[54].

In addition to plasma cells, IRE1α activation is also observed in pro–B cells[55]. UPR activation in these early stages of B cell development might result from the increased secretory demand caused by the neo-expression of cell surface proteins that are associated with V(D)J antigen receptor rearrangements[56]. Indeed, a recent study has shown that IRE1α

and XBP1s are important during the pre-B cell stage when immunoglobulin heavy chains are expressed for the first time and, importantly, that XBP1s in pre-B acute lymphoblastic leukaemia (ALL) cells provides a survival benefit for tumour cells[57].

T cells

Studies using XBP1s–GFP reporter mice have shown that IRE1α is activated in $CD4^+CD8^+$ thymic T cells and in $CD8^+$ splenic T cells, although the precise role of the UPR in early T cell development is not clear[55]. However, the activation of the IRE1α–XBP1 axis in effector $CD8^+$ T cells was reported in response to acute infection with *Listeria monocytogenes*, which was associated with the expression of high levels of killer cell lectin-like receptor G1 (KLRG1). This suggests that XBP1 is important for the terminal differentiation of effector $CD8^+$ T cells[58].

DCs

Xbp1 is constitutively spliced in DCs, and loss of XBP1 leads to significantly reduced numbers of both conventional and plasmacytoid DCs[59] (FIG. 2b). In addition, XBP1-deficient DCs have increased rates of apoptosis and are resistant to survival signals that are associated with TLR engagement (FIG. 2b). Interestingly, the ectopic expression of XBP1s in XBP1-deficient $FLT3^+$ haematopoietic progenitor cells can rescue this apoptotic phenotype[59]. Taken together, these results show that XBP1 is important for DC development and survival.

Consistent with the findings discussed above, constitutive activation of IRE1α is observed in DCs[60] when using ER stress-activated indicator (ERAI) reporter mice[61]. Interestingly, although the highest levels of IRE1α activity are observed in $CD8\alpha^+$ DCs, the deletion of XBP1 in DCs using *Cd11c*–directed Cre recombinase does not result in developmental and phenotypic abnormalities of $CD8\alpha^+$ DCs. These different findings, compared with those from the study by Iwakoshi *et al.*[59], may be explained by low levels of expression of CD11c, and hence Cre recombinase activity, in DC progenitor cells. Interestingly, however, XBP1-deficient $CD8\alpha^+$ DCs that are generated by *Cd11c*–Cre-mediated deletion of *Xbp1* have RIDD-dependent defects in cross-presentation to OT-I T cells, owing to the degradation of components of the cross-presentation machinery, such as tapasin (also known as TAPBP)[60]. This study shows that the IRE1α–XBP1 arm of the UPR is crucially involved in DC function (FIG. 2b).

Consistent with a role for ER stress in the regulation of antigen presentation, several other studies have shown that ER stress affects the surface expression of MHC class I molecules by mechanisms that are not yet fully elucidated[62,63]. In ovarian cancer, impaired MHC class I-restricted antigen presentation to $CD8^+$ T cells has been linked to reactive oxygen species (ROS)-induced ER stress and increased lipid metabolism in DCs induced by an unknown transmissible stress factor in the tumour microenvironment. Although the concept of lipid accumulation-dependent dysfunction of antigen presentation by DCs had been previously described[64], this study links ER stress-induced *Xbp1* splicing to lipid accumulation in DCs, resulting in DC antigen presentation defects[65] (FIG. 2b). In accordance with this, the deletion of XBP1 in DCs abolished the accumulation of lipids in DCs and increased T cell-

mediated antitumour immunity, resulting in decreased tumour burden and improved survival[65].

Granulocytes

Granulocytes are represented by neutrophils, basophils and eosinophils. Eosinophils are typically associated with type 2 immune responses, allergy and parasitic infections[66]. Recently, it has also been shown that eosinophils might have a role in maintaining immune homeostasis in the intestine by promoting IgA class-switching in Peyer's patches and by controlling the pool of $CD103^+$ T cells and DCs[67]. Interestingly, among all types of granulocytes, eosinophils are uniquely dependent on XBP1 in that haematopoietic deletion of *Xbp1* (*Xbp1*^{Vav1} mice) leads to the loss of fully mature eosinophils. In addition, the loss of XBP1 specifically in eosinophils using *Epx*-Cre-mediated *Xbp1* deletion results in a significantly smaller pool of eosinophils in the bone marrow, which indicates that XBP1 is also needed to sustain the viability of eosinophil-committed progenitor cells[68].

Macrophages

In macrophages, TLR signalling induces ER stress, and ER stress in turn amplifies the response to TLR ligation. For example, the TLR2 and TLR4 ligands Pam_3CSK_4 and lipopolysaccharide (LPS), respectively, induce IRE1α activation in mouse J774 macrophages. Furthermore, treatment with TLR agonists increases *Xbp1* splicing in these macrophages, which is dependent on TNF receptor-associated factor 6 (TRAF6) recruitment to IREα and which requires the NAPDH oxidase NOX2 (REF. 69). Importantly, IRE1α-induced *Xbp1* splicing in response to TLR ligation has been shown to be crucial for cytokine production, as macrophage-specific deficiency of XBP1 impairs the production of interleukin-6 (IL-6), tumour necrosis factor (TNF) and interferon-β (IFNβ)[69] (FIG. 3a).

TLR signalling also amplifies IRE1α signalling by modulating the phosphorylation status of this protein. In the absence of TLR signalling, phosphorylated IRE1α is dephosphorylated and thus inactivated by PP2A. Upon TLR ligation, however, TRAF6 interaction with IRE1α catalyses the ubiquitylation of IRE1α, which prevents its interaction with PP2A — through its adaptor, receptor for activated C kinase 1 (RACK1) — thus avoiding IRE1α dephosphorylation and inactivation[70,71] (FIG. 3b). By contrast, the induction of ER stress in bone marrow-derived macrophages strongly potentiates LPS-induced pro-inflammatory signalling, including the induction of genes encoding CXC-chemokine ligand 1 (CXCL1), CXCL2, TNF, IL-1α and IL-6, in a pathway that depends on receptor-interacting serine/threonine-protein kinase 1 (RIPK1)[72].

The IRE1α–XBP1 pathway has also been linked to increased IL-1β production through the IRE1α-dependent activation of glycogen synthase kinase 3β (GSK3β). In addition, GSK3β inhibits further *Xbp1* slicing and thereby *Tnf* transcription, which modulates the inflammatory response to ER stress and, potentially, TLR signalling[73] (FIG. 3c).

The PERK pathway has been shown to induce inflammation through the direct binding of ATF4 to the *Il6* promoter[74]. In macrophages, however, TLR signalling inhibits translation of *Atf4* mRNA and thereby its downstream target CHOP[75]. Similarly, CHOP is further suppressed by TLR–TRIF signalling in macrophages through PP2A–mediated serine

dephosphorylation of the eIF2Bε subunit[39]. These mechanisms of CHOP suppression are required for macrophage survival during an immune response. This demonstrates that specific control of the different arms of the UPR is crucial for innate immune function[69] (FIG. 3a).

Paneth cells

The conditional deletion of *Xbp1* in intestinal epithelial cells (IECs) has shown that `Paneth cells` (which are an important source of anti-microbial peptides and stem cell survival signals)[76] and, to a lesser extent, goblet cells (which are dedicated to mucus production) are highly dependent on this UPR transcription factor[77]. Paneth cells in mice with specific deletion of XBP1 in IECs are severely hypomorphic. The resultant decreased antimicrobial function has been shown to be associated with attenuated killing of *L. monocytogenes* in the intestine and increased bacterial translocation to the liver. In addition, IRE1α hyperactivation that leads to the phosphorylation of JUN N-terminal kinase (JNK) is also observed in XBP1-deficient intestinal epithelium, resulting in spontaneous superficial small intestinal enteritis[77] (FIG. 4). Moreover, deletion of *Xbp1* specifically in Paneth cells is sufficient to induce small intestinal enteritis[78]. As the spontaneous inflammation that is observed in the setting of IEC-specific deletion of *Xbp1* is reversed under germ-free conditions, these studies indicate that the UPR in IECs and, particularly, the UPR in Paneth cells is crucial to the maintenance of intestinal homeostasis in the presence of microbial commensalism. Whether XBP1 has a crucial role in the development of Paneth cells, as it does in highly secretory haematopoietic cells, is not fully clear.

