Am J Cancer Res 2022;12(5):2277-2292
www.ajcr.us /ISSN:2156-6976/ajcr0142662

Review Article

The role and therapeutic implication of endoplasmic reticulum stress in inflammatory cancer transformation

Yuan Li*, Lu Lu*, Guangtao Zhang, Guang Ji, Hanchen Xu

*Institute of Digestive Diseases, Longhua Hospital, Shanghai University of Traditional Chinese Medicine, Shanghai 200032, China. *Equal contributors.*

Received March 3, 2022; Accepted May 2, 2022; Epub May 15, 2022; Published May 30, 2022

Abstract: Endoplasmic reticulum (ER) stress occurs when proteins are affected by various factors, fail to fold properly into higher structures and accumulate in the lumen of the ER, which activates the unfolded protein response (UPR) to restore normal cellular function or induce apoptosis as a self-protective mechanism. However, a growing number of studies have shown that the three branches of ER stress and the UPR can mediate inflammation and cancer development by interacting with inflammatory transformation-related signaling pathways. Targeting the UPR, especially the use of small molecules that target the active sites of the enzymes IRE1α and PERK and BIP/GRP78 inhibitors are potential strategies for treating tumors and have shown promising results in some tumor models. Therefore, in this review, we summarize the progress of ER stress/UPR research and the signaling pathways associated with inflammatory cancer transformation, provide an in-depth description of the mechanisms of these pathways, and outline strategies in the field of UPR biology in tumor therapy to provide new ideas for the mechanisms of inflammatory cancer transformation and tumor-related treatment.

Keywords: ER stress, inflammatory cancer transformation, targeted therapy, unfolded protein response

Introduction

The endoplasmic reticulum (ER) has essential cellular functions, including the synthesis and folding of secreted and transmembrane proteins, calcium storage, and lipid synthesis for membrane biogenesis or energy storage. Disruption of any of these functions leads to ER stress and subsequent activation of an elaborate network of adaptive responses that are collectively known as the unfolded protein response (UPR). The UPR re-establishes homeostasis in vivo through transcriptional and translational control, and the UPR signals through three mechanistically distinct branches that are initiated by the ER-resident protein folding sensor inositol-requiring enzyme 1 (IRE1), protein kinase RNA-like endoplasmic reticulum kinase (PERK), and activating transcription factor 6 (ATF6) [1]. However, protein folding is an error-prone process and is therefore tightly regulated by many molecular chaperones and enzymes [2, 3]. Normally, three trans-ER membrane proteins bind specifically to the molecular chaperone heavy chain binding protein/glucose regulatory protein 78 κDa (BIP/GRP78) in the ER lumen [4], and when ER stress occurs, BIP/GRP78 dissociates, binds to unfolded or misfolded proteins in the lumen to aid in correct folding and triggers downstream pathways and effector mechanisms that remodel the ER to restore homeostasis in vivo [5, 6]. However, the UPR is not always effective in regulating ER homeostasis [7], and if stress persists, it leads to ER dysfunction, which activates relevant apoptotic pathways and mediates cell death [8].

Multiple pro-inflammatory signaling pathways are involved in the transformation of inflammation to cancer: aberrant and sustained activation of nuclear factor-κB (NF-κB) signaling promotes the malignant transformation of inflammation to cancer, and NF-κB induces the production of cytokines that regulate the immune response (e.g., TNF-α, IL-1, IL-6 and IL-8), as well as adhesion molecules that recruit leukocytes to sites of inflammation [9]. In addition, NF-κB

may also control the transformation and metastasis of epithelial cells to mesenchymal cells [10]. The upregulation of VEGF and its receptor controls tumor angiogenesis and promotes tumor progression [11]. Specific NF-κB inhibitors targeting the IKK complex are promising anticancer agents [12]. Growth factors (VEGF and TGF-β) and various cytokines, including IL-6, IL-17, IL-10, granulocyte-macrophage colony-stimulating factor (GM-CSF) and leukemia inhibitory factor (LIF), promote signal transducer and activator of transcription 3 (STAT3) activation, and STAT3 transduces signals from all members of the IL-6 and IL-10 families to promote tumor growth and disease progression [13].

Numerous studies in recent years have shown that ER stress is closely related to the inflammatory response, IRE1 activation in macrophages mediates a decisive pro-inflammatory response [14, 15], and ATF6 was shown to be activated in inflammatory bowel disease [16]. In the sophisticated and complex process of inflammatory cancer transformation, ER stress is widely involved in different signaling pathways, such as NF-κB [17], STAT [18], PI3K/AKT [19, 20], and Notch [21], to regulate inflammation to cancer transformation. Moreover, the molecular mechanism of inflammation-induced tumorigenesis is an important branch of tumor therapy, and so in this review, we will focus on ER stress, the three ER membrane receptors, and the signaling pathway associated with inflammatory cancer transformation, summarize the mechanism by which ER stress/the UPR affect inflammatory cancer transformation, outline the strategy of studying the UPR in tumor therapy, and provide new ideas for the diagnosis and treatment of tumors.

IRE1 and inflammatory cancer transformation

IRE1, which is a dual enzyme with serine/threonine kinase and ribonucleic acid endonuclease activity, is the most highly conserved gene from yeast to humans, and IRE1α is one of the isoforms that is normally expressed in most cells and tissues [22, 23]. Under ER stress conditions, the structural domain of the kinase IRE1 phosphorylates itself and activates endoribonuclease (RNase) activity [24, 25], followed by RNase domain binding to X-box binding protein 1 (XBP1) mRNA to translate the active transcription factor XBP1s [26, 27], which induces the transcriptional chaperones and lipid synthesis involved in the expression of target genes [26, 28, 29] and increases the protein folding capacity and concomitant expansion of the ER membrane area. The RNase activity of IRE1 is associated with various pathologies, such as cancer and inflammatory, metabolic and degenerative diseases, for instance, inhibiting IRE1 activity is effective in preventing MYC-driven breast cancer development [30], and the regulation of IRE1 activity is emerging as an attractive therapeutic strategy against these diseases [31].

