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REVIEWS

Review

When Endoplasmic Reticulum Proteostasis Meets the DNA Damage Response

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Sustaining both proteome and genome integrity (GI) requires the integration of a wide range of mechanisms and signaling pathways. These comprise, in particular, the unfolded protein response (UPR) and the DNA damage response (DDR). These adaptive mechanisms take place respectively in the endoplasmic reticulum (ER) and in the nucleus. UPR and DDR alterations are associated with aging and with pathologies such as degenerative diseases, metabolic and inflammatory disorders, and cancer. We discuss the emerging signaling crosstalk between UPR stress sensors and the DDR, as well as their involvement in cancer biology.

Highlights

Alteration in the genome integrity has been associated with disruption of the endoplasmic reticulum (ER) proteostasis.

The unfolded protein response (UPR) and the DNA damage response (DDR) play important roles in the development and progression of several diseases including cancer.

The UPR sensors IRE1α, PERK, and ATF6α play a role in the response to genotoxic and ER stress in cells by interacting with DNA damage proteins (e.g., ATM, ATR, p53, p21, Chk1, and Chk2).

Crosstalk between UPR and DDR may contribute to cancer progression. Indeed, CHOP and p53 play a central role in the crosstalk between UPR and DDR.

The pharmacologic modulation of the UPR could enhance the effectiveness of chemotherapy and radiotherapy.

ER Proteostasis and DDR Pathways: Two Important Mechanisms To Maintain Cell Homeostasis

Maintenance of protein homeostasis (**proteostasis**; see Glossary) is mediated by a network of interconnected quality-control processes that ensure a functional proteome [1]. Deregulation of ER proteostasis is a common feature of several metabolic, degenerative, immunological, and neoplastic diseases [2,3]. ER proteostasis surveillance is mediated by the **unfolded protein response (UPR)**, a signal transduction pathway that senses protein biogenesis defects in the ER [2]. Likewise, the mechanisms involved in **genome integrity (GI)** maintenance can prevent inherent and sporadic genetic diseases. An evolutionarily conserved mechanism, the **DNA damage response (DDR)**, ensures GI through the recognition of DNA lesions, followed by the initiation of a signaling cascade resulting in DNA repair [4]. Recently, failure in maintaining GI was associated with ER proteostasis alteration [5–10]. In addition, some studies now support a fundamental biological function of UPR sensors in the maintenance of GI and DNA damage gene expression [11–14].

In this review we describe the UPR and DDR sensors, their mechanisms of action, and their impact on global proteostasis and DDR activation. We discuss emerging connections between the UPR and the DDR, and we focus on cancer in view of the relevance of both pathways as hallmarks of the disease.

ER Proteostasis and the UPR

The ER is the gateway to the secretory pathway through which ~30% of cellular proteins transit. Proteins acquire proper folding and conformation in the ER, thus making this compartment a key contributor to cellular proteostasis [1]. ER proteostasis disruption can be caused by (i) malfunctions of ER proteostasis control mechanisms, (ii) the accumulation of improperly folded proteins, or (iii) an imbalance between protein folding capacity and demand, that lead to a condition termed ER stress.

To cope with ER stress, the UPR, a homeostatic signaling pathway that aims at restoring ER proteostasis, is triggered to increase ER protein folding and clearance capacity or to promote cell death programs if the stress cannot be resolved (Box 1) [3,16]. Under basal conditions

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Box 1. A Deadly Relationship: UPR–DDR Crosstalk and Their Involvement in Apoptosis

In response to unresolved DNA damage and ER stress, the apoptotic program is mainly orchestrated by p53 and CHOP. Both transcription factors are upregulated as a mechanism to monitor the integrity/stability of the genome and proteome. CHOP is upregulated by the UPR [94] and is directly related to the ER stress-induced apoptosis. However, CHOP-deficient cells still undergo apoptosis, suggesting the presence of an unknown pro-death signaling pathway. CHOP promotes apoptosis by repressing antiapoptotic genes and inducing pro-apoptotic genes, such as *BAD*, *BIM*, *NOXA*, *PUMA*, and *DR5* [95,96]. p53 expression is induced by several stress signals including DNA damage and oncogene activation [97]. Moreover, p53 has several non-transcriptional functions [98,99]. Senescence, cell-cycle arrest, and apoptosis are the most prominent outcomes of p53 activity [100]. Principally, p53 engages apoptosis via transcriptional regulation of the proapoptotic proteins PUMA, BIM, NOXA, as well as of extrinsic apoptotic pathway components [101]. Interestingly, crosstalk between these two transcription factors has been described. CHOP drives MDM2 expression, promoting p53 degradation [102]. It has been linked to the function and localization of p53 as a component of the ER stress-induced apoptotic pathway. ER stress promotes p53 expression through NF-κB [103], and CHOP cooperates with FOXO3a to regulate the expression of PUMA and BIM under ER stress [43,104]. Moreover, p53 is an important mediator of ER stress-dependent apoptosis through PUMA upregulation [105]. PERK activation modifies the translation of p53 (*TP53*) mRNA from the full-length to the p53ΔN40 (p53/47) isoform and actively suppresses p21 expression during ER stress, thus promoting the G2 phase of the cell cycle [106]. During chronic ER stress, p53 induces BIK expression while at the same time suppressing BiP translation, leading to dissociation of the BIK/BiP complex and apoptosis activation [107]. p53 is located at contact sites of ER/mitochondria-associated membranes (MAMs) that modulate Ca^{2+} transfer into mitochondria [108]. Moreover, p53 regulates autophagy via the proper localization of PML protein at ER/MAMs [109]. In addition, PERK and IRE1α have been identified as components of ER/MAMs [110,111], suggesting novel interactions between the UPR sensors and p53. Finally, cancer cells are exposed to several factors that alter proteostasis. To cope with this, tumor cells engage the UPR to manage these disturbances [34]. Because p53 mutations are the most recurrent alterations in cancer, leading to resistance to stressors such as DNA damage, the selective inhibition of prosurvival UPR represents a promising intervention for p53-deficient tumors by engaging apoptosis through the induction of unresolved ER stress.

