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Antigen presentation unfolded: identifying convergence points between the UPR and antigen presentation pathways

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The unfolded protein response (UPR) is an adaptive response meant to restore endoplasmic reticulum homeostasis in conditions of ER stress that subvert the folding capacity of the cell. Over the past few years, it has become clear that the functions of the UPR stretch far beyond their canonical role and intersect with seemingly unrelated functions such as innate immunity and antigen presentation. The aim of the present review is to dissect how the UPR interferes directly and indirectly with the major processes of MHC-I and MHC-II antigen presentation.

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Introduction

The unfolded protein response (UPR) is an adaptive cellular response initiated upon accumulation of improperly folded proteins in the endoplasmic reticulum (ER) and triggered by three ER-resident sensors: inositol requiring enzyme 1 (IRE1α), protein kinase R-like ER kinase (PERK) and activating transcription factor 6 (ATF6) [1,2] (Figure 1). IRE1α is a bifunctional protein that harbors a serine/threonine kinase domain and a ribonuclease (RNAse) domain in its cytoplasmic domain. Upon activation, IRE1α cleaves *Xbp1* (X-box binding protein) mRNA through an unconventional splicing reaction yielding the active transcription factor XBP1s. XBP1s is a major regulator of ER biogenesis by activating expression of genes involved in lipid biosynthesis, ER associated degradation (ERAD) and chaperone production [3••]. However, in ill-defined conditions of chronic ER stress or upon loss of XBP1, IRE1 RNAse also degrades additional mRNAs of diverse nature, mostly encoding secreted proteins [4–6]. This process is termed Regulated IRE1 Dependent Decay (RIDD) and was originally proposed to reduce the ER folding load, thus alleviating the detrimental effects of ER stress [6]. The physiological role of RIDD remains poorly understood. The second UPR sensor, PERK, mediates protein translation shutdown via phosphorylation of eukaryotic initiation factor 2α (eIF2α). At the same time, accumulation of P-eIF2α favors selective translation of mRNAs encoding for proteins involved in cell survival, ER homeostasis and the anti-oxidant response, like ATF4 and nuclear erythroid related factor 2. The third UPR sensor, ATF6, is translocated to the Golgi apparatus, where it is cleaved by site-1 and site-2 proteases. This cleavage results in the release of a transcription factor directing expression of genes encoding ER chaperones, ERAD components and molecules involved in lipid biogenesis.

Interestingly, the UPR has emerged as a crucial regulator of immune cells [7,8]. Dendritic cells (DCs), main antigen presenting cells, are key targets of this response, and the IRE1α/XBP1s axis has shown to regulate survival and antigen presentation abilities in these cells [9•,10••,11•]. Thus, being located in the ER, it might be no surprise that the UPR intersects with major pathways of antigen processing and presentation. The aim of the current review is to identify convergence points between the IRE1α and PERK pathway and antigen presentation. We did not include the ATF6 pathway, since — mainly due to lack in good research tools — this pathway remains understudied.

IRE1α in MHC-I antigen presentation

Cytosolic antigens presented by MHC-I are primarily processed by the proteasome, a proteolytic protein complex that generates sources of peptides for MHC-I loading [12]. These peptides are imported into the ER by the transporter associated with antigen processing (TAP). Binding of peptides by newly synthesized MHC-I

molecules is facilitated by the peptide-loading complex (PLC), composed of MHC-I heavy chain and β2 microglobulin, TAP, tapasin, calreticulin and ERp57 [12]. Notably, IRE1α regulates expression of several members of the MHC-I antigen presentation pathway (Figure 2). Via XBP1s, IRE1α induces the expression of Rpn1/2, members of the regulatory subunit of 26S of the proteasome [3••]; calnexin, a chaperone assisting in folding of MHC-I molecules; and the PLC members calreticulin and Erp57, which is a target shared with ATF6 [3••,12]. Upon ER stress, XBP1s downregulates TAP1 expression indirectly, through transcriptional induction of the microRNA-346 [13]. This evidence indicates that tonic IRE1α-mediated XBP1 splicing is required to control gene expression of key members of the MHC-I antigen presentation machinery.