Pathological causes of UPR activation

It is clear that the UPR has a crucial function under physiological conditions, particularly during periods of high secretory demand, as shown by the loss of numerous haematopoietic cells (such as DCs, eosinophils and plasma cells) and parenchymal cells (such as hepatocytes, pancreatic β-cells, acinar cells of the salivary glands and Paneth cells) when important elements of the UPR are absent[79]. In addition to this physiological UPR, ER stress can further result from various intrinsic and environmental factors, such as inadequate energy supply (as observed during hypoxia and nutrient deprivation) and increased secretory demand during exposure to pathogens and inflammatory stimuli[80]. These environmental challenges induce UPR activation and thereby contribute to inflammation through various mechanisms.

Hypoxia

Hypoxia inhibits oxygen-dependent protein-folding processes, which directly affects disulfide bond formation during post-translational folding of proteins and *cis–trans* prolyl isomerization in the ER[81], leading to ER stress. Hypoxia can occur in adipose tissue in the setting of obesity, probably as a result of the diffusion limit of oxygen imposed by the hypertrophic adipocytes. Adipocyte hypoxia has been shown to be associated with the induction of ER stress and the increased expression of CHOP, which is at least partly responsible for the reduced expression of adipocytokines that provide important anti-

inflammatory functions[82]. This raises the possibility that hypoxia-induced ER stress may be linked to obesity-related metabolic diseases.

Hypoxia, owing to inefficient vascularization, is also a hallmark of the tumour microenvironment and is one of the factors that accounts for UPR activation in solid tumours. UPR activation in tumours triggers protective responses that enable the tumour to cope with conditions of low oxygen and nutrient supply[83]. Splicing of *XBP1* mRNA was recently shown to provide a survival benefit to highly aggressive triple-negative breast cancer cells. The inhibition of *XBP1* in these tumour cells using RNA interference decreased tumour growth and particularly affected angiogenesis, which links XBP1 to tumour hypoxia. Moreover, it was shown that XBP1 directly interacts with the central mediator of the cellular response to hypoxia, hypoxia-inducing factor 1α (HIF1α), and assists in regulating the expression of HIF1α target genes[84]. As HIF1α also has a prominent role in the antitumour immune response by inhibiting the effector functions of tumour-infiltrating lymphocytes[85], targeting the UPR and HIF1α as connected pathways in solid tumours might provide a therapeutic benefit by boosting antitumour immune responses.

ROS

The oxidizing environment of the ER is optimized for disulfide bond formation, and the redox status of the ER is tightly regulated in mammalian cells[86]. This environment is primarily derived from ROS that are generated by endoplasmic reticulum oxireductin 1 (ERO1), with protein disulfide isomerase being responsible for disulfide bond formation. However, cellular ROS production increases considerably and to supraphysiological levels under ER stress and inflammatory conditions. These conditions are closely connected in a reciprocal manner such that they induce self-reinforcing pathways that may further promote inflammation[4,87]. ROS can be induced by a wide variety of immunological signals. These include, for example, TLR and TNF receptor signalling, which further trigger inflammatory responses by enhancing the phosphorylation of IκB to induce nuclear factor-κB (NF-κB) signalling[88]. Conversely, it has been shown that extracellular sources of ROS can induce ER stress, possibly by disrupting Ca^{2+} retention in the ER[89]. Once they are produced, ROS can also promote NLRP3 (NLR family, pyrin domain containing 3) inflammasome activation[90] and can regulate lymphocyte function[88] and, as discussed above, NOX2-derived ROS in macrophages are required for XBP1-dependent cytokine production following TLR2 and TLR4 ligation.

In mouse models of diabetes, ER stress and ROS production have recently been linked to inflammasome activation and pancreatic β-cell death in a pathway that involves the induction of thioredoxin-interacting protein (TXNIP). This protein reduces the anti oxidant effect of thioredoxin. Two recent studies have shown that ER stress-induced inflammasome activation and pancreatic β-cell apoptosis were preceded by increased *Txnip* mRNA expression through a pathway that involves IRE1α[27] and/or PERK[91]. As a consequence, the genetic deletion of TXNIP partly protects against diabetes progression[27].

Pathogens

Many pathogens interfere with the function of the host ER as part of their infectious life cycle, and can therefore activate distinct arms of the UPR. Pathogen-induced UPR activation can be beneficial to the host by enabling an innate immune response directed against the invading pathogens. However, invading pathogens can selectively modulate UPR pathways to promote their own survival[92].

Viral replication requires the host ER for the production of viral structural and non-structural proteins, and as such viral replication interferes with the host protein synthesis machinery[93]. Not surprisingly, viral infection can trigger the UPR (reviewed in REF. 94). The IRE1α-mediated arm of the UPR can block viral replication in the case of respiratory syncytial virus (RSV), probably through RIDD-dependent viral RNA degradation, as XBP1 is not required for defence against RSV[95]. However, some viruses, such as Japanese encephalitis virus, use RIDD to their advantage to degrade host RNAs without affecting viral RNA[96]. Similarly, many viruses have evolved mechanisms to circumvent the disadvantageous consequences of the UPR; the selective activation of the ATF6α- and IRE1α-mediated arms of the UPR sustains viral replication by increasing the production of ER chaperones, and viruses simultaneously block PERK-mediated UPR activation to circumvent a translational block and/or ER stress-induced apoptosis. For example, herpes simplex virus type 1 selectively blocks the activation of the PERK-mediated arm of the UPR through the association of viral glycoprotein gB with the luminal domain of PERK[97]. Also, whereas hepatitis C virus (HCV) induces IRE1α and ATF6α activation, it suppresses the downstream effects of XBP1s to prevent the activation of ERAD, which enables HCV replication and contributes to the persistence of the virus in infected hepatocytes[98,99].

An important example of how the UPR protects the host from bacterial infection has come from studies using *Caenorhabditis elegans*. In this nematode, infection with *Pseudomonas aeruginosa* induces a p38 MAPK-driven innate immune response, which in turn triggers the IRE1α–XBP1 pathway of the UPR. XBP1 activation is protective for the host, as *xbp-1*-mutant larvae exhibit ER disruption and increased lethality in response to infection. Interestingly, lethality could also be prevented by the loss of p38 MAPK, which shows that it is not the infection itself but rather the innate immune response that is lethal in the absence of a simultaneous protective XBP1-dependent UPR response[100].

A recent study in primary bronchial epithelial cells has further supported the link between an innate immune response and the UPR by showing that virulence factors that are derived from *P. aeruginosa* strongly induce UPR activation in a p38 MAPK-dependent manner, as evidenced by *Xbp1* splicing and the induction of BiP and CHOP. However, induction of GADD34 occurred through the activation of the ISR, which was associated with the improved survival of host cells[101].

L. monocytogenes has a well-documented ability to induce the UPR, which was recently shown to occur without the active infection of cells by secretion of the cytolysin listeriolysin O. This toxin induces all branches of the UPR, possibly by altering intracellular Ca^{2+} homeostasis, which ultimately leads to apoptosis[102]. Similarly, the AB_5 subtilase cytotoxin from Shiga-toxigenic *Escherichia coli* cleaves BiP, thus inducing all three arms of the UPR

and resulting in ER stress-induced cell death[103]. Pathogen-associated molecular patterns may also activate specific arms of the UPR. For example, *Streptomyces* spp. produce a toxin (trierixin) that directly inhibits *Xbp1* splicing[44]. By contrast, TLR2 and TLR4 ligands trigger the IRE1α– XBP1 arm of the UPR in macrophages while suppressing ATF4–CHOP signalling to promote macrophage survival during infections[69,75]. Thus, pathogens can either subvert or induce the UPR during their life cycles, and UPR induction may alert the immune system to the presence of these pathogens.

Cell damage and immunogenic cell death

Dying cells can elicit inflammatory responses both through the induction of cell surface receptors that are recognized by immune cells, such as the ER-resident protein calreticulin (CRT; also known as CALR), and through secreted factors, including high mobility group box 1 (HMGB1) and ATP[104,105]. HMGB1 activates all arms of the UPR in endothelial cells, resulting in increased expression of intercellular adhesion molecule 1 (ICAM1) and P-selectin, which probably function to attract immune cells to dying cells[106]. In splenic DCs, HMGB1 exposure induces UPR activation with increased levels of BiP and *Xbp1* splicing; this pathway seems to be important for mounting an immune response, as silencing of *Xbp1* is associated with the downregulation of the costimulatory cell surface receptors CD80 and CD86, decreased MHC class II expression and, subsequently, impaired stimulation of T cells in co-culture systems[107].