(non-stressed), it is believed that ER stress sensors are maintained in an inactive state through the binding to the ER luminal chaperone **binding immunoglobulin protein** (**BiP**), whereas the accumulation of misfolded proteins triggers BiP release from the stress sensors, thereby allowing their activation (Figure 1) [16]. Execution of the UPR results in (i) reduced levels of misfolded proteins in the ER resulting from transient attenuation of mRNA translation, (ii) improved ER folding capacity by increasing the expression of ER-resident chaperone proteins, (iii) enhanced ER protein clearance by increasing its degradation capacity (e.g., through **ER-associated degradation**, **ERAD** [17]), and (iv) enhanced export capacity (e.g., through the upregulation of the expression of several genes whose products are involved in ER cargo exit) (Figure 1) [18].

The UPR is transduced by three ER-resident proteins, IRE1α, PERK, and ATF6α, whose primary function is to activate the signaling pathways whose aim is to restore ER proteostasis [2]. However, when ER stress cannot be resolved, these UPR sensors activate death signaling pathways (Box 1) [1]. IRE1α is a type I transmembrane protein, that exhibits kinase and endoRNase activities in its cytosolic domain. Under ER stress, IRE1α oligomerizes and then *trans*-autophosphorylates, which triggers a conformational change that activates the RNase domain. IRE1α RNase activation, together with the tRNA ligase RTCB, induces non-conventional splicing of X-box binding protein 1 (XBP1) mRNA, [2,19–21]. The spliced XBP1 mRNA encodes the transcription factor XBP1s which promotes the transcription of several genes whose products are involved in the ER proteostasis, such as foldases, oxidoreductases, and ERAD components (Figure 1) [2,15]. Alternatively, IRE1α RNase degrades multiple mRNAs and miRNAs in a sequence-specific process termed regulated IRE1α-dependent decay (RIDD) of RNA [22]. Although RIDD activity has been proposed to be necessary for the maintenance of ER homeostasis [23,24] as well as for the pathogenesis of diabetes [25], cancer [26], and inflammatory conditions [27,28], the majority of the available evidence is difficult to interpret because of concomitant activation of *Xbp1* mRNA splicing and RIDD activity.

Glossary

Binding immunoglobulin protein (BiP): a key endoplasmic reticulum (ER) chaperone and master regulator of ER functions under ER stress. The detection of misfolded proteins by the three UPR sensors is partly dependent on BiP.
Cell-extrinsic factor: any factor that is independent of the genetic background or DNA alterations, such as hypoxia, glucose deprivation, and inadequate amino acid supplies.
Cell-intrinsic factor: any factor that is dependent on the genetic background or DNA, such as oncogene activation, chromosome number alterations, chromosome rearrangements, and hyperploidy.
DNA damage response (DDR): a cellular response that involves DNA damage recognition, followed by the initiation of a cellular signaling cascade that promotes DNA repair and can modulate cell-cycle progression, chromatin structure, and transcription both at sites of DNA damage and globally. The DDR induced by DSBs is controlled by three related kinases: ataxia-telangiectasia mutated (ATM), ATM and Rad3-related (ATR), and DNA-dependent protein kinase (DNA-PKcs).
DNA double-strand breaks (DSB): different classes of DNA damage such as UV light, radiation, DNA-damaging drugs, and oxidative stress can lead to DNA rupture in both strands. If DNA is not repaired correctly, DSBs can cause deletions, translocations, and fusions of the DNA.
ER-associated degradation (ERAD): the principal quality-control mechanism that targets misfolded ER proteins for cytosolic degradation. ERAD targets are destroyed by the cytoplasmic ubiquitin–proteasome system. Many ER chaperones participate in the ERAD complex, including BiP, EDEM1, OS9, and XTP3B. The UPR sensor IRE1α and SEL1L– HRD1 complexes are the two most conserved branches of ER quality-control mechanisms.
Genome integrity (GI): includes all processes that maintain the integrity of DNA, such as sensing, signaling, and repair of DNA damage, processing of DNA damage in the context of chromatin and chromosomes, cell-cycle checkpoint control, and apoptosis control. Effective maintenance of GI is essential for healthy organisms, in aging, and for disease prevention.