Importantly, to translate these findings into a productive immune synapse, these studies must be extended to DCs. This is an important issue as DC subsets display unique features regarding UPR activation that distinguish them from other cell types. First, DCs are constitutive targets of XBP1s activation across tissues [9•,10••,11•], and high expression of XBP1s is a hallmark of the cDC1 lineage of DCs [10••,11•]. Second, cDC1s are particularly sensitive to perturbations in IRE1α signaling, as it has been noticed that XBP1 deficiency leads to changes in the transcriptome and counteractivation of RIDD, which curtails their antigen cross-presentation abilities [10••]. Thus, microarray analysis of XBP1 KO cDC1s show reduced expression of reported targets related with MHC-I folding/peptide loading including Rpn1, Rpn2 and tapasin. Subsequent analysis in IRE1α KO DCs revealed that some of these genes were degraded by RIDD, activated specifically upon XBP1 loss [10••] (Figure 2). Functionally, XBP1 KO cDC1s have no general defects in protein secretion and express normal levels of MHC-I molecules, but display a reduced trend in MHC-I presentation of the endogenous male antigen H-Y [10••]. Importantly, none of these features are noticed in cDC2s indicating that the IRE1α/XBP1s axis does not operate in this cell type in steady state [10••].

While loss of XBP1s hampered MHCI presentation, enforced XBP1s expression improved the efficacy of DC vaccines in melanoma settings, by promoting presentation of transfected antigens via MHC-I/MHC-II [14,15].

These data support a model in which IRE1α RNAse emerges as a 'double-edge sword' of MHC-I antigen presentation. On one hand, IRE1α promotes gene expression of key members of the MHC-I antigen presentation machinery via induction of the transcription factor XBP1s, but under conditions promoting RIDD, IRE1α negatively regulates the process by degrading mRNAs encoding for targets of the same pathway. Thus, fine-tuning IRE1α activity may emerge as a relevant regulator of the MHC-I presentation machinery. The kinase domain of IRE1α has not been yet associated with the regulation of antigen presentation.

IRE1α in cross-presentation

Cross-presentation allows extracellular antigens that are phagocytosed or endocytosed to be presented onto MHC-I molecules. Although several cell types can cross-present, cDC1s are particularly specialized in cross-presentation *in vivo* and emerged as crucial regulators of tumor and pathogen immunity [16–20]. Cross-presentation can occur via two mechanisms: the phagosome to cytosol pathway, in which exogenous antigens are directed to phagosomes, and then exported into the cytosol for processing following the conventional proteasome-MHC-I pathway [20–22]; and the vacuolar pathway, which involves peptide loading of MHC-I directly within endosomes by a TAP-independent mechanism [20–24].

The role of the IRE1α axis in cross-presentation is still poorly understood, but preliminary evidence connects this branch predominantly with the phagosomal pathway (Figure 2). The ER is a donor of membrane and proteins to nascent phagosomes [25–29], and many reported MHC-I-related XBP1s targets (Sec61, calnexin, calreticulin, Erp57 [3••]) or RIDD targets (tapasin [10••]) are directed to phagosomes [3••,25–28]. Interestingly, the chaperone BiP, key regulator of the UPR, is also found in this compartment [30•]. Furthermore, two members of the ERGIC (ER–Golgi intermediate compartment, structure proposed to sort ER-related proteins to phagosomes) [21,28], ERGIC-53 and ERGIC-3, are regulated by XBP1s and RIDD respectively [3••,10••]; and p97, one of the few ERAD components involved in cross-presentation [31,32], is co-transcriptionally regulated by XBP1s and ATF6 [3••].

Functionally, XBP1-deficient cDC1s are unable to cross-present dead cell-associated antigens *in vitro* and *in vivo* [10••]. This defect is attributed to RIDD, and it is restored to normal levels in cells lacking IRE1α endonuclease activity [10••]. Interestingly, the two first modules of cross-presentation including uptake of particulate antigens and export of proteins into the cytosol are not affected by XBP1 ablation, indicating that this axis of the UPR operates later in the process [10••]. Among possible mechanisms are the identification of tapasin and ERGIC3 as RIDD targets, but this remains an open question [10••]. To date, it is unclear why cross-presentation does not depend on late developmental expression of XBP1s but depends on RIDD. One explanation may be related to kinetic issues, in which cross-presentation does not require *de novo* gene transcription but requires protein translation, which is directly prevented by RIDD. Along these lines, it becomes highly important to obtain proteomic data of DC subsets lacking UPR members.