Even before cells die and intracellular components such as HMGB1 are released to elicit inflammation, stressed cells induce immune responses; for example, the cell surface expression of CRT is a recognition signal for engulfment by antigen-presenting cells. Human bladder carcinoma T24 cells that are exposed to photo-dynamic therapy, which causes the ROS-mediated induction of ER stress, increase their cell surface expression of CRT and secretion of ATP through pathways involving PERK[108]. Interestingly, this was associated with the increased engulfment of cancer cells by DCs and increased DC expression of CD80, CD86 and MHC class II, as well as increased IL-1β and nitric oxide production, all of which are important for an effective antitumour $CD8^+$ T cell response[108]. Increased cell surface expression of CRT also occurs in a PERK-dependent manner in cancer cells that have non-physiological increases in chromosome content (this is known as hyperploidy and occurs in the early stages of various cancers) and this is an important immunosurveillance system against hyperploidy in cancers[109].

Whether UPR activation can drive the specific upregulation of ligands that are recognized by innate immune cells, including natural killer cells, requires further research. Interestingly, CHOP has been linked to cell death in human colon cancer HCT116 cells through the upregulation of death receptor 5 (DR5; also known as TNFRSF10B), which is a receptor for TNF-related apoptosis-inducing ligand (TRAIL; also known as TNFSF10). However, in this setting, DR5 drives apoptosis in a ligand-independent manner through the activation of caspase 8 (REF. 110). In addition, it is important to recognize that, although UPR activation in tumour cells can sometimes increase their immunogenicity and is therefore beneficial to the host, some tumours can also take advantage of the UPR to prevent antitumour immune responses (BOX 2). Elucidating the crosstalk between UPR activation in tumour cells, the

release of damage-associated molecules, cell surface receptor expression and immune activation is of great importance to improve antitumour immune responses.

The UPR as an inflammatory nidus

ER stress is implicated in various chronic pathological conditions that involve inflammation (such as metabolic diseases, inflammatory bowel diseases, atherosclerosis and neurodegenerative diseases, among others). The investigation of the pathogenic mechanisms involved has revealed a reciprocal regulation between ER stress and inflammation — whereby ER stress can directly initiate inflammatory pathways, and, in turn, pro-inflammatory stimuli such as ROS, TLR ligands and cytokines can trigger ER stress — such that the resulting UPR activation can further amplify inflammatory responses[111].

ER stress-induced inflammatory signalling

NF-κB, a master transcriptional regulator of pro-inflammatory pathways, is activated by the interaction of IRE1α with TRAF2 in response to ER stress, which leads to the recruitment of IκB kinase (IKK) and the phosphorylation and subsequent degradation of IκB. This releases NF-κB for translocation to the nucleus[112] (FIG. 5). The PERK– eIF2α-mediated and ATF6-mediated branches of the UPR activate NF-κB through different mechanisms from IRE1α. Engaging the PERK–eIF2α signalling pathway in response to ER stress halts overall protein synthesis and increases the ratio of NF-κB to IκB, owing to the shorter half-life of IκB, thereby favouring NF-κB-dependent transcription[113,114] (FIG. 5). ATF6α activation through exposure to the bacterial subtilase cytotoxin can induce the phosphorylation of AKT to activate NF-κB[115,116] (FIG. 5).

JNK, together with p38 and ERK, is one of the stress-inducible MAPKs that mediate a wide variety of responses, including but not limited to proliferation, autophagy and inflammation. The IRE1α–TRAF2 complex can, in addition to the activation of NF-κB, recruit apoptosis signal-regulating kinase 1 (ASK1; also known as MAP3K5) and can subsequently activate JNK, leading to the increased expression of pro-inflammatory genes through enhanced activator protein 1 (AP1) activity[117,118] (FIG. 5). Loss of XBP1 in IECs of the small intestine results in the hyperactivation of IRE1α, which drives inflammatory responses, including cytokine production, that are partly mediated by the phosphorylation of JNK[77]. ER stress in human cancer cell lines has also been shown to trigger ERK activation through PI3K, which was associated with increased resistance to ER stress-induced cell death[119].

UPR activation in immune cells and various stromal cells leads to the induction and secretion of cytokines, such as IL-6 and TNF[120,121]. In macrophages, XBP1s directly binds the *Tnf* and *Il6* promoters to regulate their expression[69], and ATF4 — downstream of PERK activation — functions as a transcription factor for *Il6* (REF. 74) (FIG. 5). ER stress in pancreatic β-cells can trigger the activation of the NLRP3 inflammasome and IL-1β secretion through IRE1α-mediated and PERK-mediated induction of TXNIP[27] (FIG. 5).

Conversely, cytokines themselves can directly regulate the UPR. IL-10, for example, can inhibit inflammation-induced ER stress by blocking the shuttling of ATF6p50 to the nucleus in a pathway that involves p38 MAPK[122]. However, circulating pro-inflammatory cytokines

including IL-1, IL-6, CXCL8 (also known as IL-8) and TNF, can trigger UPR activation in the liver and can thereby stimulate the release of products of the acute phase response (APR), which amplify inflammatory responses to eliminate infection and to restore tissue homeostasis. Upon ER stress in hepatocytes, ATF6α and CREBH traffic to the Golgi to undergo S1P- and S2P–mediated cleavage; the cytosolic active transcription factors that are released induce the expression of APR genes, including those encoding C-reactive protein and serum amyloid P component[111] (FIG. 5).

The pathological UPR in inflammatory disease

UPR-associated inflammatory pathways are increasingly being recognized to be involved in various complex inflammatory diseases. We discuss below several examples of autoimmune, metabolic and neoplastic conditions in which the UPR may have an important role.

Inflammatory bowel disease

Over the past decade, genome-wide association studies (GWAS) have identified various susceptibility loci for Crohn's disease and ulcerative colitis, which are chronic inflammatory diseases of the gastrointestinal tract, collectively known as inflammatory bowel disease (IBD)[123,124]. Many of these risk genes encode proteins that have an important role in proteostasis. Orosomucoid-like 3 (*ORMDL3*), which is a risk locus for both Crohn's disease[125] and ulcerative colitis[126] (as well as, interestingly, asthma[127]), encodes an ER transmembrane protein that activates ATF6α in lung epithelial cells and induces the expression of SERCA2B (also known as ATP2A2), which might be associated with airway remodelling[127]. In addition, ORMDL3 represses serine palmitoyltransferase activity and thereby decreases ceramide levels, which might protect against apoptosis[128]. However, the mechanism by which ORMDL3 is involved in IBD pathogenesis is unstudied. Candidate gene approaches have also identified anterior gradient 2 (*AGR2*)[129] and *XBP1* as risk loci for Crohn's disease and ulcerative colitis. AGR2 is a member of the protein disulfide isomerase family and is particularly highly expressed by the secretory cells of the intestinal tract. In line with this, $Agr2^{-/-}$ mice have decreased expression of mucin 2 (MUC2) in goblet cells and abnormal localization of Paneth cells in the small intestine, which coincides with UPR activation and the development of spontaneous ileocolitis[130].

The conditional deletion of *Xbp1* in IECs causes ER stress and results in spontaneous inflammation of the small intestine and increased susceptibility to dextran sodium sulfate (DSS)-induced colitis[77]. As for AGR2 deficiency, the deletion of XBP1 in IECs particularly affects secretory cells, as $Xbp1^{\Delta IEC}$ mice have decreased numbers of goblet cells and severely hypomorphic Paneth cells with decreased antimicrobial peptide production, which is associated with an increased susceptibility to infection with *L. monocytogenes*[77]. It is not completely clear how UPR activation in AGR2-deficient and $Xbp1^{\Delta IEC}$ mice eventually causes intestinal inflammation. $Xbp1^{\Delta IEC}$ mice show signs of IRE1α-dependent JNK phosphorylation and NF-κB activation; blockade of NF-κB activation, genetic deletion of IRE1α in IECs, or the systemic deletion of TNF receptor 1 protects $Xbp1^{\Delta IEC}$ mice from spontaneous enteritis[78,123]. Therefore, IRE1α– NF-κB signalling, in a pathway that is driven

by TNF, has a crucial role in the development of inflammation upon deletion of XBP1 in IECs.

As autophagy compensates for ER stress (BOX 1), the genetic deficiency of autophagy in *Xbp1*$^{\Delta IEC}$ mice is associated with even more severe spontaneous enteritis that extends transmurally[78]. Indeed, signs of ER stress have been detected in Paneth cells in patients with Crohn's disease who carry the risk allele of autophagy-related 16-like 1 (*ATG16L1*^{T300A})[131]. Moreover, as the *ATG16L1*^{T300A} risk allele encodes a protein that is otherwise functionally intact but that has increased sensitivity to caspase 3-mediated cleavage[132,133], and as XBP1 deletion in IECs leads to caspase 3 activation[77], it is possible that in humans environmentally and/or genetically determined ER stress can reveal the phenotypic manifestations of this common risk variant[134]. The epithelium of the small intestine may be particularly sensitive to ER stress-induced caspase 3 activation and *ATG16L1*^{T300A} cleavage as there is evidence for ER stress even under baseline, non-inflammatory conditions[135].