PERK is a ubiquitously expressed type I transmembrane serine/threonine kinase. Under ER stress, PERK oligomerizes and *trans*-autophosphorylates to acquire full kinase catalytic activity and to phosphorylate the eukaryotic translation initiator factor 2 (eIF2α), thereby attenuating general protein synthesis [2,29]. This limits the entry of newly synthesized proteins in the ER while allowing the selective translation of a growing set of specific mRNAs such as those encoding activating transcription factor 4 (ATF4), a transcription factor that promotes the antioxidant response, amino acid metabolism, ER folding capacity, and upregulation of macroautophagy, and therefore has an important prosurvival role (Figure 1) [2]. In addition, ATF4 expression engages the apoptotic program through the expression of CHOP protein (also known as GADD153), a transcription factor that upregulates the proapoptotic members of the BCL-2 family and GADD34 (Box 1) [2,30].

ATF6α is a single-pass type II transmembrane protein located in the ER under resting conditions. ATF6α bears a bZIP transcription factor on its cytosolic domain that is released upon ER stress [2,31]. The accumulation of improperly folded proteins in the ER causes ATF6α to be exported to the Golgi apparatus and processed by the S1P and S2P proteases [15]. This process mainly leads to the release of the cytosolic fragment domain of ATF6α [15]. In the nucleus, the ATF6α cytosolic domain, simultaneously with XBP1s, upregulates the expression of CHOP and other genes involved in the regulation of ER size, protein-folding capacity, and the ERAD (Figure 1) [32,33].

Remarkably, reprogramming of UPR signaling has been linked to the acquisition of several distinctive hallmarks of cancer [34]. Tumor cells are exposed to several **cell-extrinsic** and **cell-intrinsic** perturbations that promote selective pressure to engage UPR signaling [18,34]. In general, IRE1α and PERK signaling contribute to cancer progression by promoting tumor growth and cell survival in different type of tumors [26,35–38]. However, only a few studies link ATF6α activity and cancer. The expression of ATF6α is elevated in colorectal cancer but not in normal mucosa [39], and its expression correlates with poor prognosis [40]. In human epidermoid carcinoma cells, ATF6α signaling increases Rheb expression, which in turn activates mTOR signaling (Figure 2) [41]. In addition, protein disulfide isomerase 5 (PDIA5)-dependent activation of ATF6α was described to be instrumental in the acquisition of imatinib resistance in chronic myeloid leukemia (Figure 2) [42]. Although the role of UPR signaling in tumor biology is supported by strong evidence [34,38,43], the specific molecular relationship to genomic instability has not been studied in depth.

GI and the DDR

Preservation of GI presents a challenge because DNA is constantly exposed to endogenous and exogenous sources of damage. To ensure genome protection, cells have evolved mechanisms to detect and repair DNA lesions, namely the DDR. The DDR comprises different pathways that can be triggered either by single-strand breaks (SSBs) or **DNA double-strand breaks (DSBs)**. These damages are repaired by specific mechanisms (e.g., mismatch-mediated repair (MMR); nucleotide excision repair, (NER); or base excision repair, (BER) for SSBs; non-homologous end -joining, (NHEJ); and homologous recombination, (HR) for DSBs) [44].

DSBs are one of the most harmful injuries to the genome [4]. Failure of DSB repair contributes to the genomic instability that drives cancer development [4,45]. The response to DSBs is controlled by three kinases that are members of the phosphoinositide 3-kinase (PI3K)-related kinases family: **ATM**, **ATR,** and **DNA-PKcs** [4]. These kinases coordinate the phosphorylation of numerous proteins, ultimately regulating a broad spectrum of cellular processes such as DNA replication and repair, cell-cycle progression regulation, and apoptosis or senescence initiation (Figure 1) [46]. Depending on the mechanisms inducing DSBs and the cellular context, different kinase pathways

H2AX phosphorylation (γH2AX): upon DSB induction, the histone variant H2AX is phosphorylated on serine 139 by ATM, ATR, or DNA-PK, generating phosphorylated H2AX, namely γH2AX. γH2AX induction is one of the earliest events detected in cells and human biopsies following exposure to DNA damaging agents. γH2AX is a key marker of DSB damage, allowing the activation and relocalization of repair proteins to DSB sites as well as signal amplification.

Oxidative stress: imbalance between the production of reactive oxygen species (ROS, free radicals) and antioxidant defenses. Amino acids such as proline, arginine, lysine, and threonine are particularly vulnerable to oxidative damage, both as free molecules or within proteins. Moreover, oxidative damage can also affect the integrity and stability of DNA and RNA.

Proteostasis: a network of interconnected quality-control processes in the cell that maintain a functional proteome. Chaperones, foldases, oxidoreductases, and glycosylating enzymes ensure that secretory proteins are properly folded, modified, and assembled into multiprotein complexes in the ER before they transit further downstream in the secretory pathway.