Prolonged ER stress activates IRE1 [32], IRE1α/XBP1 axis further promoted the phosphorylation of STAT3 Tyr705 in primary effusion lymphoma (PEL) by inducing the release of IL-6, IL-10 and VEGF to enable the survival of PEL cells [33]. In human melanoma cells, spliced/activated XBP1 induced IL-6 expression by directly binding to the IL-6 promoter, which further promoted STAT3 phosphorylation and enhanced the oncogenic effects of STAT3 [34]. However, IL-6 and its biological effects activated by STAT3 not only play an important part in tumor progression, but also are closely related to tumor-associated macrophages (TAMs) [35-37]. Some investigators have specifically observed XBP1s expression in TAMs, which promotes the growth and metastasis of colorectal cancer (CRC) by enhancing the expression of the protumor cytokines IL-6, VEGFα, and IL-4, triggering STAT3 signaling by activating downstream SIRPα [38, 39]. 7S,15R-dihydroxy-16S, 17S-epoxy-docosapentaenoic acid (diHEP-DPA) use reduced SIRPα expression in TAMs and effectively reversed TAM conditioned medium (TCCM)-induced epithelial-mesenchymal transition (EMT) [39, 40]. In M1-like TAM, the mesenchymal/stem-like phenotype of oral squamous cell carcinoma (OSCC) was shown to be linked to the IL-6/STAT3/THBS1 feedback loop [41]. In addition, the RNase activity of IRE1α also regulates phosphatidylinositol (PI3K) levels during premiR2137 maturation and mediates ER stress-related degradation (ERAD) via the PI3K/AKT/mTOR pathway in breast cancer cells [42, 43].

Notch signaling is an intercellular transmission mechanism in which the interactions between Notch receptors and membrane-bound Notch

ligands expressed on juxtaposed cells regulate the fate of one cell via neighboring cells [44-46] and is a major factor in stem cell maintenance in many tumors [47]. Dll1 in mammary stem cells activates Notch signaling in macrophages and enhances mammary stem cell self-renewal through macrophage-derived WNT ligands [48]. Deletion of Notch3 under ER stress conditions allows BIP/GRP78 to interact with IRE1α, leading to its ubiquitination and inactivation [49]. Targeting Notch3 in with the presence of ER stress inducers could be a therapeutic approach for T-cell acute lymphoblastic leukemia (T-ALL): the Notch3-dependent IRE1α/XBP1 axis disrupts the conversion of prosurvival UPR signaling to the proapoptotic UPR signal, promoting CHOP-mediated apoptosis [50]. In addition, the NOTCH signaling pathway directly regulates the expression of ERAD genes (e.g., Sel1l, Hrd1, Os9, Edem1) [51]. Sel1l deletion significantly activates three branches of the UPR, leading to the accumulation of mis/unfolded proteins and apoptosis. The IRE1α/XBP1 signaling pathway can act as a compensatory mechanism to suppress Sell deletion-induced ER stress, and PERK deletion significantly restores immune cell numbers and inhibits thymocyte apoptosis in Sel1lCKO mice [52]. Despite the opposite effect of ERAD on Notch signaling [53, 54], ER stress inhibits GLP-1 (a Notch receptor body)/Notch-mediated aberrant proliferation, promoting tumor formation, and the IRE1/XBP1 branch of the UPR is an important weapons. The UPR may not distinguish between gain-of-function or loss-of-function when correcting aberrantly folded mutant Notch receptors but simply identifies these proteins as “corrected misfold” [55, 56]. More studies are needed to provide insight into whether the compensatory mechanism by which IRE1α/XBP1 promotes ER homeostasis after ERAD/Notch deletion is based on two conserved protein regulatory systems [57] or on a regulatory mechanism associated with inflammatory signaling pathways under different conditions.

PERK and inflammatory cancer transformation

PERK is a MAM-rich component that interacts with multifunctional mitochondria-associated ER membrane (MAM) tethering proteins and regulates the exchange of metabolites, such as lipids, reactive oxygen species (ROS) and Ca^{2+}, at the contact site [58]. In contrast to IRE1, PERK has a different function in determining cell fate [59, 60]. When stimulated by unfolded proteins, PERK oligomerizes, phosphorylates itself and subsequently phosphorylates eukaryotic translation initiation factor 2α (eIF-2α) to promote the transcription of ATF4, which accumulates at the promoters of target genes, including CHOP, GADD34 and ATF3 [61-63]. The PERK/ATF4/CHOP signaling pathway is thought to play a key role in inducting apoptosis of liver cells, podocyte, PC12 cells in vitro and in vivo [64-66], and joint involvement of CHOP and ATF4 is required for the induction of cell death [61]. In other words, sustained PERK signaling can promote apoptosis [59]. To further support this hypothesis, one investigator used the ERα bioregulator BHPI to induce breast cancer cell apoptosis and found that this treatment activated PERK but suppressed IRE1α/XBP1 expression due to the functional inhibition of ERα, suggesting that PERK activation was sufficient to induce apoptosis [67].

On the other hand, sustained activation of PERK causes phosphorylation of the downstream signal eIF2α at serine 51 [68]. eIF2α activates NF-κB by reducing the level of IκBα in mouse embryonic fibroblasts [69]. NF-κB, a key molecule between chronic inflammation and cancer [70], acts as a central regulator of immune response and inflammation by upregulating many chemokines CXCL1, CXCL2, CXCL3 and cytokines TNF-α, IL-1β, IL-6, IL-8. Activated NF-κB also affects cell proliferation and apoptosis by targeting Bcl2, IAPs and cell cycle proteins [71], it also participates in adaptive immune responses through B cells and T cells, which further exacerbate inflammation [72]. This is associated with reduced genetic stability and gene mutations in tumorigenesis and progression [73]. But this effect is not absolute. NF-κB in LTED breast cancer cells, however, is activated independent of PERK and eIF2α phosphorylation, whereas STAT3, which is a stress response mediator, is phosphorylated by PERK to increase NF-κB DNA binding activity [69]. In addition, specific STAT3 nuclear translocation inhibitors significantly reduce NF-κB DNA binding activity in breast cancer cells, suggesting that DNA-level interactions could mediate full activation of NF-κB by STAT3. Thus, PERK transmits stress signals from

the ER to the nucleus by activating STAT3 and promoting NF-κB activation [69, 74, 75]. However, not only PERK kinase, but also other inflammatory factors such as high levels of IL-6 stimulation provide a link between STAT3 and NF-κB in tumors [76, 77], while synergistically participating with TNF-α in the activation of NF-κB and STAT3 signaling pathways. Together, they play an important role in inflammation and tumorigenesis [78], an event which has been shown to promote CRC cell growth [79].

As previously mentioned, downstream of PERK, CHOP and ATF4 work together to cause apoptosis, which is clear, but the downstream signal eIF2α also plays an important role, which shows that PERK can activate NF-κB in breast cancer cells through both eIF2α-dependent/independent phosphorylation, while STAT3 acts as a stress mediator that further promotes NF-κB activation and subsequently transmits stress signals to the nucleus in cancer cells to produce a strong regulatory effect. This finding suggests that PERK induces apoptosis when cells are subjected to various adverse stimuli, but in breast cancer cells, ER signaling is delivered to the nucleus through multiple inflammatory transformation signaling pathways, which ultimately results in reduced cancer cell proliferation and apoptosis, which may be related to tumor cell immune escape but is always the result of many factors.