At protein level, IRE1α was shown to be pre-assembled in a hetero-oligomeric complex with Sec61, the translocon that imports polypeptides into the ER and that acts as a putative export channel for antigens from phagosomes to the cytosol [33,34•,35]. Association of IRE1α with Sec61 appears to limit XBP1 splicing [34•,35,36•]. These data suggest that IRE1α may modulate cross-presentation by protein–protein interactions, extending its role beyond gene transcription or mRNA degradation. Nevertheless, the precise role of the translocon in cross-presentation needs to be fully elucidated as it was recently reported that Sec61 inhibits cross-presentation independently of antigen export into the cytosol [37]. From the UPR perspective, it is currently unknown whether the UPR sensors are present in phagosomes and if the IRE1α–Sec61 protein complex plays any role on the process. These are technically challenging questions to address due to the scarcity of cDC1s in tissues.

Despite the established connections between IRE1α and key proteins in the antigen presentation pathway, the role of XBP1 in cross-presentation remains controversial. On one hand, overexpression of XBP1s in GM-CSF DCs has shown to potentiate cross-presentation [14], but pharmacological induction of the UPR prevents it [38••]. In a model of p53/K-RAS driven ovarian cancer, activation of XBP1 in tumor associated DCs blunts cross-presentation and MHC-II antigen presentation, due to XBP1-mediated accumulation of oxidized lipid metabolites [38••,39,40]. Silencing of XBP1 in tumor CD11c expressing cells enhanced protective T cell responses and delayed tumor progression [38••]. Remarkably, this cancer type recruits predominantly CD11b$^+$ DCs (a surface marker of cDC2s [41]), which in contrast to cDC1s, do not activate RIDD upon XBP1 loss [38••]. Thus, depending on the DC lineage, the pathological setting and whether the levels of ER stress are manageable by DCs, IRE1α and XBP1s may play opposite roles on antigen presentation. Systematic work considering DC heterogeneity, and the extent of ER stress are required to elucidate the physiological settings in which this UPR branch is beneficial or detrimental to immunity. Furthermore, the type of antigen should also be carefully examined, taking into account the notion that soluble antigens can access the ER in DCs for cross-presentation [42] and also that certain pathogen toxins can invade the ER for IRE1α activation [43].

IRE1α in MHC-II antigen presentation

XBP1s was originally discovered as a regulator of MHC-II gene expression in B cells [44,45] prior to its discovery as a UPR factor. Despite this evidence, functional studies in steady state cDC1s and cDC2s show that antigen presentation in MHC-II is unaffected by XBP1 deficiency [10••]. In ovarian cancer, XBP1 ablation in DCs leads to augmented infiltration of CD4$^+$ T cells, suggesting a negative role of the pathway in CD4$^+$ T cell activation conditions of sustained ER stress [38••]. However, it remains unknown whether this scenario is altered under infection and injury, considering that sensing of microbes enhance antigen presentation [30•,46] and that IRE1α is a relevant sensor downstream of several PRRs for many aspects of innate immunity [43,47,48]