In addition to IRE1α, the intestinal and lung epithelia express IRE1β (encoded by *ERN2*), particularly in goblet cells. *Ern2*$^{-/-}$ mice have increased basal levels of BiP in the intestinal epithelium, aberrant MUC2 accumulation in the ER of goblet cells[136] and increased sensitivity to DSS-induced colitis[137].

Various other perturbations in UPR signalling have been associated with intestinal inflammation. Mice that lack CREB3L1 (also known as OASIS)[138,139], ATF6α, S1P or p58IPK are more susceptible to DSS-induced colitis[137,186]. Furthermore, nonphosphorylatable Ser51Ala eIF2α-mutant mice have defective UPR signalling in IECs, leading to secretory dysfunction of Paneth cells and increased sensitivity to oral *Salmonella enterica* subsp. *enterica* serovar Typhimurium infection and DSS-induced colitis[140].

Forward genetic approaches using *N*-ethyl-*N*-nitrosourea mutagenesis have yielded mouse strains (known as Winnie and Eeyore) that carry single missense mutations in *Muc2*. These mutations cause misfolding of MUC2, which results in strong UPR activation and spontaneous ulcerative colitis-like colitis, characterized by inflammatory responses that involve both innate and adaptive immunity (including the IL-23–T helper 17 cell inflammatory axis)[141,142].

Together, these studies show that the UPR is important in maintaining intestinal epithelial homeostasis in a highly complex intestinal luminal environment challenged by microorganisms and other external factors. However, intestinal inflammation can also be promoted by ER stress in the haematopoietic system of mucosal tissues, as shown by studies using HLA-B27 transgenic rats[143], and the contribution of UPR activation in distinct cell types to intestinal inflammation requires further research.

Diabetes mellitus

Pancreatic β-cells rapidly increase protein synthesis during acute and chronic stimulation and are therefore dependent on a well-developed ER and on protein-quality control mechanisms. β-cell-specific deletion of IRE1α or XBP1 results in impaired β-cell

proliferation, defective proinsulin synthesis and processing, and decreased insulin secretion[144]. Similarly, genetic deletion of PERK leads to ER stress-induced loss of pancreatic β-cells and a progressive decline in endocrine (but also exocrine) pancreatic function, with hyperglycaemia developing within 4 weeks[145], which further emphasizes the central role of the UPR in pancreatic β-cell survival and diabetes. In Akita mice, the oxidative folding of proinsulin by ER-resident oxireductases, which is required to obtain the native shape of proinsulin and to allow its trafficking from the ER further down the secretory pathway, is impeded by the expression of a mutant form of proinsulin (Ins2 C96Y). This results in the accumulation of misfolded proinsulin proteins in the ER, which triggers UPR activation, β-cell inflammation and eventually β-cell death. This leads to diabetes in the mice as early as 4 weeks of age[146,147], which is similar to PERK-deficient mice[148]. Importantly, IRE1α oligomer formation, which is indicative of high levels of chronic ER stress, is a crucial propagator of the phenotype of Akita mice, as pharmacological inhibition of IRE1α kinase activity alleviates the disease phenotype[26].

ER stress-induced JNK activation occurs in the adipose and liver tissue of obese mice, whether obesity is induced by a high-fat diet or genetically through leptin deficiency (*ob*/*ob* mice). Obese mice develop insulin resistance through ER stress-mediated JNK-induced phosphorylation of insulin receptor substrate 1 (IRS1), which impairs insulin action and causes insulin resistance[149]. Importantly, lower levels of XBP1s in the livers of obese mice were recently shown to result from inducible nitric oxide synthase (iNOS; also known as NOS2)-dependent — and thus inflammation-dependent — *S*-nitrosylation of the RNase domain of IRE1α, although the kinase domain was unaffected. This resulted in decreased levels of protective XBP1s but maintained the levels of pro-inflammatory phosphorylated JNK. This study thereby demonstrates how obesity-induced inflammation can alter UPR signalling and provides a new link between inflammation, UPR activation and metabolic dysfunction[150].

ROS production that is secondary to ER stress can be another trigger for inflammation as ROS production activates the NLRP3 inflammasome and IL-1β secretion in β-cells through increased levels of TXNIP, either as a result of RIDD-dependent decay of the *Txnip*-suppressing miR-17 or through the PERK pathway, ultimately leading to β-cell apoptosis and diabetes[27,91]. Indeed, the suppression of JNK activity protects β-cells from oxidative stress and ameliorates glucose tolerance[151]. Although this is a field of extensive research, much still needs to be learned about the interplay between ER stress, inflammation and the development of metabolic diseases such as diabetes, as the UPR could be an attractive signalling pathway for therapeutic intervention.

Non-alcoholic steatohepatitis

The crucial role of the UPR in the liver was first discovered in 2000, when it was shown that XBP1 was required for liver development[152]. In the liver, the ER and UPR are highly important for lipid synthesis and metabolism, in addition to their well-known role in protein quality control[153]. UPR activation in the liver has been extensively studied in light of the increasing prevalence of `non-alcoholic fatty liver disease` (NAFLD), which is the leading cause of non-alcoholic and non-viral liver-associated illness and death in the

United States[154]. Hepatic steatosis, which is the mildest form of NAFLD, can progress to non-alcoholic steatohepatitis (NASH) through a process that involves free fatty acid and lipid accumulation in hepatocytes followed by a series of innate immune responses in leukocytes, including in liver-resident macrophages that are known as Kupffer cells[155]. It has been shown that ER stress can induce liver steatosis through effects on lipid synthesis and inflammation, but high-fat feeding-induced steatosis itself can also trigger ER stress, thereby providing a positive feedback loop that amplifies liver inflammation and injury[156]. In turn, UPR activation can modulate inflammatory signalling to induce liver inflammation, partly through JNK activation, and κB phosphorylation leading to NF-κB activation[112,113], which is an important mediator of methionine- and choline-deficient (MCD) diet-dependent development of NASH[157]. In addition, the accumulation of lipids in hepatocytes can lead to mitochondrial dysfunction with increased ROS levels, which further triggers downstream inflammatory responses. The importance of ROS in the development of NASH has specifically been shown in mice deficient in NRF2 (also known as NFE2L2), a protein that is crucially involved in the antioxidant response and that can be induced by PERK; *Nrf2*$^{-/-}$ mice develop NASH more rapidly than wild-type mice when fed high-fat, high-cholesterol or MCD diets[158].

Cancer

The activation of the UPR in cancers can initiate transcriptional programmes that allow tumour cells to combat harsh environmental conditions such as hypoxia, oxidative stress and low nutrient availability. In addition, these transcriptional programmes can actively shape a tumorigenic proinflammatory milieu. For example, UPR activation in prostate cancer cells results in the transcriptional upregulation of *IL6* and *TNF*[59], the promoters of which contain functional binding sites for XBP1s[69]. These proinflammatory mediators may promote inflammation-induced malignancies[160,161]. Moreover, both the PERK-mediated[162] and IRE1α-mediated[163] arms of the UPR in tumour cells can increase the transcription of genes that encode pro-angiogenic mediators such as vascular endothelial growth factor A (VEGFA), fibroblast growth factor 2 (FGF2) and IL-6 (REFS 162–164).

Intriguingly, UPR activation in cancer cells can also affect the antitumour immune response. Soluble factors that are secreted by ER-stressed tumour cells, but not by non-stressed tumour cells, can upregulate proinflammatory cytokine expression in macrophages, including the tumorigenic cytokines IL-6, IL-23p19 and TNF[165]. These soluble factors are also involved in dampening the antitumour immune response by inhibiting antigen presentation by antigen-presenting cells to cytotoxic CD8^{+} T cells[65,166]. The mechanism by which this occurs is only partly elucidated but may include ROS-induced ER stress in DCs, transmitted through an as yet undefined factor, which increases lipid synthesis through XBP1 activation and thereby disrupts antigen presentation[65].

Conclusions

Much has been learned about the functions of the UPR beyond being simply a means to manage ER stress. The UPR has also now been recognized for its role in immune cell differentiation and function, and in regulating immune and inflammatory responses,

including those associated with infections, tumours and autoimmune responses. It is clear that the UPR, and thus a certain level of ER stress, is crucial for cellular and, consequently, tissue homeostasis (the ‘eustress’ response). Therefore, understanding how the balance tips towards a pathophysiological UPR (the ‘distress’ response) that is associated with disease, and how this balance can be manipulated to enable appropriate immune responses and to restore homeostasis, are important directions for future research.

With the development of therapeutic agents that enhance proteostasis or that interfere with specific components of the UPR (BOX 3), used either alone or together, the hope is that an improved understanding of the UPR in immunity and inflammation will eventually lead to the development of novel therapeutic strategies for chronic immune-mediated diseases.