Unfolded protein response (UPR): a signal transduction pathway that senses the fidelity of protein folding in the ER lumen. The UPR transmits information about protein folding status to the nucleus and cytosol to adjust the protein folding capacity of the cell. The UPR is transduced by three principal ER-resident proteins: inositol-requiring protein 1α (IRE1α), PKR-like ER kinase (PERK), and activating transcription factor 6α (ATF6α).

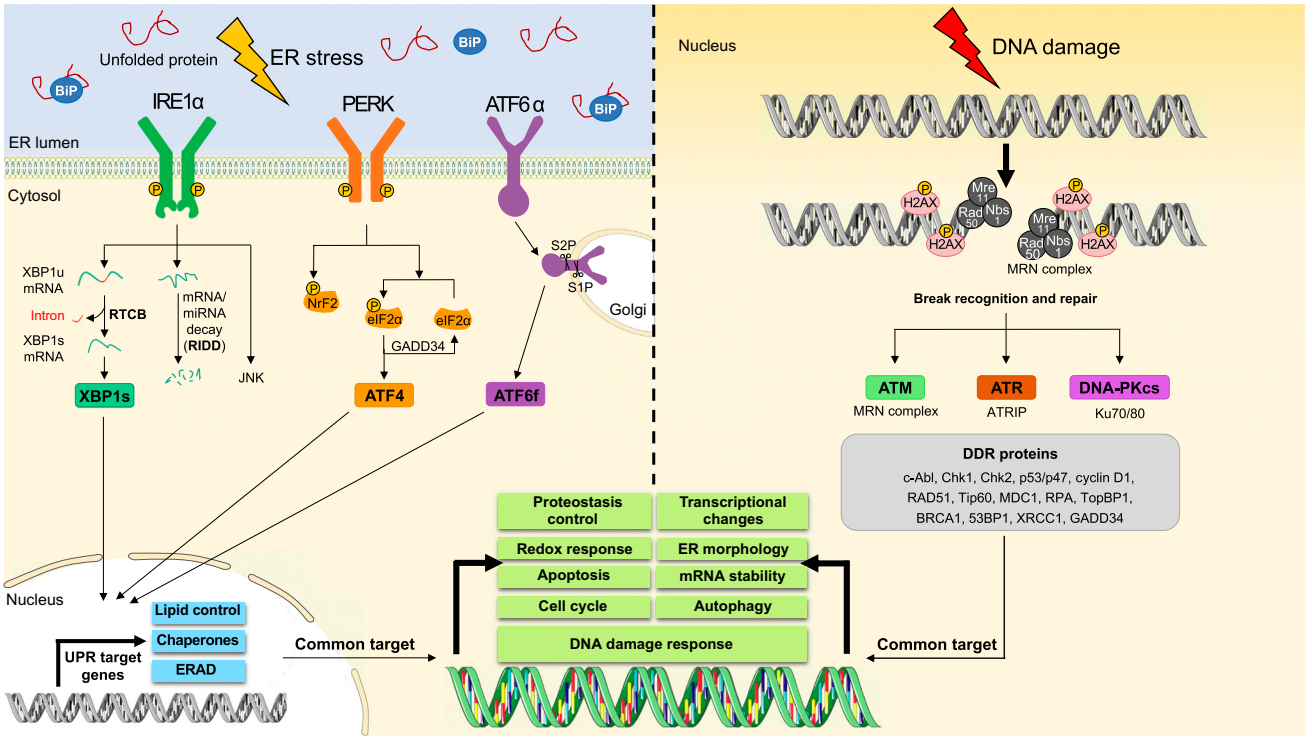

Figure 1. Unfolded Protein Response (UPR) and DNA Damage Sensors. All three ER stress sensors (PERK, IRE1α, and ATF6) are localized at the ER membrane, and under ER stress they activate signaling events that increase protein-folding capacity and reduce protein load on the ER. In response to DNA damage, ATM is activated and recruited to DSBs by the MRE11–RAD50–NBS1 complex, and ATR is recruited to RPA-coated single-stranded DNA by its binding partner ATRIP. DNA-PKcs, meanwhile, is recruited and activated by Ku-bound DSB ends. The UPR transcription factors and DNA damage proteins determine cell fate by regulating distinct subsets of target genes that govern the recovery of ER homeostasis and the DDR. The green boxes depict the common targets and functions induced by ER stress and genotoxic stress. The blue boxes depict UPR functions that are induced by ER stress. The gray box depicts DDR proteins involved in the UPR. Abbreviations: ER, endoplasmic reticulum; DDR, DNA damage response; DSB, double-strand break; P, phosphorylation. This figure was created using Servier Medical Art templates licensed under a Creative Commons Attribution 3.0 Unported License.

are favored, such as ATM–Chk2 signaling together with the MRE11–RAD50–NBS1 (MRN) complex [4]. ATR–Chk1 is recruited and activated to DSBs by single-stranded DNA coated with replication protein A (RPA) together with its partner ATR-interacting protein (ATRIP) [4]. The MRN complex is recruited to DNA DSBs immediately after their occurrence, recruiting ATM to the chromatin and stimulating its kinase activity [4]. ATM activates a widespread DSB signaling cascade that begins with **H2AX phosphorylation** (γH2AX). γH2AX is a marker of DNA damage, its phosphorylation is one of the first responses to a DSB, and the intensity of the response is proportional to the number and size of DSB foci [47]. Chk2 is activated by ATM and redistributed throughout the nucleus where it functions together with Chk1 in the cell-cycle checkpoint signaling network and DNA repair [48]. Chk1 activation after DNA damage is a key function of ATR because activated Chk1 is essential for S and G2/M phase cell-cycle regulation [4]. The activation of Chk1 and Chk2 induces the phosphorylation of transcription factor p53 and subsequent transcription of p53 target genes [49,50]. These cellular mechanisms are crucial for the maintenance of GI and prevention of diseases.