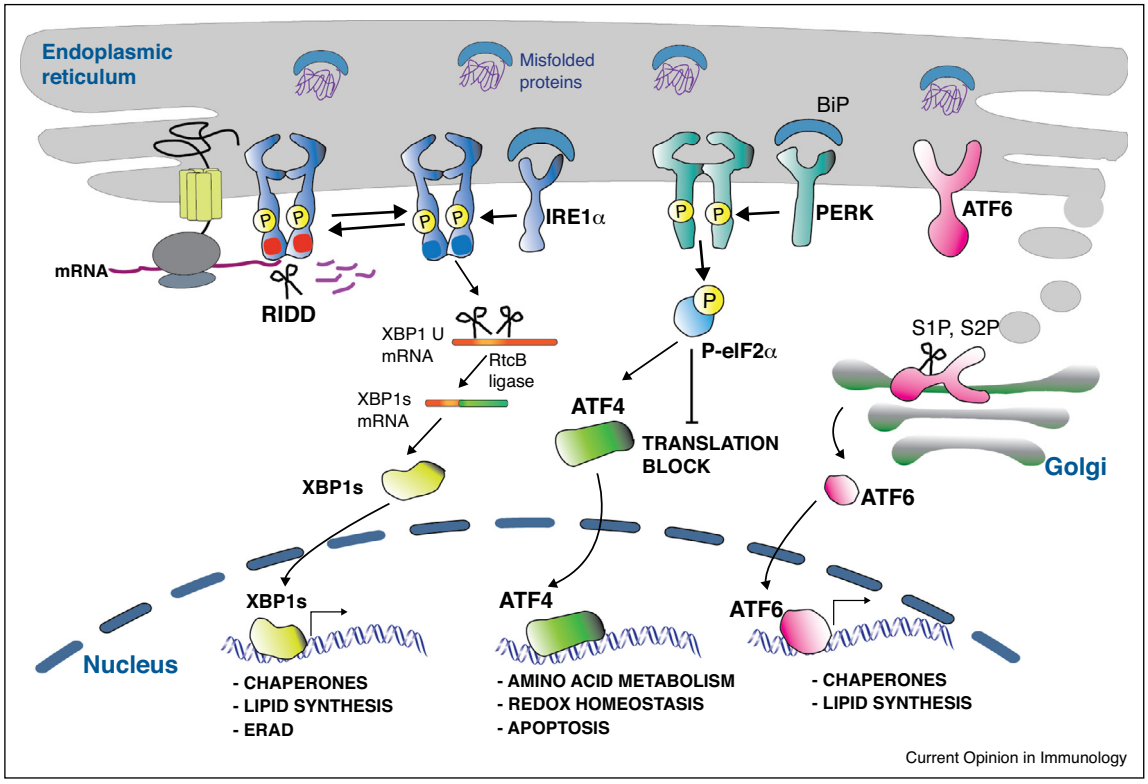
Altogether, depending on the state of activation, IRE1α regulates many steps of the antigen presentation machinery. However, the overall picture is far from complete and several issues remain to be solved. Future studies considering DC subtypes, defined inflammatory settings and quantification of adaptive versus terminal UPR are required to better understand the contribution of this pathway to DC function. Furthermore, an important challenge is to dissect whether IRE1α, as a major regulator of ER biogenesis, influences directly or indirectly antigen presentation processes. For this, it is necessary to exclude all additional aspects related to ER homeostasis that may coincidentally influence this process, including overall protein folding and survival.

The integrated stress response shapes the immunopeptidome

The discovery that most peptides presented on MHC-I molecules are derived from *de novo* protein synthesis generated through the formation of Drips (defective ribosomal products), rather than cellular turnover of proteins implicated a paradigm shift in the field of antigen presentation [49]. Similarly, evidence is accumulating that also 'cryptic' peptides can be presented, derived from antigens that are buried in non-coding regions or generated from non-AUG start codons [50,51••]. These protein products are often the result of alternative translation pathways, which become particularly prominent in conditions of stress, such as host translation inhibition or viral infection (Figure 1 and Figure 3).

Activation of the PERK branch (as well as three other kinases of different stress pathways collectively referred to as the 'integrated stress response' (ISR)) [52] (see Figure 3) induces phosphorylation of eIF2α, which not only inhibits cap-dependent protein synthesis, but also permits selective translation of mRNAs harboring upstream open reading frames (uORFs) in their 5′ untranslated region (5′ UTR). Interestingly, Starck *et al.* demonstrated that tracer peptides inserted within uORFs of the ATF4 5′UTR are processed and presented in MHC-I molecules to antigen specific T cells, a feature that appeared preserved in conditions of ER stress or oxidative stress [51••]. Also the 5′UTR of chaperones like Bip, contains uORFs that remain translated independent of canonical protein synthesis. This relies on the induction of an alternative initiation factor, the monomeric protein eIF2A, that becomes upregulated during ER stress [51••]. Importantly, this alternative translation initiation factor coordinates non-canonical leucine (CUG)