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Glossary

ER-associated degradation (ERAD)
A pathway that removes terminally misfolded proteins from the endoplasmic reticulum (ER) through their retrotranslocation to the cytosol, which targets them for degradation by the ubiquitin-proteasome system.

Unfolded protein response (UPR)
A highly conserved pathway that regulates the balance between the folding capacity of the endoplasmic reticulum (ER) and protein synthesis.

Integrated stress response (ISR)
An ancient stress response that modulates protein biosynthesis by integrating various types of stress signals, including endoplasmic reticulum (ER) stress, amino acid deprivation, virus infection and oxidative stress.

Paneth cells
Highly specialized small-intestinal epithelial cells that shape the composition of the microbiota through the secretion of antimicrobial proteins and that sustain and modulate epithelial stem cells by the secretion of niche factors.

Acute phase response (APR)
A group of systemic and innate physiological processes in the early response to infection or injury.

Crohn’s disease

An inflammatory disease of the small and large intestines that is thought to arise from an inappropriate immune response towards the intestinal microbiota in a genetically susceptible host.

Ulcerative colitis

A chronic disease of the colon with unknown aetiology, characterized by inflammation and ulceration in the colon.

Non-alcoholic fatty liver disease (NAFLD)

Liver disease characterized by the accumulation of fat (steatosis) in the liver which is often associated with obesity. Although NAFLD is benign it can progress towards steatohepatitis and even cirrhosis.

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Box 1|Autophagy as a compensation strategy for ER stress

In response to the challenge of misfolded proteins, autophagy has a crucial function as an adaptive ‘self-eating’ process by which cellular components are encapsulated within autophagosomes and degraded. Similarly to the unfolded protein response (UPR), autophagy can result in either cell survival or cell death[167,168]. The mechanisms by which the UPR induces autophagy are incompletely understood, but probably involve signalling through PKR-like ER kinase (PERK)–eukaryotic translation initiation factor 2α (eIF2α) and inositol-requiring enzyme 1α (IRE1α)[169].

Activating transcription factor 4 (ATF4) and C/EBP homologous protein (CHOP) function both independently and together to induce a large array of autophagy genes[170]. In addition, eIF2α phosphorylation, in response to polyQ72 aggregate-induced endoplasmic reticulum (ER) stress, is associated with autophagosome formation and protection against neuronal cell death[42]. In another example, using unfolded dysferlin as a model of muscular dystrophy, spliced X-box binding protein 1 (XBP1s) was shown to be crucial for autophagy induction and protection against neurodegeneration[171]. Furthermore, UPR pathways can activate AMPK, which attenuates AKT–mTOR signalling to enhance autophagy[172].

A direct demonstration that autophagy can compensate for ER stress derives from studies of ER stress-induced small intestinal inflammation[77], in which concomitant deletion of epithelial XBP1 and epithelial associated autophagy related protein 7 (ATG7) or autophagy-related 16 like 1 (ATG16L1) results in increased ER stress and severe transmural Crohn’s disease-like enteritis, compared with deletion of XBP1 alone, which only induces mild superficial inflammation (FIG. 4c). In this model, the induction of autophagy depends on the phosphorylation of eIF2α[78]. In the case of intestinal epithelial stress that is associated with inflammatory bowel disease, autophagy probably functions to selectively remove inflammatory ER membranes (see below). In the cancer setting, ER stress induces the activation of the PERK–eIF2α –ATF4 signalling pathway to increase tumour cell survival through the induction of autophagy[173,174].

The precise mechanism by which autophagy decreases ER stress remains unclear. Autophagy was previously considered to be a non-specific process (bulk macro-autophagy), but selective autophagy processes that precisely target organelles such as the mitochondria and peroxisomes into autophagosomes have now been described. Autophagy of the ER (ER-phagy) has been described in yeast[175], and more recently also in mammalian cells. In mammalian cells, ER-phagy depends on the FAM134 reticulon family of proteins, which function as ER transmembrane receptors that bind LC3 proteins and GABA type A receptor-associated protein (GABARAP), thereby initiating ER degradation by autophagy[176]. It remains to be determined whether autophagy directly degrades stressed ER membranes that contain misfolded proteins and whether FAM134 proteins or the selective autophagy receptors NBR1, optineurin, p62 and NDP52 are involved.

Box 2|Transmission of ER stress

Can immune cells sense endoplasmic reticulum (ER) stress in other cells? Intriguing studies have shown that the activation of the unfolded protein response (UPR) in tumour cells can, through an unknown transmissible factor, induce ER stress in macrophages involving the upregulation of mRNAs encoding binding immunoglobulin protein (BiP), C/EBP homologous protein (CHOP) and GADD34 and increased splicing of the mRNA encoding X-box binding protein 1 (XBP1). This occurs in a Toll-like receptor 4 (TLR4)-dependent manner, which suggests that a TLR4 ligand is the transmissible factor. Importantly, ER stress-induced cell death was not responsible for the observed transmissible ER stress, which indicates that there is active secretion of the transmissible factor rather than a passive leakage of damage-associated molecules from dying cells[165]. Macrophages that were stimulated by neighbouring ER-stressed tumour cells had increased inflammatory responses, which is in keeping with previous observations that TLR4 ligation amplifies pro-inflammatory cytokine signalling and may be the responsible signalling moiety[69]. In addition to macrophages, dendritic cells (DCs) are also susceptible to an ER stress-transmissible factor that is secreted by tumour cells and that interferes with DC-mediated antigen cross-presentation to $CD8^+$ T cells and results in a less effective antitumour immune response[166]. It was recently shown that XBP1s–induced increases in lipid metabolism in DCs could be the underlying mechanism of impaired MHC class I-mediated antigen presentation to cytotoxic T cells[65].

It is not clear whether the unidentified transmissible factor is a byproduct of ER stress in tumour cells or is actively secreted by these cells to modulate the antitumour response. Identification of the ER stress-transmissible factor would greatly enhance our understanding of how tissue-specific ER stress can become systemic in nature. In addition, this could provide possible new therapeutic targets to improve the antitumour immune response.

Box 3|Therapeutic opportunities

Tauro-ursodeoxycholic acid (TUDCA) and 4-phenyl butyrate (PBA) are small-molecule chaperones that contribute to proper protein folding in the endoplasmic reticulum (ER); they have proved successful in alleviating ER stress-induced hyperglycaemia, restoring insulin sensitivity and ameliorating fatty liver disease in obese mice[177]. TUDCA and PBA have also been shown to reduce ER stress in the intestinal epithelium and thereby decrease the severity of dextran sodium sulfate (DSS)-induced colitis[178]. In addition, lipopolysaccharide (LPS)-induced lung inflammation was reduced by PBA, through decreasing ER stress and modulating the nuclear factor-κB (NF-κB) and hypoxia-inducing factor 1 α (HIF1α) signalling pathways[179].

In haematological malignancies that produce large amounts of protein, such as multiple myeloma, blocking the 26S proteasome with bortezomib induces the activation of the PKR-like ER kinase (PERK)-mediated unfolded protein response (UPR) pathway, which increases activating transcription factor 4 (ATF4) and C/EBP homologous protein (CHOP) activity and sensitizes multiple myeloma cells to apoptosis[180]. In addition, blockade of inositol-requiring enzyme 1 α (IRE1α) endonuclease activity with the small-molecule inhibitor MKC-3946 increases the death of multiple myeloma cells in response to the proteasome inhibitor bortezomib[181]. In line with this, $CD138^+$ plasma cells from patients with multiple myeloma are highly prone to cell death after treatment with STF-083010, another specific IRE1α RNase domain inhibitor, which further illustrates the importance of X-box binding protein 1 (XBP1) in plasma cells. In addition, STF-083010 has potent cytotoxic effects in multiple myeloma cell lines and xenograft models[182].

Sunitinib is a receptor tyrosine kinase inhibitor that targets the receptors for platelet-derived growth factor (PDGF) and vascular endothelial growth factor (VEGF) and thereby affects tumour angiogenesis and tumour cell proliferation. It has been approved by the United States Food and Drug Administration for the treatment of renal cell carcinoma and gastrointestinal stromal tumours. However, sunitinib also seems to influence the kinase activity of IRE1α[183] and protein kinase R (PKR)-dependent phosphorylation of eukaryotic translation initiation factor 2α (eIF2α)[184]. Therefore, sunitinib is potentially beneficial for the treatment of UPR-prone cancers but it has also been shown to have negative effects on the anti-viral immune response, as measured by decreased levels of interferon-β (IFNβ) in response to infection with encephalomyocarditis virus, which was dependent on decreased RNase L activity[184]. This study exemplifies that broadly targeting the UPR might have important side effects that must be considered.