UPR and DDR Signaling in GI

Maintaining GI is crucial to prevent diseases such as cancer, but once cancer occurs cancer cells exploit cellular mechanisms to promote their own survival. Genotoxic stress is key to most cancer

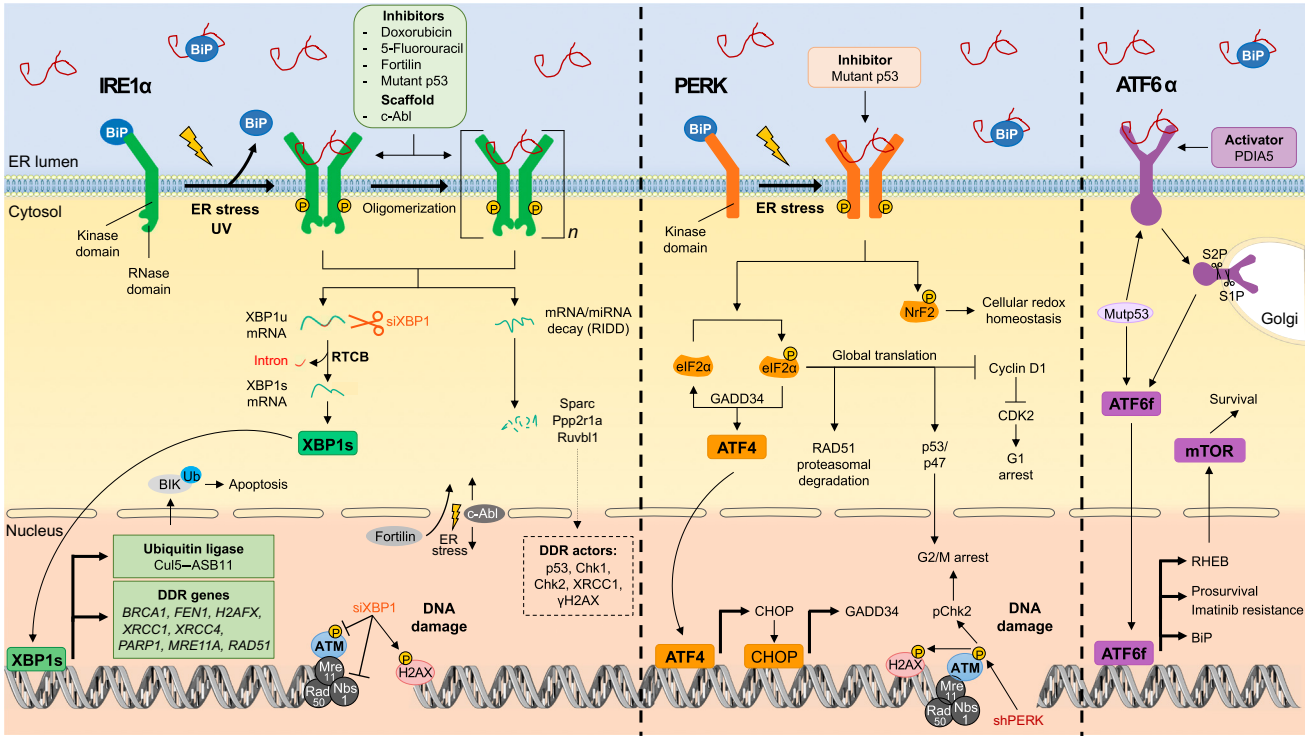

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Figure 2. Unfolded Protein Response (UPR) Sensors Involved in the DNA Damage Response (DDR). IRE1α is maintained in a repressed state through an association with BiP. Upon endoplasmic reticulum (ER) or genotoxic stress, misfolded proteins dock to BiP, thus triggering dissociation from IRE1α. This triggers IRE1α dimerization and *trans*-autophosphorylation that cause its activation. IRE1α may also bind to misfolded proteins, leading to its oligomerization. IRE1α promotes *XBP1* mRNA splicing and regulated IRE1α-dependent decay (RIDD) of mRNAs. Transcription factor XBP1s notably governs the expression of genes involved in the DDR as well as ubiquitin ligases. RIDD activity governs mRNA expression and thus impacts on DDR proteins. IRE1α activity can be modulated by fortilin, c-Abl, p53, doxorubicin, and 5-fluorouracil. Knockdown of XBP1 reduces ATM phosphorylation, MRN complex expression, and increases γH2AX. The mechanism of PERK repression and activation is the same as for IRE1α. Activated PERK phosphorylates eIF2α, which in turn shuts down global translation and concomitantly increases the expression of transcription factor ATF4. The arrest of global translation impact son Rad51, p47, and p53 and also inhibits cyclin D1 expression, ultimately dysregulating the G1 and G2/M cell-cycle phases. ATF4 transcription factor binds to CHOP itself, thus inducing *GADD34* transcription and creating a feedback mechanism. PERK silencing increases phospho-ATM, thus triggering γH2AX and Chk2 activation and impacting on the cell cycle. ATF6 is exported from the ER to the Golgi where it is cleaved by S1P and S2P proteases, allowing release of its cytosolic domain, which is a potent transcription factor named ATF6f. PDIA5 and mutant p53 increase ATF6 activity, promoting imatinib resistance in cancer and allowing RHEB expression and mTOR signaling. Abbreviations: mutp53, mutant p53; P, phosphorylation; Ub, ubiquitination. This figure was created using Servier Medical Art templates licensed under a Creative Commons Attribution 3.0 Unported License.