Figure 1



The unfolded protein response (UPR). The sensors IRE1α and PERK and ATF6 coordinate the UPR in mammals. IRE1α and PERK are activated upon binding of misfolded proteins and release of the chaperone BiP, which triggers their oligomerization and trans-phosphorylation. The endonuclease domain of IRE1α mediates an alternative splicing reaction of the mRNA encoding for XBP1 unspliced (XBP-1 U) to generate the mRNA encoding for its active form, XBP1 spliced (XBP1s), which is generated by religation by the RNA ligase RtcB. In addition, hyperactivation of the endonuclease activity of IRE1α also executes RIDD (regulated IRE1-dependent decay) that leads to the degradation of certain mRNAs, which are proximal to being translated at the ER. PERK phosphorylates eIF2α and induces transient inhibition of global protein translation. However, some mRNAs bearing small upstream open reading frames in their 5′ untranslated regions escape the translation shutdown; such as the mRNA encoding ATF4, which is a transcription factor that triggers expression of CHOP, GADD34 and additional factors related to amino acid metabolism and redox control. ATF6 is activated upon BiP release and in contrast with the other UPR sensors, ATF6 is translocated to the Golgi, where it undergoes sequential processing and removal of its luminal domain. The remaining transactivation domain of ATF6 moves to the nucleus and acts as a transcription factor coordinating the expression of genes encoding for molecules involved in chaperone pathways or lipid biosynthesis.

codon initiation, representing a shift in antigens and modulating T cell immune response [50].

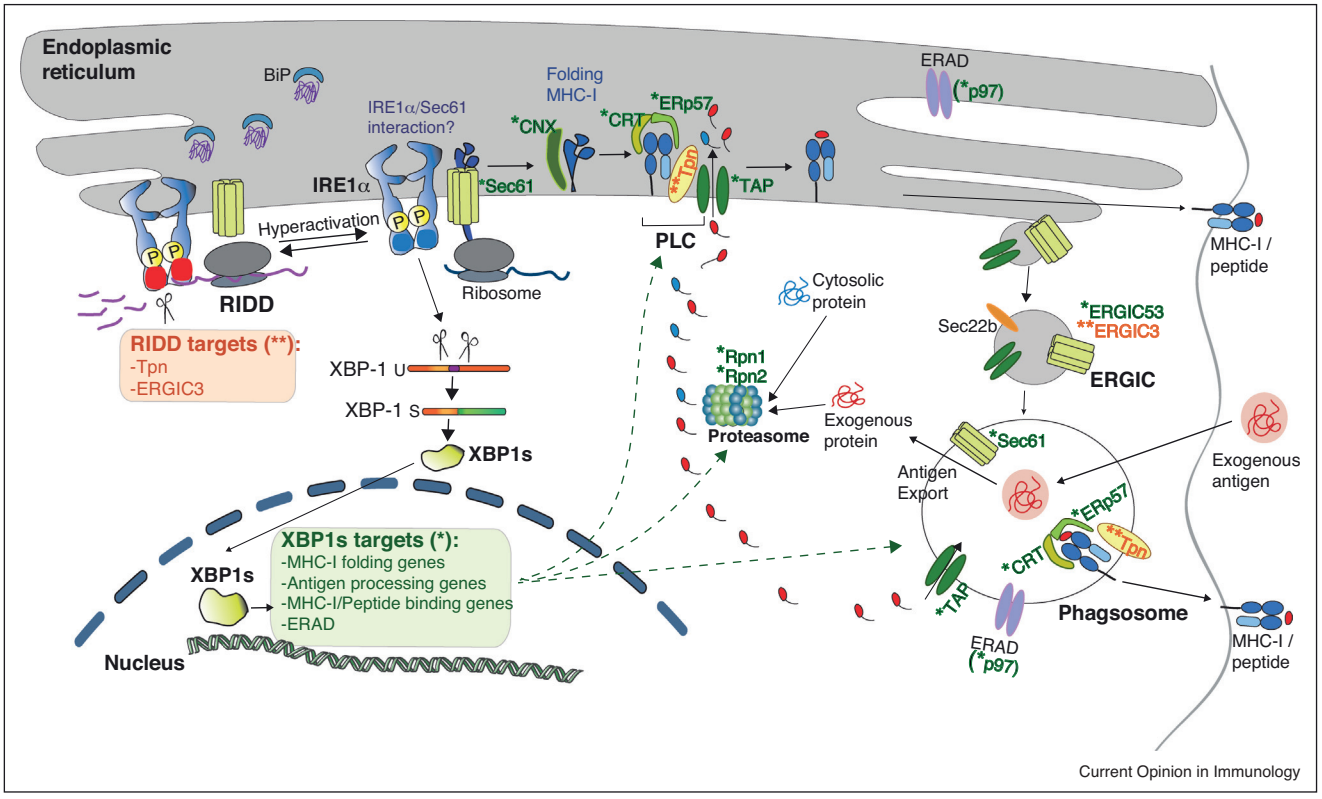
Besides the initiation of alternative translation, the ISR is also important for the induction of autophagy. A systems biology approach to determine factors contributing to the magnitude of the T cell response upon vaccination with the yellow fever vaccine YF-17D in humans marked GCN2 and autophagy as central players [53]. Atg5 and Atg7, two proteins implicated in LC3-associated phagocytosis play a crucial role in this process [53,54••]. In conclusion, while the tight link between regulation of translation, generation and preservation of peptides and antigen presentation is becoming more and more clear, we only have seen the tip of the iceberg and the coming years might bring more insights in this emerging field.