Finally, given the recent reports showing that UPR activation in cancers can modulate the tumour immune microenvironment, antigen presentation by dendritic cells and thereby antitumour immune responses, targeting the UPR in cancers may improve tumour recognition by the immune system or, synergistically, may improve the efficacy of immunotherapy in cancer.

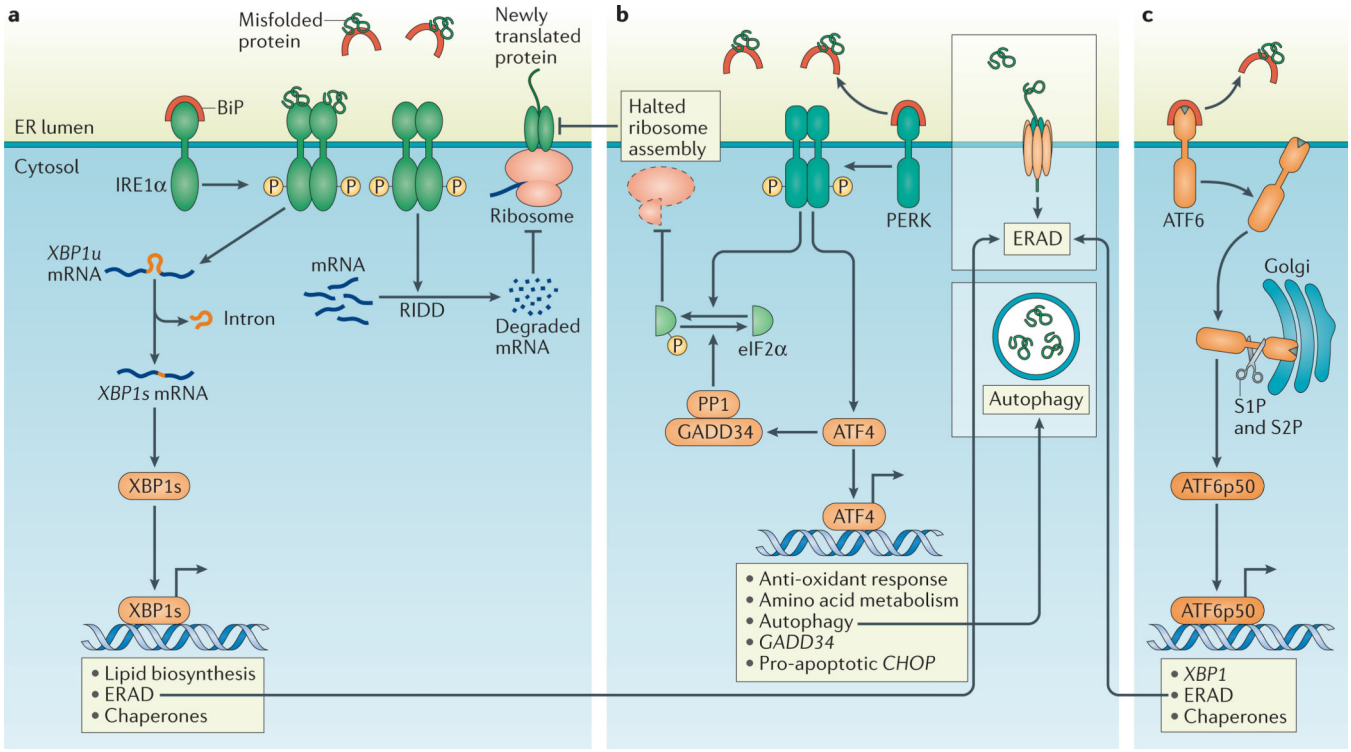

Figure 1. The accumulation of unfolded proteins in the ER lumen activates the three arms of the UPR

a | Dissociation of binding immunoglobulin protein (BiP) from inositol-requiring enzyme 1α (IRNEa1tuα). or dirct binding of misfolded proteins to IRE1α, activates the endoribonuclease domain of IRE1α, which non-conventionally splices an intron from unspliced X-box binding protein 1 (*XBP1u*) mRNA to produce *XBP1s* mRNA that encodes a potent transcriptional activator, XBP1s. Among the target genes of XBP1s are genes encoding proteins that increase the protein-folding capacity of the endoplasmic reticulum (ER) and that assist in the degradation of misfolded proteins by ER-associated degradation (ERAD; see inset box). In addition, the entry of newly synthesized proteins into the ER is limited by the degradation of mRNA through regulated IRE1α-dependent decay of mRNA (RIDD). **b** | PKR-like ER kinase (PERK)-dependent phosphorylation of eukaryotic translation initiation factor 2α (eIF2α) inhibits ribosome assembly, which causes a translational block and allows the cell to manage temporary ER stress. Activating transcription factor 4 (ATF4) escapes translation inhibition under ER stress conditions and induces the transcription of genes that promote survival, including those involved in compensatory autophagy (see inset box). Once ER stress is resolved, eIF2α is dephosphorylated by the GADD34–protein phosphatase 1 (PP1) complex to restore protein translation. However, if ER stress-induced damage is irreversible, the terminal unfolded protein response (UPR) is activated to induce apoptosis, mainly through C/EBP homologous protein (CHOP). **c** | Upon BiP dissociation from ATF6α during ER stress, ATF6α travels to the Golgi compartment where it is processed by the Golgi enzymes site 1 protease (S1P) and S2P to produce a cytosolic p50 fragment. ATF6p50 functions as a transcription factor that activates transcriptional programmes that increase ER capacity and protein folding, and that remove misfolded proteins from the ER for degradation (ERAD; see inset box).

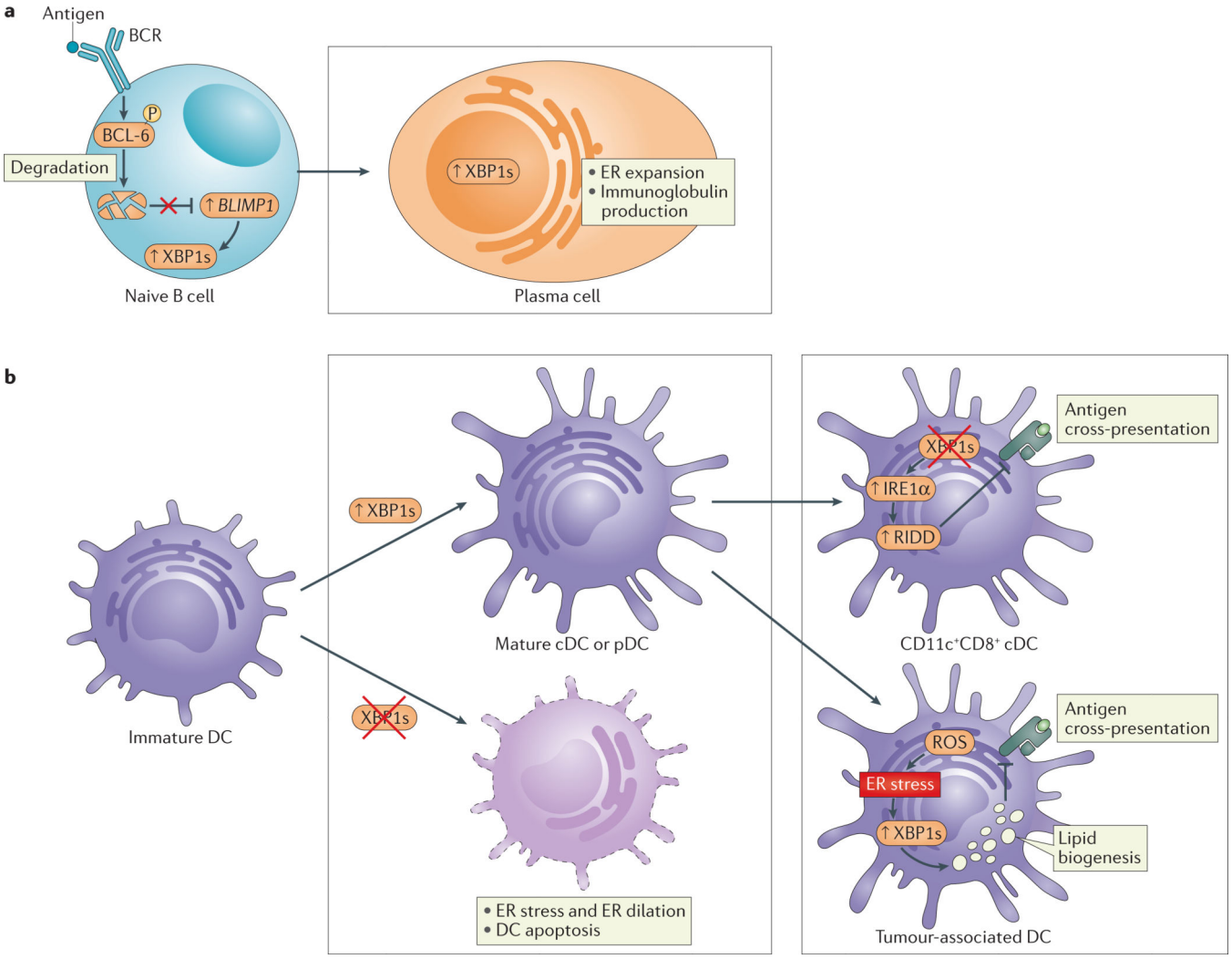

Figure 2. XBP1 has a crucial role in plasma cell differentiation and DC differentiation and function