ATF6 and inflammatory cancer transformation

ATF6 is one of the three sensors of the UPR and is anchored to the ER membrane with its C-terminus located in the ER lumen and its N-terminal end toward cytoplasmic side. In the absence of ER stress, inactive ATF6 is a 90-κDa ER transmembrane protein [80, 81]. Under ER stress conditions, ATF6 interacts with BIP/GRP78 by cleaving the disulfide bond and translocating from the ER lumen to the Golgi apparatus, where it is sequentially cleaved by the Golgi apparatus by site 1 and site 2 proteases (S1P and S2P) [81, 82]. These modifications release a 50-κDa N-terminal cytoplasmic fragment containing the transcriptionally active bZIP structural domain. Activated p50-ATF6 translocates into the nucleus and regulates the expression of downstream target genes such as GRP78 and XBP1 [81, 83]. Sterol regulatory element binding protein (SREBP) regulates genes involved in cholesterol and fatty acid homeostasis and is also an ER membrane-bound transcription factor. SREBP is activated through the same protein hydrolysis mechanism as ATF6, and it is also cleaved by the proteases S1P and S2P in the ER [82, 83]. ATF6 forms a complex, stimulated cholesterol gene by interacting with SREBP2 and synthesizing cholesterol de novo [84, 85].

ATF6 regulates the inflammatory cancer transformation signaling pathway to exercise dual roles in tumor cells. ATF6 can mediate the PI3K/AKT/mTOR pathway, enabling ERAD-mediated increases in ER folding capacity in breast cancer cells [43]. However, inhibitor of DNA binding 1 (ID1) activates NF-κB signaling by promoting nuclear translocation of NF-κB p65, which enhances IL-6 expression and secretion in ovarian cancer cells, and subsequently activates STAT3 and promotes ATF6 transcription through protein phosphorylation at Y705, culminating in the induction of ER stress to promote cellular autophagy, which is one of the important reasons for making ovarian cancer harder to cure [86]. ATF6 is also expressed in ulcerative colitis-associated CRC as a marker of precancerous atypical changes [87]. In intestinal epithelial cells, ATF6 is regulated by CSNK2B and ACSL1, which exacerbates inflammation by reducing the transcription of its target genes HSP90B1 and HSPA5 and activating NF-κB [16]. CSNK2B has recently been reported to be a novel oncogene that promotes CRC cell proliferation by activating the mTOR signaling pathway [88] and regulates negative elongation factor complex member E (NELFE) overexpression to promote gastric cancer progression [89]. In hepatocellular carcinoma, tumor necrosis factor α-inducible protein 1 (TNFAIP1) blocks NF-κB activation through selective downregulation of CSNK2B [90]; therefore, we predict that CSNK2B may be a potential target gene for controlling CRC, gastric cancer and liver cancer in the future. In addition, after selective cleavage of BIP/GRP78 by chymotrypsin cytotoxin SubAB, investigators found that ATF6 preferentially dephosphorylates CCAAT/enhancer binding protein (C/EBP) and mTOR-dependent dephosphorylation of akt and subsequently blunts NF-κB activation by TNF-α, thereby protecting mice from endotoxic lethality and collagen arthritis [91].

Cancer-related regulation of inflammatory processes are not monolithic; Notch interacts with transcription factors such as STAT3, NF-κB, the proinflammatory factor IL-6 and its signaling pathway, and the JNK signaling pathway [92, 93]; Notch1 and Notch target genes enhance NF-κB activity through multiple mechanisms [94-96], and the Notch and NF-κB signaling pathways exert bidirectional regulation through different mechanisms and exert different effects under physiological and pathological conditions. The different regulatory mechanisms of the branches of the UPR with the same targets need to be explored in depth, and as mentioned earlier, the deletion of PERK but not IRE1 rescues thymus development in mice [52]. The mechanisms by which different branches of the UPR jointly regulate inflammatory cancer transformation deserve to be explored at multiple levels.

ER stress inhibitors in inflammatory cancer transformation

Recent drug discoveries have opened the door to approaches that require selective regulation of UPR signaling, and this research has identified a number of novel small molecules that target the enzymatic activity of specific UPR regulators [97-101]. Considering the presence of aberrant UPR signaling in cancer, controlling its pharmacological output to limit tumor growth is considered a very reasonable strategy. IRE1α, PERK, and ATF6 are promising targets to control disease progression as the first responders to the UPR. In particular, there have been many efforts to develop small molecule modulators of the active sites of IRE1α and PERK, while only one ATF6 inhibitor has been reported. Ceapins, which are a new class of pyrazolamides, have been demonstrated to specifically inhibit the ATF6α branch of the UPR by blocking nuclear translocation in ATF6α-treated and ER-stressed U2-OS cell line [102].

First-generation inhibitors of IRE1 activity target the structural domain of ATP kinase, an ATP-competitive IRE1α kinase that inhibits RNase attenuators [103], such as sunitinib; sunitinib, in turn, inhibits VEGFR and PDGFR and effectively inhibits IRE1 phosphorylation by inhibiting autophosphorylation and the subsequent RNase activation [104, 105]. In a study of renal cell carcinoma, sunitinib attenuated EGFR loss-induced MAPK (pERK1/2) and pAKT expression and further inhibited EGFR-/- cell proliferation [106]. In contrast to first-generation drugs, second-generation IRE1 inhibitors are compounds that directly target the RNase structural domain and dose-dependently inhibit endogenous IRE1α oligomerization, in vivo XBP1 mRNA cleavage and ER-localized mRNA decay [107]. The known inhibitors that directly target the RNase structural domain are characterized by the fact that they share a common hydroxyaryl aldehyde (HAA) fraction [108] and include B-I09 [109], STF-083010, 4μ8C, toyocamycin, and a series of MKC compounds [97]; among them, B-I09 has been shown to control the aggressiveness of chronic lymphocytic leukemia cells in vivo [109], and the small molecules STF-083010 and 4μ8c react specifically by forming a specific lysine residue (Lys907) with the Schiff base in the RNase structural domain [108]. In addition to forming reversible Schiff bases with Lys907, both agents establish hydrophobic contacts with His910 and Phe889 and form hydrogen bonds with Tyr892 in the IRE1 RNase structural domain [110], thereby blocking their function. This strategy has shown favorable therapeutic effects on diseases; for example, the use of STF-083010, MKC-3946 and toyocamycin inhibited the growth of multiple myeloma [99, 109, 111-113], and 4μ8c was shown to reduce inflammation in a mouse model of arthritis [114]. In addition, the salicylaldehyde MKC-8866 effectively inhibited IRE1 RNase activity and exerted tumor-suppressive effects to slow tumor recurrence in a mouse xenograft model (PDX) of triple-negative breast cancer (TNBC) [115] and in a glioblastoma multiforme (GBM) model [116]. Recent studies have shown that MKC-8866 also induces the regression of breast tumors caused by MYC overexpression [30]. Whether this covalent inhibitor can also produce desirable effects in other types of cancer is still being tested.