The ER as a hub to orchestrate vesicular transport

While many chaperones, and ERAD components are direct UPR targets, indirect effects of the UPR, interfering with cellular biological processes such as lipid droplet formation or organelle trafficking, are likely to influence antigen presentation.

Being the largest organelle in the cell, the ER communicates extensively with other membraneous compartments, by formation of membrane contact sites (MCS). The ER has emerged as a central hub in orchestrating lysosomal/endosomal positioning and fusion/fission [55]. Two major pools of intracellular endosomes and lysosomes can be found: a perinuclear relatively immobile cloud of vesicles localized around the microtubule-organizing center (MTOC) and a highly dynamic fraction in

Figure 2



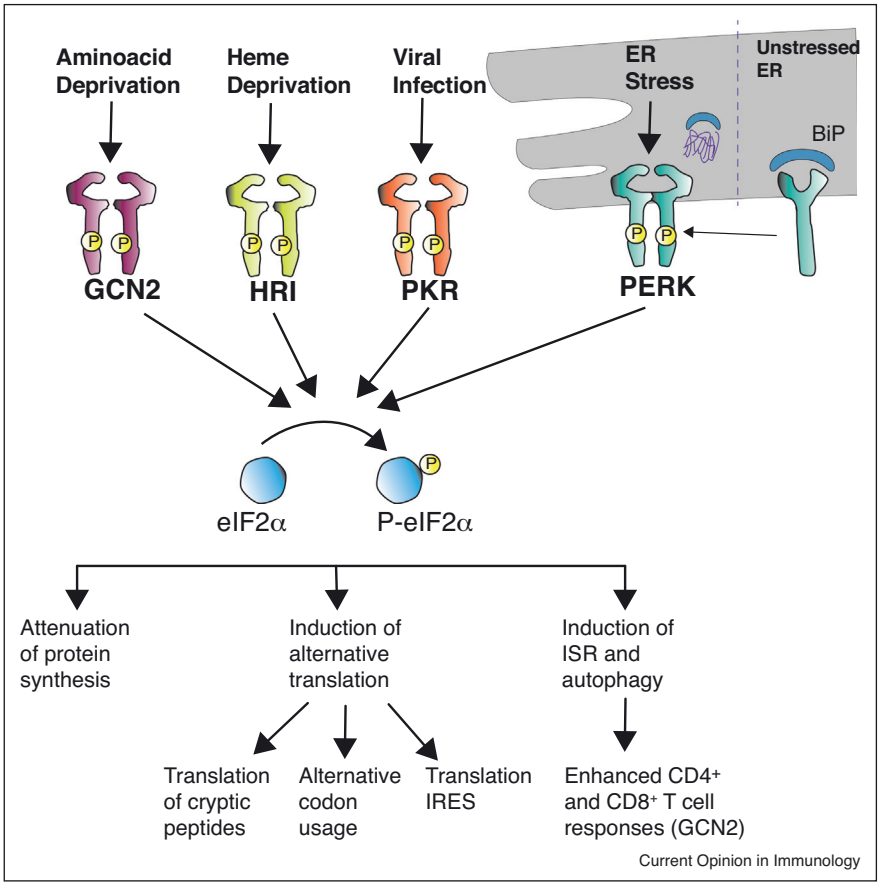
The IRE-1α/XBP1s axis in major histocompatibility complex (MHC)-I biosynthesis, MHC-I/antigenic peptide binding and antigen cross-presentation. Upon physiological ER stress, BiP dissociates from IRE1α leading to its activation. The ribonuclease domain of activated IRE1α mediates the splicing of XBP1 mRNA, which originates XBP1 spliced (XBP1s), a transcriptional regulator of genes coding for proteins involved in MHC-I folding; members of the protein loading complex (PLC) and the proteasome, the translocon Sec61, ERGIC53 of the ER to Golgi (ERGIC) compartment; and ERAD genes (p97), which can be found in the endoplasmic reticulum (ER) or in phagosomes (depicted with an asterisk in green). Alternatively, under conditions evoking RIDD (regulated IRE-1α-dependent decay), IRE1α is hyperactivated and its ribonuclease domain starts degrading ER-localized mRNAs, which include tapasin (Tpn) from the PLC and ERGIC 3 (depicted with a double asterisk, in orange).