a | B cell receptor (BCR) ligation induces the phosphorylation of B cell lymphoma 6 (BCL-6) and its subsequent ubiquitylation and degradation. BCL-6 degradation derepresses B lymphocyte-induced maturation protein 1 (*BLIMP1*) in naive B cells to activate cellular programmes that are crucial for the development of plasma cells. These include activation of the unfolded protein response (UPR) and X-box binding protein 1 (*XBP1*) splicing, which is required for the expansion of the endoplasmic reticulum (ER) and increased protein (immunoglobulin) synthesis involved in plasma cell differentiation. **b** | XBP1 is crucial for the differentiation of conventional dendritic cells (cDCs) and plasmacytoid DCs (pDCs) from immature progenitors (left). Loss of XBP1 in progenitor cells abrogates maturation and decreases DC survival. XBP1 deletion in mature $CD11c^+$ DCs results in inositol-requiring enzyme 1α (IRE1α) hyperactivation, leading to regulated IRE1α-dependent decay (RIDD)-dependent degradation of components of the MHC class I–mediated antigen cross-presentation machinery; as such, ER stress in DCs interferes with their function (right, top). By contrast, increased XBP1s in response to the production of reactive oxygen species

(ROS) in tumour-associated DCs leads to augmented lipid biogenesis that is associated with the disruption of MHC class I–mediated antigen cross-presentation (right, bottom).

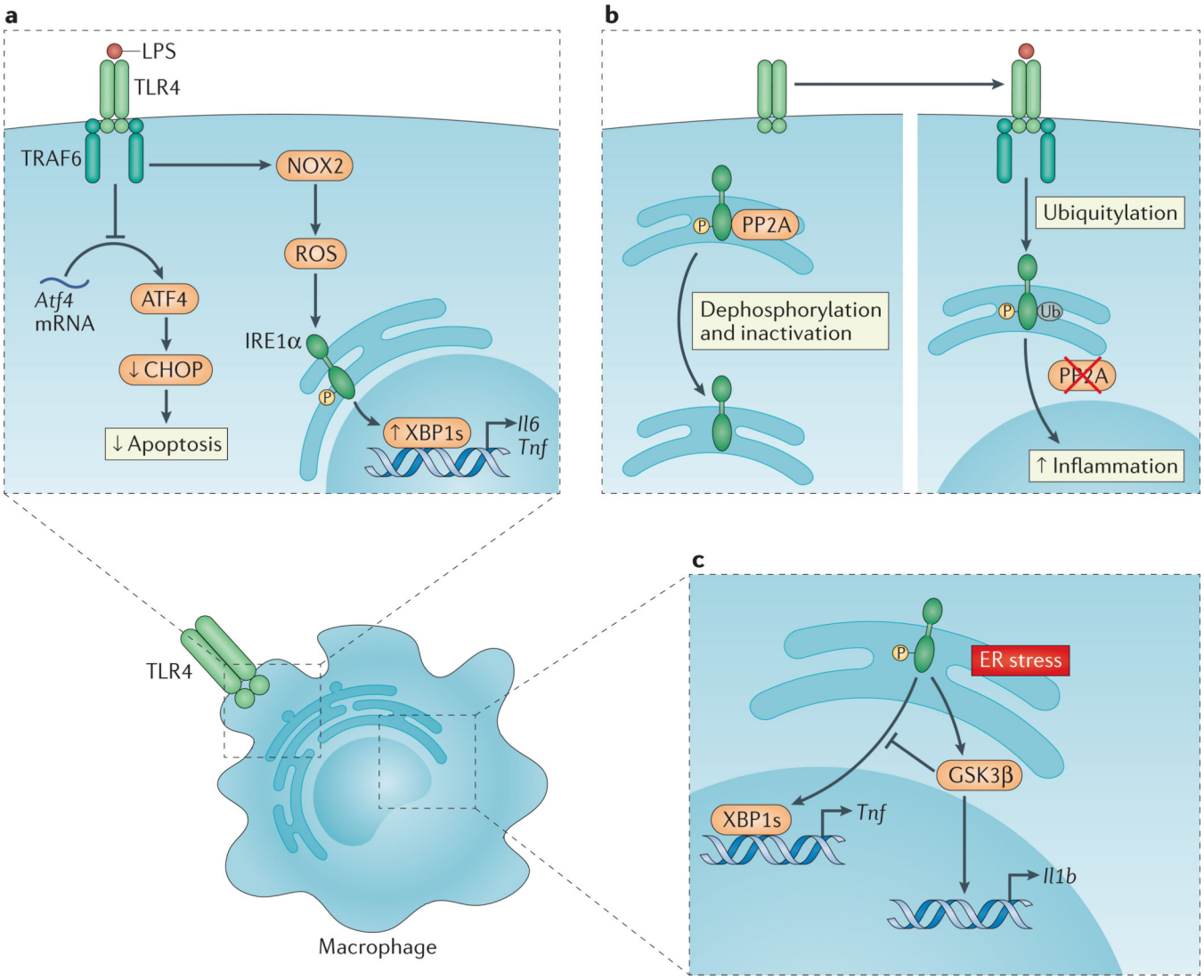

Figure 3. TLR signalling and the UPR coordinate immune responses in macrophages

a | Upon Toll-like receptor (TLR) ligation, the inositol-requiring enzyme 1α (IRE1α) arm of the unfolded protein response (UPR) is activated through a mechanism that requires TNF receptor-associated factor 6 (TRAF6) recruitment to the TLR and reactive oxygen species (ROS) production by the NADPH oxidase NOX2. Spliced X-box binding protein 1 (XBP1s) functions as a transcription factor for the pro-inflammatory cytokines interleukin-6 (*Il6*) and tumour necrosis factor (*Tnf*). In a separate pathway, translation of activating transcription factor 4 (*Atf4*) mRNA is inhibited by TLR4 ligation, which decreases C/EBP homologous protein (CHOP) levels and apoptosis in activated macrophages. This favours macrophage survival and as such facilitates the immune response. **b** | In the absence of TLR signalling, phosphorylated IRE1α is subject to protein phosphatase 2A (PP2A)-mediated dephosphorylation and inactivation (left panel). Upon TLR ligation, however, TRAF6 interacts with and catalyses the ubiquitylation of IRE1α, which prevents PP2A–mediated dephosphorylation and inactivation of IRE1α, thereby amplifying inflammation (right panel). **c** | Endoplasmic reticulum (ER) stress-induced activation of IRE1α can induce *Il1b*

transcription through glycogen synthase kinase 3β (GSK3β), which simultaneously inhibits *Xbp1* splicing and thereby the transcription of XBP1s target genes, including *Tnf*.