In addition to these pharmacological inhibitors, investigators found that kinase inhibitory RNA enzyme attenuators (KIRAs) inhibit IRE1 RNase activity as ATP-competing ligands, suggesting that inhibition of the kinase site may have an inhibitory effect on RNase activity of pancreatic β-cell tumors [103, 117]; interestingly, the peptide fragments of the IRE1 cytoplasmic structural domain itself affect its oligo-

merization and subsequent RNase activity [118, 119]. Therefore, a team has demonstrated that methotrexate, cefoperazone, folinic acid and fludarabine phosphate inhibit IRE1 RNase activity in vitro and in human GBM cell models based on IRE1 peptide fragment interactions; the researchers identified peptides and FDA-approved compounds and sensitized them to the established GBM chemotherapy treatment temozolomide to address the clinical relevance of IRE1 inhibition in oncology. Because these agents are structurally homologous to the region of IRE1 and are therefore complementary, they provide greater selectivity for IRE1 binding and reduce off-target effects than other treatments [120]. In conclusion, blocking IRE1 has been shown to be beneficial in inhibiting tumor progression in mouse models, emphasizing that specific targeting of the UPR can have beneficial effects on disease.

GSK2606414, a potent first-generation PERK inhibitor, has a half inhibitory concentration (IC50) that is less than 1 nM. However, the dose required to completely block PERK autophosphorylation is 30 nM under extreme ER stress conditions [121]. It was shown that the PERK-ATF4-CHOP pathway is involved in stress-induced neuronal damage in the hypothalamus. The PERK phosphorylation inhibitor GSK2606414 significantly decreased ATF4, CHOP and CHOP mRNA expression, blocking activation of the downstream ATF4-CHOP signaling pathway [122]. GSK2606414 treatment also inhibited RANKL-induced MAPK and NF-κB pathway activation and maintained osteoblast homeostasis [123]. The second-generation inhibitor GSK2656157 is an ATP-competitive inhibitor of PERK with an IC50 of 0.9 nmol/L. GSK2656157 is highly selective for PERK with an IC50 value of >100 nmol/L against 300 kinases [98], and there are efforts to improve the physical properties and pharmacokinetics by decreasing inhibitor lipophilicity [124]. This compound showed antitumor effects in immunocompromised mouse xenograft models of multiple myeloma and pancreatic cancer [98], and the inhibitory effect was independent of the inhibition of eIF2α phosphorylation [125]. In contrast, investigators also identified that the potent salubrinal derivative Sal003 could attenuate eIF2α phosphorylation without inhibiting PERK [126], and this agent specifically prevented the dephosphorylation of eIF2α by blocking eIF2α phosphatase activity of glioblastoma multiforme [127, 128]. In addition, an integrative stress response inhibitor (ISRIB) was reported known as symmetrical bis (ethylene glycol) amide, which binds and activates elongation initiation factor 2β and subsequently releases eIF2α phosphorylation-mediated inhibition of protein translation [129]; this agent has been shown to cause tumor regression and prolong patient survival in patient-derived models of advanced prostate cancer [130]. In addition to these two generations of inhibitors, AMG'44 [131] has not been tested on various cancer models, although it is said to be the highly selective for PERK compared to the more than 300 kinases tested. Kinase inhibitor research for preclinical development is fraught with challenges. The reaction mechanisms usually occur in an unpredictable manner via multiple enzymatic reactions. However, although inhibitors that simultaneously target different kinases sound promising for cancer therapy, there are many difficulties in clarifying the mechanisms.

BIP/GRP78, which is an important molecular chaperone of the UPR, is essential for maintaining ER homeostasis. BIP/GRP78 is also one of the typical markers of tumor cells and is closely associated with the aggressive growth, invasiveness and metastasis of tumors [132], thus, the development of related inhibitors is a potential strategy for the treatment of cancer. Some established GRP78 inhibitors, such as (-)-epigallocatechin gallate (EGCG), bind to the ATP-binding structural domain of GRP78 and block its function [133, 134] and have been shown to protect against hormone-related cancers (breast, prostate) [135]. Potassium-3-beta-hydroxy-20-oxo-substituted-5-en-17-α-yl sulfate (PHOS) inhibits the proliferation of CRC cells and induces apoptosis in cancer cells by inhibiting GRP78 activity [136]. In addition, KP1339/IT-139 can deplete key molecular chaperones such as GRP78 and further induce HCT116 cells apoptosis through the specific disruption of ER homeostasis in combination with enhanced KP1339-mediated protein damage [137]. However, in recent years, the novel inhibitor HA15, which targets GRP78, has been reported and is the the main compound of thia-