treatments because the collapse of DDR activation and DNA repair mechanisms triggers cell death [51,52]. Interestingly, in patients with a poor prognosis there is a significant correlation between higher BiP expression and chemoresistance [18,38]. Moreover, in a panel of cancer cell lines, genotoxic drugs promote changes in ER structure in a process mediated by transcriptional activation of p53 (one of the main tumor-suppressors and a key player in the DDR, Box 1), which upregulates the expression of receptor expression-enhancing proteins 1 and 2 (REEP1/2) and p53-induced gene 8 (PIG8), three ER-shaping proteins [53].

To date few lines of evidence connect the UPR and SSB repair. Among them, HMGB1, a protein mainly involved in MMR and BER, was shown to be associated with the UPR after ER stress in Huntington's disease. Nonetheless, this link was revealed using a bioinformatic analysis and thus should be confirmed experimentally [54]. In addition, the key BER protein, APEX1, was shown to be induced at the transcriptional level by ER stress in human hepatoma cancer cells [55]. Lastly, ChIP-seq experiments revealed that XBP1s binds to the promoter region of several

BER, MMR, and NER genes [12,56]. In summary, the links between the UPR and SSBs are mainly due to transcriptional control of DDR genes (*BRCA1*, *FEN1*, *H2AFX*, *XRCC1*, *XRCC4*, *PARP1*, *MRE11A*, and *RAD51*) by UPR sensors or ER stress stimuli (Figure 2). Aside from this compilation of evidence, most of the links are found to be established upon DSB repair, highlighting the important role of this mechanism in the DDR and UPR proteostasis.

ATM was recently shown to differentially regulate proteostasis under DNA damage conditions and **oxidative stress** in human osteosarcoma cells. Oxidative stress is a natural biological process to which all cells are subjected, and occurs in many different pathologies such as degenerative, metabolic, immunological diseases, and cancer [57]. In *C. elegans*, it has been observed that the collapse of proteostasis, associated with the accumulation and aggregation of misfolded proteins, is directly associated with oxidative stress that is characteristic of aging [58]. Indeed, the expression of mutated forms of ATM that are resistant to oxidative stress has a slight effect on the DDR, but favors the clearance of toxic protein aggregates [6]. Loss of ATM function under conditions of oxidative damage causes wide cellular stress because ATM functions are not limited to its participation in DNA repair or in a specific cellular compartment [6,59]. It is possible to speculate that, under physiological conditions, ATM plays a role as an oxidative stress sensor, additionally sensing alterations in other cell compartments including the ER [10,60]. Accordingly, in *S. cerevisiae*, the ATM/ATR ortholog, Mec1, is a key component of the signaling network that promotes survival in response to proteotoxic stress [61]. Mec1 regulates the expression of genes linked to proteostasis, and its inactivation leads to widespread protein aggregation and cell death [61]. Interestingly, protein aggregation is resolved by the activation of autophagy, which facilitates aggregate clearance [61]. Similarly, in mouse fibroblasts, inhibition of chaperone-mediated autophagy leads to hyperphosphorylation and destabilization of the MRN complex and regulated degradation of Chk1 protein [62]. This suggests that autophagy may contribute to GI by ensuring nuclear proteostasis (Figure 1). It has been demonstrated that alterations in the functionality of DDR proteins (e.g., ATM) correlate with several pathologies other than cancer, such as neurodegenerative syndromes [63,64] and systemic autoimmune diseases [65–67].

UPR Sensors in the DDR

Several studies have reported functional links between UPR and DDR signaling. We detail in the following text the most recent studies in the field, mainly associated with the roles of the sensors IRE1α and PERK.