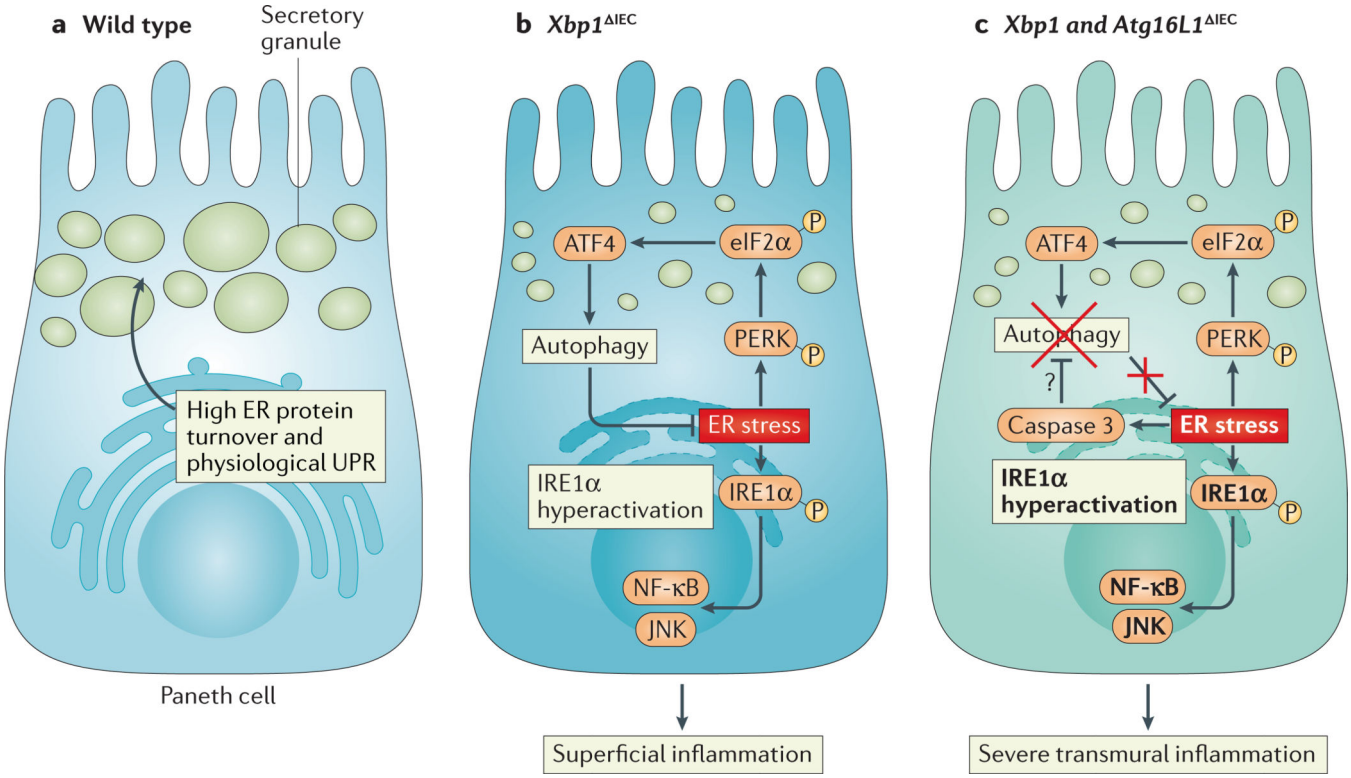

Figure 4. UPR signalling in intestinal epithelial cells

a | Intestinal epithelial cells, particularly Paneth cells, have a well-developed endoplasmic reticulum (ER) to manage their high secretory demands, including the production of antimicrobial proteins such as lysozyme and defensins. **b** | Deletion of X-box binding protein 1 (XBP1) in the small intestinal epithelium (*Xbp1*$^{\Delta IEC}$ mice) induces ER stress, resulting in hypomorphic Paneth cells that have signs of inositol-requiring enzyme 1α (IRE1α) hyperactivation and downstream activation of nuclear factor-κB (NF-κB) and JUN N-terminal kinase (JNK). The induction of autophagy through the PKR-like ER kinase (PERK)-eukaryotic translation initiation factor 2α (eIF2α)-activating transcription factor 4 (ATF4) axis of the unfolded protein response (UPR) alleviates ER stress. **c** | Simultaneous deletion of XBP1 and autophagy-related 16 like 1 (ATG16L1) in the small intestinal epithelium thus further increases ER stress and ER stress-induced inflammation. Hypothetically, ER stress, which induces caspase 3, could be an important pathway responsible for the degradation of ATG16L1 in patients carrying the Crohn's disease risk allele *ATG16L1*^{T300A}, which is prone to caspase 3-mediated cleavage.

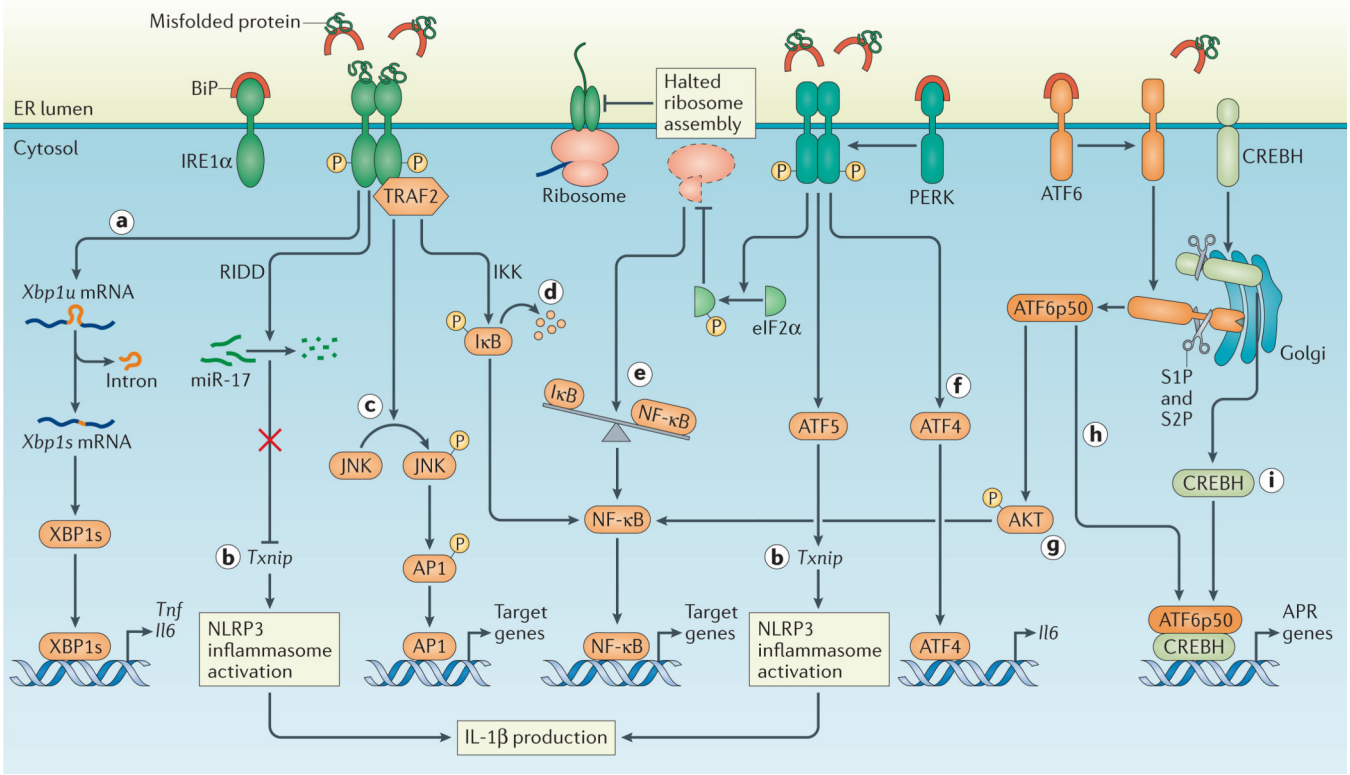

Figure 5. The UPR as an inflammatory nidus

a | Inositol-requiring enzyme 1α (IRE1α) activation and subsequent splicing of X-box binding protein 1 (*Xbp1*) produces the transcription factor XBP1s that directly binds the promoters of tumour necrosis factor (*Tnf*) and interleukin-6 (*Il6*). **b** | Regulated IRE1α-dependent decay (RIDD)-dependent degradation of miR-17, which in unstressed conditions represses thioredoxin-interacting protein (*Txnip*), allows for increased TXNIP levels and NLRP3 inflammasome activation with upregulation of IL-1β. In addition, *Txnip* can be induced through the PKR-like ER kinase (PERK)-activating transcription factor 5 (ATF5) pathway to induce inflammasome activation. **c** | Activated IRE1α forms a complex with TNF receptor-associated factor 2 (TRAF2) to induce phosphorylation of Jun N-terminal kinase (JNK) and upregulation of pro-inflammatory genes through activated activator protein 1 (AP1). **d** | In addition, the IRE1α –TRAF2 complex recruits IκB kinase (IKK), and subsequent phosphorylation of IκB leads to its degradation, which releases nuclear factor-κB (NF-κB) for nuclear translocation. **e** | Translation attenuation by PERK-dependent phosphorylation of eukaryotic translation initiation factor 2α (eIF2α) results in decreased translation of both IκB and NF-κB. However, owing to the shorter half-life of IκB, the net result is an increased NF-κB to IκB ratio, which promotes inflammation. **f** | ATF4 directly binds the *Il6* promoter. **g** | ATF6α induces NF-κB signalling via AKT phosphorylation. **h,i** | Site 1 protease (S1P)- and S2P–mediated cleavage of ATF6α and CREBH allows their cleavage fragments to translocate to the nucleus and induce genes of the acute phase response (APR). BiP, binding immunoglobulin protein.