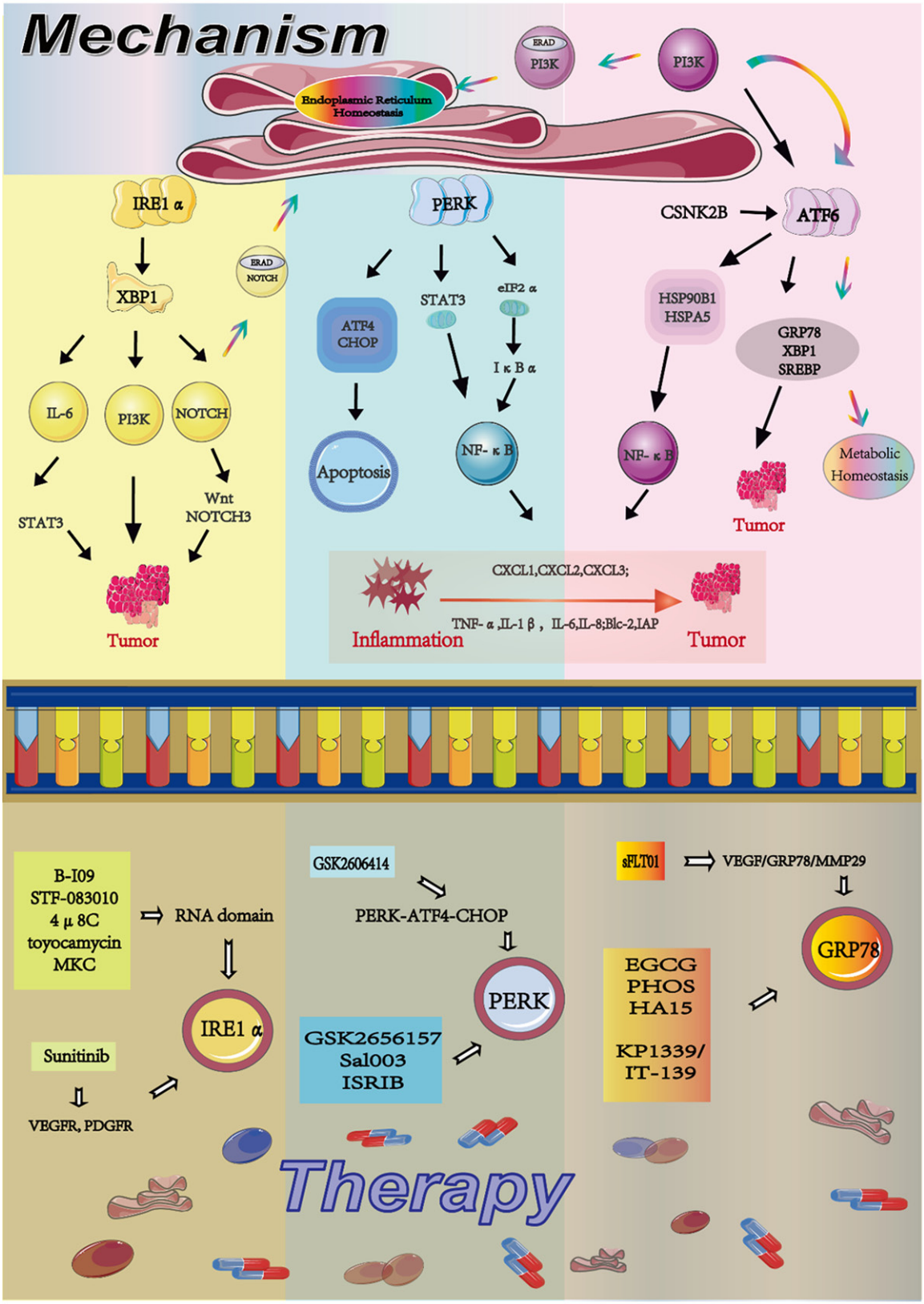

Figure 1. The role and therapeutic implication of endoplasmic reticulum stress in inflammatory cancer transformation. UPR exerts pro-survival and pro-death effects by the dual role of in inflammatory and cancer responses. The mechanisms and signaling pathways of the transformation of inflammation to cancer and UPR-targeting drugs that

inhibit cancer development via the three branches of the UPR. IRE1 mediates tumorigenesis through the STAT, PI3K/AKT/mTOR, and NOTCH signaling pathways with the participation of multiple inflammatory factors, especially IL-6, IL-10, and VEGF. IRE1 and PERK are potent targets for the treatment and prevention of tumors. Targeted therapies for UPR response inhibits cancer progression. IRE1α: inositol-requiring enzyme 1; PERK: protein kinase RNA-like endoplasmic reticulum kinase; ATF6: activating transcription factor 6; XBP1: X-box binding protein 1; GRP78: glucose regulatory protein 78 κDa; SREBP: Sterol regulatory element binding protein; IL-6: Interleukin-6; PI3K: Phosphatidylinositol 3-kinase; ATF4: activating transcription factor 4.

zole benzenesulfonamide, which acts by inhibiting ATPase activity [138], shows antitumor effects and can overcome drug resistance in melanoma and breast, pancreatic and adrenocortical cancers [138, 139]. In addition, targeting GRP78 with HA15 also resulted in apoptosis in lung cancer cells, which was accompanied by ER stress and autophagy [140]. The inhibitor sFLT01 was shown to inhibit prostate cancer DU145 cell invasion and metastasis by regulating the VEGF/GRP78/MMP2&9 axis [141]. This protein consists of a second immunoglobulin (IgG)-like structural domain of Flt-1, which is fused to the CH3 structural domain of IgG1 Fc by fusion to human IgG1 Fc or IgG1 Fc using the polyglycine linker 9Gly [142] and has been shown to exhibit potent and significant antitumor activity in vivo in numerous preclinical subcutaneous tumor models, including H460 non-small-cell lung cancer, HT29 colon cancer, Karpas 299 lymphoma, MOLM-13 AML (acute myeloid leukemia), 786-O and RENCA renal cell carcinoma (RCC) [143].

Conclusion and future

A growing number of studies have revealed the dual roles of ER stress, especially the UPR, in inflammatory and cancer responses but have not yet elucidated the molecular mechanisms underlying the switch between survival and death, and the branches of the UPR pay multiple roles in regulating the transformation of inflammation to cancer. Targeting the UPR may be a plausible strategy for developing cancer drugs: a high level of basal ER stress and constitutive UPR activation exist in tumor cells [144, 145]. However, drugs that exacerbate ER stress/the UPR may also be cytotoxic to cancer cells [138]. Understanding how the UPR regulates the balance of inflammatory and cancer responses is necessary.

Therefore, this review summarizes the different mechanisms and signaling pathways of the transformation of inflammation to cancer and UPR-targeting drugs that inhibit cancer development via the three branches of the UPR (**Figure 1**). IRE1 mediates tumorigenesis through the STAT, PI3K/AKT/mTOR, and NOTCH signaling pathways with the participation of multiple inflammatory factors, especially IL-6, IL-10, and VEGF. Its first-generation inhibitors are ATP-competitive IRE1α kinase inhibitors and RNase attenuators, and second-generation inhibitors include a number of compounds that directly target the structural domain of RNase. Another important receptor, PERK, not only induces apoptosis with downstream CHOP and ATF4 but also allows eIF2α to interact with NF-κB and STAT3 to transmit stress signals, and inhibitors of PERK inhibit PERK and eIF2α phosphorylation, ATF4 translation and CHOP mRNA expression. In addition, inhibitors of BIP/GRP78, EGCG, PHOS, KP1339/IT-139, and HA15 have shown antitumor effects in a variety of cancer models through targeted depletion (**Table 1**). Overall, IRE1 and PERK are potent targets for the treatment and prevention of tumors, and targeted studies of both branches may yield promising therapeutic strategies.

Acknowledgements

This work was supported by National Nature Science Foundation of China, Nos. 81874206, 82104466; Shanghai Frontiers Science Center of Disease and Syndrome Biology of Inflammatory Cancer Transformation (2021KJ03-12); Shanghai Rising-Star Program, No. 20QA1409300; and the Program for Young Eastern Scholar at Shanghai Institutions of Higher Learning, No. QD2019034.

Disclosure of conflict of interest

None.