IRE1α Signaling

In *S. cerevisiae*, exogenous expression of mammalian XBP1 was found to play a role in NHEJ DSB repair pathway through the regulation of H4 acetylation [68]. Initially, the regulatory network governed by Xbp1s was studied in mouse plasma, pancreatic β, and skeletal myotube cells, revealing that Xbp1s regulates the transcription of a cluster of DNA repair genes under ER stress [56]. Similar experiments were performed in human hepatic cells confirming that XBP1s directly controls the transcription of multiple DDR genes and the levels of γH2AX (Figure 2) [12]. Moreover, silencing of XBP1s causes an increase in the formation of γH2AX foci as well as a reduction in the expression of MRN complex proteins and ATM phosphorylation (Figure 2), suggesting that increased DNA damage is coupled to a reduction in damage recognition and processing [69]. XBP1s is not only involved in the regulation of DDR genes but is also directly linked to genotoxic stress response (Figure 2). In human oropharyngeal carcinoma cells, UV irradiation increases the phosphorylation of IRE1α and the expression of XBP1s, thereby triggering an increase in interleukin-6 expression [69]. In addition, in human colorectal cancer cells, exposure to genotoxic drugs, such as doxorubicin and 5-fluorouracil, was found to reduce IRE1α expression and *XBP1* mRNA splicing in a p53-dependent manner [70]. However, these

results should be interpreted with caution because genotoxic stress-induced phenotypes are diverse, and the responses depend on the cell type and the agent used. XBP1s regulates the expression of Cul5–ASB11, a ubiquitin ligase targeting BIK, a proapoptotic protein [70]. Decreased XBP1s expression reduces the level of Cul5–ASB11 and increases the expression of BIK protein in response to DNA damage. This leads to increased apoptosis, whereas apoptosis is prevented under ER stress [70]. Consequently, the ubiquitination and degradation of BIK regulates cell fate in opposite ways depending on the stress conditions (Figure 2) [70]. It is important to note that, in human multiple myeloma cell lines, doxorubicin has been proposed as a pharmacological inhibitor of IRE1α because it reduces *XBP1* mRNA splicing and RIDD activity, which in turns lead to decreased cell survival [71,72]. This could extend the hypothesis that some genotoxic drugs could also act as pharmacological inhibitors of IRE1α in cells such as multiple myeloma [71], colorectal cancer [70], and triple-negative breast cancer [36].

The activity of UPR stress sensors can be regulated by their binding to cofactors (activators and inhibitors), in addition to post-translational modifications [15]. The concept of the UPRosome emerged to visualize UPR stress sensors as platforms onto which different components assemble not only to generate composite signals but also to crosstalk with other signaling pathways to regulate various cellular processes [73]. An example of these multiple interactions is provided by fortilin, a prosurvival molecule that acts through p53 to inhibit ER stress-induced cell death [74]. Fortilin directly interacts with IRE1α, inhibiting its kinase and endoRNase domains [74]. Moreover, fortilin silencing increases the expression of XBP1s, which is associated with increased DNA fragmentation and apoptosis *in vivo*. This suggests that XBP1s expression increases DNA damage signaling and modulates the expression of DNA repair genes (Figure 2) [56,74].

A novel IRE1α function associated with the decay of mRNA encoding proteins involved in DDR has recently been identified. In mouse embryonic fibroblasts, genotoxic drugs exclusively engaged RIDD activity in the absence of *Xbp1* mRNA splicing [11]. In this model, IRE1α deficiency impairs the ability to repair the genome following DNA damage, thus disrupting cell-cycle control and the phosphorylation of checkpoint kinases and histone H2AX [11]. At the molecular level, DNA damage triggers the activation of c-Abl tyrosine kinase that operates as a scaffold protein to stabilize IRE1α oligomers and to favor RIDD activity [11]. The role IRE1α activity in controlling the DDR through RIDD was also validated in fly and mouse models, highlighting a relevant role for this UPR signaling branch in sustaining cell survival and DNA repair in response to genotoxic stress [11]. In addition, RIDD activity may play protective roles in glioblastoma, *in vitro* assay some mRNA that encode for proteins related with DNA damage, can be cleaved by the endonuclease domains of IRE1α [26]. These studies highlight the new findings regarding the RNase activity of IRE1α and its role under pathological conditions, where XBP1s promotes cell death whereas RIDD enables cell survival [26].

PERK Signaling

A direct molecular relationship between PERK and GI is not well documented. However, the activation of PERK–p-eIF2α–ATF4 signaling by SSBs was recently described to support cell survival under nutrient-restricted conditions [75]. Because the PERK–NRF2 branch contributes to the transcriptional regulation of several genes that mediate the antioxidant response, its alteration has been associated with increased levels of reactive oxygen species (ROS) following ER stress and the accumulation of oxidative DNA lesions [76]. Downregulation of PERK in human breast cancer cells correlates with increased global phosphorylation of ATM as well as increased phosphorylation of its downstream effector Chk2, leading to an increase in γH2AX (Figure 2) [77]. It is interesting to highlight that, as discussed in the previous section, XBP1s downregulation causes an increase in γH2AX foci but triggers a reduction in ATM phosphorylation [69]. Loss of PERK