the periphery [56]. Studies done in bone marrow derived DCs revealed that LPS-induced maturation of DCs is associated with perinuclear clustering of lysosomes around the MTOC. This prevents phago-lysosomal fusion, delays degradation of the antigen and favors cross-presentation [30•]. How activation of the UPR might interfere with these processes is still poorly understood, but it is well known that ER stress influences the formation of MCS [57]. Furthermore, lysosomal distribution and tubulation, two processes intimately associated with antigen presentation, are regulated by the so-called BORC complex. One of its central actors, Blos1, has been identified as the universal IRE1/RIDD target [58,59]. Also formation of the ERGIC complex, lipid body formation and autophagy, all processes closely intertwined with antigen presentation, appear (at least partially) controlled by members of the UPR or the ISR [60–62]. In general, the formation of different endosomal compartments, trafficking and selection of cargo for loading on MHC-I or MHC-II containing vesicles are likely to be orchestrated by ER emanating events, but fine details on how the UPR might shape these responses remain to be established.

Concluding remarks

From a narrow association with protein folding in secretory cells, the UPR is branching out as a signaling pathway with far stretching implications, also in seemingly unrelated functions such as antigen presentation. The UPR directly controls expression of several chaperones and proteins implicated in MHC-I folding, but also in antigen processing and loading. Besides, also major cellular biological processes including translational control, autophagy or regulation of endosomal and lysosomal function -all orchestrated from the UPR-, could affect the immunopeptidome and antigen presentation. Notably, being an organelle intricately involved in the control of lipid metabolic pathways, it could be possible that ER stress also alters the lipid repertoire presented on CD1d molecules. It is clear that this field is emerging, and more

Figure 3



The integrated stress response (ISR) shapes the immunopeptidome. Four eIF2α-kinases constitute the ISR: GCN2 ('general control nonderepressible 2'), HRI ('heme-regulated eIF2 kinase'), PKR ('protein kinase R') and PERK ('PKR like ER kinase'). These proteins integrate different upstream stresses, ranging from amino acid deprivation, viral infection, heme deprivation and ER stress, to jointly coordinate an ancient stress response conserved from yeast to mammals. Phosphorylation of eIF2α blunts global protein synthesis and at the same time, it allows the initiation of alternative translation pathways that rely on the use of IRES ('internal ribosomal entry site'), alternative start codons or translation of so-called cryptic peptides hidden within UTRs. This causes a shift in the immunopeptidome. Often this depends on other translation initiation factors that become prominently induced in stress conditions. Finally, the ISR (particularly via GCN2) also regulates the induction of autophagy pathways, which generally enhances antigen presentation to $CD4^+$ and $CD8^+$ T cells.

research is needed to understand its implications in homeostasis and disease.

Conflict of interest

Nothing declared.

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