Address correspondence to: Guang Ji and Hanchen Xu, Institute of Digestive Diseases, Longhua Hospital, Shanghai University of Traditional Chinese Medicine, South Wanping Road 725, Shanghai 200032, China. E-mail: jiliver@vip.sina.com (GL); hanson0702@126.com (HCX)

Table 1. Candidates to target UPR for cancer therapy

Candidates	Molecular formula	Therapeutic effects associated with ER stress	Indications	References
Sunitinib	$C_{22}H_{27}FN_4O_2$	Inhibits VEGFR and PDGFR, inhibits autophosphorylation and the subsequent IRE1α RNase activation	Renal cell carcinoma	[104-106]
B-I09	$C_{16}H_{17}NO_5$	Inhibits endogenous IRE1α oligomerization, in vivo XBP1 mRNA cleavage and ER-localized mRNA decay	B cell chronic lymphocytic leukemia	[109]
STF-083010	$C_{15}H_{11}NO_3S_2$	Forms Schiff bases with Lys907and hydrogen bonds with Tyr892 in the IRE1 RNase structural domain	Multiple myeloma	[97, 99]
4μ8C	$C_{11}H_8O_4$	Forms Schiff bases with Lys907and hydrogen bonds with Tyr892 in the IRE1 RNase structural domain	Rheumatoid arthritis	[97, 108, 110, 114]
Toyocamycin	$C_{12}H_{13}N_5O_4$	Inhibits endogenous IRE1α oligomerization, in vivo XBP1 mRNA cleavage and ER-localized mRNA decay	Multiple myeloma	[97]
MKC-3946, MKC-8866	$C_{21}H_{20}N_2O_3S$ $C_{18}H_{19}NO_7$	Inhibits endogenous IRE1α oligomerization, in vivo XBP1 mRNA cleavage and ER-localized mRNA decay	Multiple myeloma, triple-negative breast cancer, glioblastoma multiforme	[97, 109, 115]
Methotrexate	$C_{20}H_{22}N_8O_5$	Inhibits IRE1 RNase activity	Glioblastoma multiforme	[120]
Cefoperazone	$C_{25}H_{27}N_9O_8S_2$	Inhibits IRE1 RNase activity	Glioblastoma multiforme	[120]
Folinic acid	$C_{20}H_{23}N_7O_7$	Inhibits IRE1 RNase activity	Glioblastoma multiforme	[120]
Fludarabine phosphate	$C_{10}H_{13}FN_5O_7P$	Inhibits IRE1 RNase activity	Glioblastoma multiforme	[120]
GSK2606414, GSK2656157	$C_{24}H_{20}F_3N_5O$ $C_{23}H_{21}FN_6O$	Inhibits PERK, inhibits eIF2α phosphorylation (or not), ATF4 translation and CHOP mRNA expression	Hypothalamic neuronal injury, bone loss, multiple myeloma, pancreatic adenocarcinoma	[98, 122, 123, 125]
Sal003	$C_{18}H_{15}Cl_4N_3OS$	Blocks eIF2α phosphatase activity	Glioblastoma multiforme	[126, 127]
ISRIB	$C_{22}H_{24}Cl_2N_2O_4$	Releases eIF2α phosphorylation-mediated inhibition of protein translation	Prostate cancer	[129, 130]
AMG'44	$C_{34}H_{29}ClN_4O_2$	Inhibits PERK	/	[131]
EGCG	$C_{22}H_{18}O_{11}$	Binds to the ATP-binding structural domain of GRP78 and block its function	Breast cancer, prostate cancer	[133-135]
PHOS	$C_{21}H_{31}KO_6S$	Inhibits GRP78 activity	Colorectal cancer	[136]
KP1339/IT-139	$C_{14}H_{12}Cl_4N_4NaRu$	Depletes GRP78 and disrupts ER homeostasis specifically	Colorectal cancer	[137]
HA15	$C_{23}H_{22}N_4O_3S_2$	Inhibits ATPase activity	Melanoma, breast cancer, pancreatic cancer, adrenocortical carcer, lung cancer	[138-140]

References

[1] Grandjean JMD and Wiseman RL. Small molecule strategies to harness the unfolded protein response: where do we go from here? J Biol Chem 2020; 295: 15692-15711.

[2] Mitsiadis TA, Henrique D, Thesleff I and Lendahl U. Mouse serrate-1 (Jagged-1): expression in the developing tooth is regulated by epithelial-mesenchymal interactions and fibroblast growth factor-4. Development 1997; 124: 1473-1483.

[3] Mitsiadis TA, Graf D, Luder H, Gridley T and Bluteau G. BMPs and FGFs target Notch signalling via jagged 2 to regulate tooth morphogenesis and cytodifferentiation. Development 2010; 137: 3025-3035.

[4] Chevet E, Hetz C and Samali A. Endoplasmic reticulum stress-activated cell reprogramming in oncogenesis. Cancer Discov 2015; 5: 586-597.

[5] Ibrahim IM, Abdelmalek DH and Elfiky AA. GRP78: a cell's response to stress. Life Sci 2019; 226: 156-163.

[6] Hetz C, Zhang K and Kaufman RJ. Mechanisms, regulation and functions of the unfolded protein response. Nat Rev Mol Cell Biol 2020; 21: 421-438.

[7] Wang M and Kaufman RJ. Protein misfolding in the endoplasmic reticulum as a conduit to human disease. Nature 2016; 529: 326-335.

[8] Tan YY, Zhou HY, Wang ZQ and Chen SD. Endoplasmic reticulum stress contributes to the cell death induced by UCH-L1 inhibitor. Mol Cell Biochem 2008; 318: 109-115.

[9] Guttridge DC, Albanese C, Reuther JY, Pestell RG and Baldwin AS Jr. NF-kappaB controls cell growth and differentiation through transcriptional regulation of cyclin D1. Mol Cell Biol 1999; 19: 5785-5799.

[10] Huber MA, Azoitei N, Baumann B, Grünert S, Sommer A, Pehamberger H, Kraut N, Beug H and Wirth T. NF-kappaB is essential for epithelial-mesenchymal transition and metastasis in a model of breast cancer progression. J Clin Invest 2004; 114: 569-581.

[11] Xie TX, Xia Z, Zhang N, Gong W and Huang S. Constitutive NF-kappaB activity regulates the expression of VEGF and IL-8 and tumor angiogenesis of human glioblastoma. Oncol Rep 2010; 23: 725-732.

[12] Rahman MM and McFadden G. Modulation of NF-κB signalling by microbial pathogens. Nat Rev Microbiol 2011; 9: 291-306.

[13] Schindler C, Levy DE and Decker T. JAK-STAT signaling: from interferons to cytokines. J Biol Chem 2007; 282: 20059-20063.