significant attenuates tumor cell proliferation via increased oxidative DNA damage, leading to G2/M cell-cycle checkpoint activation [77]. Under ER stress, PERK activation has been shown to negatively regulate DNA replication in the absence of DNA damage markers via phosphorylation of the adaptor protein claspin and Chk1 activation [14]. Suppression of general protein translation by eIF2α phosphorylation reduces cyclin D1 synthesis, leading to reduced activity of the cyclin D1–CDK4 complex followed by inhibition of CDK2, hence ensuring cell-cycle arrest at G1 phase (Figure 2) [78]. Under ER stress, PERK activity induces the expression of p47, a truncated p53 isoform, which in turn triggers the upregulation of 14-3-3σ proteins that target the phosphatase CDC25. This prevents activation of the cyclin B/CDK1 complex and promotes G2/M arrest, facilitating ER stress resolution by acting in conjunction with PERK to repress protein synthesis and ER protein load [79,80]. Interestingly, PERK signaling promotes radioresistance in human breast and lung cancer cells by increasing DSB repair signaling [81,82], and promotes chemoresistance in human colon cancer cells via the PERK/NRF2/MRP1 axis [83]. These data open the possibility that PERK inhibitors could potentially be used as a chemosensitization treatment [83].

ATF6α Signaling

In a human breast cancer cell model, expression of mutant p53 was shown to enhance the prosurvival activity of ATF6α and to inhibit both the IRE1α and PERK branches, dampening activation of CHOP and c-Jun N-terminal kinases (JNKs) [13]. This selective activation is necessary for cell invasion, migration, and survival [13]. Furthermore, p53 mutants exhibit increased ATF6α activity (Figure 2) [13]. In addition, ATF6α expression and the engagement of senescence have been described in cells subjected to oncogene activation or UV irradiation [84]. Finally, ATF6α expression was shown to contribute to radioresistance in glioblastoma cells by upregulating BiP expression (Figure 2) [85]. Nevertheless, the signaling crosstalk between ATF6α and the DDR and its regulation is not fully characterized, and further experimental evidence will be necessary to elucidate how this UPR branch interacts with the cellular machinery in charge of genome stability.

Most reports available to date focus on the roles of IRE1α and PERK as transcriptional regulators of genes encoding DNA damage proteins, which in turn modulate processes such as cell-cycle progression and apoptosis engagement that impact on cell fate. The accumulated evidence points towards a direct molecular interconnection between ER proteostasis and DNA damage surveillance, opening an exciting new field of research to explore the reciprocal and bilateral regulatory interactions between these two homeostatic signaling pathways.

Concluding Remarks

Several reports have recently pointed towards interactions between the UPR and the DDR. This suggests a relationship between the ER stress signaling and DNA damage and repair pathways, but the significance of these observations for disease onset is unknown, and important issues remain to be clarified (see Outstanding Questions). Furthermore, new insights about the role of UPR sensors in the maintenance of GI open up new perspectives regarding therapeutic targets. A library of chemotherapeutic compounds (>80 compounds) was recently shown to induce immunogenic cell death through PERK and IRE1α activation. Future research will be necessary to evaluate additional markers of UPR activation in cancer cells [86] following exposure to radiotherapy or chemotherapeutic drugs such as etoposide, doxorubicin, oxaliplatin, paclitaxel, or temozolomide – given their extensive use as standard of care in tumor management. Moreover, administration of these drugs is associated with IRE1α activation in some cancer models [11,26,71,87,88]. Finally, it is necessary to explore new models to study the UPR and chemotherapeutic responses in cancer. Currently, solid tumors are a

Outstanding Questions

Do DDR associated proteins participate in UPR signaling and regulation?

Could the UPR impact on chemotherapy- or radiotherapy-induced genotoxic stress and therefore modulate the response to cancer treatment?

Post-translational modifications such as ubiquitination are crucial for DDR signaling. Does the UPR interfere with DDR protein stability by modulating post-translational modifications?

What are the most relevant cancer models for studying the UPR and its effects on the DDR?

suitable model for studying the effects of UPR activation in cancer. These types of models have been useful for addressing the role of the UPR in cancer, but confounding factors such as metabolic stress, hypoxia, and drug availability will always be a limitation. Furthermore, it would be interesting to study UPR and cancer in suspended or anchor-free cell models. In these models, current work is exploring the link between UPR and the immune response [89–91], leaving aside the role of chemotherapy or radiotherapy. Indeed, the use of anchor-free cancer cells and the generation of UPR sensor knockout cells can avoid confounding factors. However, anchor-free cell models also have limitations related to the expression of surface antigens or damage-associated molecular patterns (DAMPs) that could be regulated by the UPR under DNA damage conditions.

The identification of a fundamental biological function for mRNA decay in the maintenance of GI represents a unique example of selective and specific activation of RIDD activity that has clear physiological implications. Remarkably, IRE1α is frequently affected by loss-of-function mutations in various types of cancer [38], contrasting with the notion that cancer cells depend on IRE1α to survive in hypoxic conditions [34,90]. We speculate that the genetic alterations in IRE1α seen in cancer may synergize with oncogenes to promote genomic instability. Overall, a direct interconnection is emerging between the pathways that ensure the integrity of the proteome and the genome. It will be necessary to explore in depth how the UPR regulates gene expression, ribosome profile, and protein expression in the context of genotoxic stress using different multiomic strategies [92,93] to evaluate the global modulation of the DNA damage response. As evidenced in this review, the crosstalk between the UPR and the DDR is of great interest in the context of UPR biology, especially but not exclusively in cancer biology and treatment.

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