[14] Martinon F, Chen X, Lee AH and Glimcher LH. TLR activation of the transcription factor XBP1 regulates innate immune responses in macrophages. Nat Immunol 2010; 11: 411-418.

[15] Keestra-Gounder AM, Byndloss MX, Seyffert N, Young BM, Chávez-Arroyo A, Tsai AY, Cevallos SA, Winter MG, Pham OH, Tiffany CR, de Jong MF, Kerrinnes T, Ravindran R, Luciw PA, McSorley SJ, Bäumler AJ and Tsolis RM. NOD1 and NOD2 signalling links ER stress with inflammation. Nature 2016; 532: 394-397.

[16] Stengel ST, Fazio A, Lipinski S, Jahn MT, Aden K, Ito G, Wottawa F, Kuiper JWP, Coleman OI, Tran F, Bordoni D, Bernardes JP, Jentzsch M, Luzius A, Bierwirth S, Messner B, Henning A, Welz L, Kakavand N, Falk-Paulsen M, Imm S, Hinrichsen F, Zilbauer M, Schreiber S, Kaser A, Blumberg R, Haller D and Rosenstiel P. Activating transcription factor 6 mediates inflammatory signals in intestinal epithelial cells upon endoplasmic reticulum stress. Gastroenterology 2020; 159: 1357-1374.

[17] Xia Y, Shen S and Verma IM. NF-κB, an active player in human cancers. Cancer Immunol Res 2014; 2: 823-830.

[18] Siveen KS, Sikka S, Surana R, Dai X, Zhang J, Kumar AP, Tan BK, Sethi G and Bishayee A. Targeting the STAT3 signaling pathway in cancer: role of synthetic and natural inhibitors. Biochim Biophys Acta 2014; 1845: 136-154.

[19] Pene F, Claessens YE, Muller O, Viguié F, Mayeux P, Dreyfus F, Lacombe C and Bouscary D. Role of the phosphatidylinositol 3-kinase/Akt and mTOR/P70S6-kinase pathways in the proliferation and apoptosis in multiple myeloma. Oncogene 2002; 21: 6587-6597.

[20] Engelman JA. Targeting PI3K signalling in cancer: opportunities, challenges and limitations. Nat Rev Cancer 2009; 9: 550-562.

[21] Allenspach EJ, Maillard I, Aster JC and Pear WS. Notch signaling in cancer. Cancer Biol Ther 2002; 1: 466-476.

[22] Sepulveda D, Rojas-Rivera D, Rodríguez DA, Groenendyk J, Köhler A, Lebeaupin C, Ito S, Urra H, Carreras-Sureda A, Hazari Y, Vasseur-Cognet M, Ali MMU, Chevet E, Campos G, Godoy P, Vaisar T, Bailly-Maitre B, Nagata K, Michalak M, Sierralta J and Hetz C. Interactome screening identifies the ER luminal chaperone Hsp47 as a regulator of the unfolded protein response transducer IRE1α. Mol Cell 2018; 69: 238-252.

[23] Liu Y, Shao M, Wu Y, Yan C, Jiang S, Liu J, Dai J, Yang L, Li J, Jia W, Rui L and Liu Y. Role for the endoplasmic reticulum stress sensor IRE1α in liver regenerative responses. J Hepatol 2015; 62: 590-598.

[24] Ron D and Walter P. Signal integration in the endoplasmic reticulum unfolded protein response. Nat Rev Mol Cell Biol 2007; 8: 519-529.

[25] Lewy TG, Grabowski JM and Bloom ME. BiP: master regulator of the unfolded protein response and crucial factor in flavivirus biology. Yale J Biol Med 2017; 90: 291-300.
[26] Ambrose RL and Mackenzie JM. West Nile virus differentially modulates the unfolded protein response to facilitate replication and immune evasion. J Virol 2011; 85: 2723-2732.
[27] Lewy TG, Offerdahl DK, Grabowski JM, Kellman E, Mlera L, Chiramel A and Bloom ME. PERK-mediated unfolded protein response signaling restricts replication of the tick-borne flavivirus langat virus. Viruses 2020; 12: 328.
[28] Tan Z, Zhang W, Sun J, Fu Z, Ke X, Zheng C, Zhang Y, Li P, Liu Y, Hu Q, Wang H and Zheng Z. ZIKV infection activates the IRE1-XBP1 and ATF6 pathways of unfolded protein response in neural cells. J Neuroinflammation 2018; 15: 275.
[29] Su HL, Liao CL and Lin YL. Japanese encephalitis virus infection initiates endoplasmic reticulum stress and an unfolded protein response. J Virol 2002; 76: 4162-4171.
[30] Zhao N, Cao J, Xu L, Tang Q, Dobrolecki LE, Lv X, Talukdar M, Lu Y, Wang X, Hu DZ, Shi Q, Xiang Y, Wang Y, Liu X, Bu W, Jiang Y, Li M, Gong Y, Sun Z, Ying H, Yuan B, Lin X, Feng XH, Hartig SM, Li F, Shen H, Chen Y, Han L, Zeng Q, Patterson JB, Kaipparettu BA, Putluri N, Sicheri F, Rosen JM, Lewis MT and Chen X. Pharmacological targeting of MYC-regulated IRE1/XBP1 pathway suppresses MYC-driven breast cancer. J Clin Invest 2018; 128: 1283-1299.
[31] Bergmann TJ and Molinari M. Three branches to rule them all? UPR signalling in response to chemically versus misfolded proteins-induced ER stress. Biol Cell 2018; 110: 197-204.
[32] Goltyaev MV, Varlamova EG, Novoselov SV and Fesenko EE. Activation of signal pathways of apoptosis under conditions of prolonged er-stress caused by exposure of mouse testicular teratoma cells to selenium-containing compounds. Dokl Biochem Biophys 2020; 490: 9-11.
[33] Gonnella R, Gilardini Montani MS, Guttieri L, Romeo MA, Santarelli R and Cirone M. IRE1 Alpha/XBP1 axis sustains primary effusion lymphoma cell survival by promoting cytokine release and STAT3 activation. Biomedicines 2021; 9: 118.
[34] Chen C and Zhang X. IRE1α-XBP1 pathway promotes melanoma progression by regulating IL-6/STAT3 signaling. J Transl Med 2017; 15: 42.
[35] Multhoff G and Radons J. Radiation, inflammation, and immune responses in cancer. Front Oncol 2012; 2: 58.
[36] Yu H, Kortylewski M and Pardoll D. Crosstalk between cancer and immune cells: role of STAT3 in the tumour microenvironment. Nat Rev Immunol 2007; 7: 41-51.
[37] Komohara Y, Jinushi M and Takeya M. Clinical significance of macrophage heterogeneity in human malignant tumors. Cancer Sci 2014; 105: 1-8.
[38] Zhao Y, Zhang W, Huo M, Wang P, Liu X, Wang Y, Li Y, Zhou Z, Xu N and Zhu H. XBP1 regulates the protumoral function of tumor-associated macrophages in human colorectal cancer. Signal Transduct Target Ther 2021; 6: 357.
[39] Toledano N, Gur-Wahnon D, Ben-Yehuda A and Rachmilewitz J. Novel CD47: SIRPα dependent mechanism for the activation of STAT3 in antigen-presenting cell. PLoS One 2013; 8: e75595.
[40] Wang L, Choi HS, Su Y, Lee B, Song JJ, Jang YS and Seo JW. 7S,15R-Dihydroxy-16S,17S-Epoxy-docosapentaenoic acid, a novel DHA epoxy derivative, inhibits colorectal cancer stemness through repolarization of tumor-associated macrophage functions and the ROS/STAT3 signaling pathway. Antioxidants (Basel) 2021; 10: 1459.
[41] You Y, Tian Z, Du Z, Wu K, Xu G, Dai M, Wang Y and Xiao M. M1-like tumor-associated macrophages cascade a mesenchymal/stem-like phenotype of oral squamous cell carcinoma via the IL6/Stat3/THBS1 feedback loop. J Exp Clin Cancer Res 2022; 41: 10.
[42] Hamid SM, Citir M, Terzi EM, Cimen I, Yildirim Z, Dogan AE, Kocaturk B, Onat UI, Arditi M, Weber C, Traynor-Kaplan A, Schultz C and Erbay E. Inositol-requiring enzyme-1 regulates phosphoinositide signaling lipids and macrophage growth. EMBO Rep 2020; 21: e51462.
[43] Fan P, Cunliffe HE, Maximov PY, Agboke FA, McDaniel RE, Zou X, Ramos P, Russell ML and Jordan VC. Integration of downstream signals of insulin-like growth factor-1 receptor by endoplasmic reticulum stress for estrogen-induced growth or apoptosis in breast cancer cells. Mol Cancer Res 2015; 13: 1367-1376.
[44] Simpson P. Lateral inhibition and the development of the sensory bristles of the adult peripheral nervous system of Drosophila. Development 1990; 109: 509-519.
[45] Louvi A and Artavanis-Tsakonas S. Notch signalling in vertebrate neural development. Nat Rev Neurosci 2006; 7: 93-102.
[46] Artavanis-Tsakonas S, Rand MD and Lake RJ. Notch signaling: cell fate control and signal integration in development. Science 1999; 284: 770-776.
[47] Takebe N, Miele L, Harris PJ, Jeong W, Bando H, Kahn M, Yang SX and Ivy SP. Targeting Notch, Hedgehog, and Wnt pathways in cancer stem cells: clinical update. Nat Rev Clin Oncol 2015; 12: 445-464.

[48] Chakrabarti R, Celià-Terrassa T, Kumar S, Hang X, Wei Y, Choudhury A, Hwang J, Peng J, Nixon B, Grady JJ, DeCoste C, Gao J, van Es JH, Li MO, Aifantis I, Clevers H and Kang Y. Notch ligand Dll1 mediates cross-talk between mammary stem cells and the macrophageal niche. Science 2018; 360: eaan4153.

[49] Sun S, Shi G, Sha H, Ji Y, Han X, Shu X, Ma H, Inoue T, Gao B, Kim H, Bu P, Guber RD, Shen X, Lee AH, Iwawaki T, Paton AW, Paton JC, Fang D, Tsai B, Yates JR 3rd, Wu H, Kersten S, Long Q, Duhamel GE, Simpson KW and Qi L. IRE1α is an endogenous substrate of endoplasmic-reticulum-associated degradation. Nat Cell Biol 2015; 17: 1546-1555.

[50] Giuli MV, Diluvio G, Giuliani E, Franciosa G, Di Magno L, Pignataro MG, Tottone L, Nicoletti C, Besharat ZM, Peruzzi G, Pelullo M, Palermo R, Canettieri G, Talora C, d'Amati G, Bellavia D, Screpanti I and Checquolo S. Notch3 contributes to T-cell leukemia growth via regulation of the unfolded protein response. Oncogenesis 2020; 9: 93.

[51] Camelo S, Raoul W, Lavalette S, Calippe B, Cristofaro B, Levy O, Houssier M, Sulpice E, Jonet L, Klein C, Devevre E, Thuret G, Duarte A, Eichmann A, Leconte L, Guillonneau X and Sennlaub F. Delta-like 4 inhibits choroidal neovascularization despite opposing effects on vascular endothelium and macrophages. Angiogenesis 2012; 15: 609-622.

[52] Liu X, Yu J, Xu L, Umphred-Wilson K, Peng F, Ding Y, Barton BM, Lv X, Zhao MY, Sun S, Hong Y, Qi L, Adoro S and Chen X. Notch-induced endoplasmic reticulum-associated degradation governs mouse thymocyte β-selection. Elife 2021; 10: e69975.

[53] Choi MS, Yoo AS and Greenwald I. sel-11 and cdc-42, two negative modulators of LIN-12/Notch activity in C. elegans. PLoS One 2010; 5: e11885.

[54] Sundaram M and Greenwald I. Suppressors of a lin-12 hypomorph define genes that interact with both lin-12 and glp-1 in Caenorhabditis elegans. Genetics 1993; 135: 765-783.

[55] Yamakawa T, Yamada K, Sasamura T, Nakazawa N, Kanai M, Suzuki E, Fortini ME and Matsuno K. Deficient Notch signaling associated with neurogenic pecanex is compensated for by the unfolded protein response in Drosophila. Development 2012; 139: 558-567.

[56] Tien AC, Rajan A, Schulze KL, Ryoo HD, Acar M, Steller H and Bellen HJ. Ero1L, a thiol oxidase, is required for Notch signaling through cysteine bridge formation of the Lin12-Notch repeats in Drosophila melanogaster. J Cell Biol 2008; 182: 1113-1125.

[57] Hwang J and Qi L. Quality control in the endoplasmic reticulum: crosstalk between ERAD and UPR pathways. Trends Biochem Sci 2018; 43: 593-605.

[58] Muñoz JP, Ivanova S, Sánchez-Wandelmer J, Martínez-Cristóbal P, Noguera E, Sancho A, Díaz-Ramos A, Hernández-Alvarez MI, Sebastián D, Mauvezin C, Palacín M and Zorzano A. Mfn2 modulates the UPR and mitochondrial function via repression of PERK. EMBO J 2013; 32: 2348-2361.

[59] Lin JH, Li H, Zhang Y, Ron D and Walter P. Divergent effects of PERK and IRE1 signaling on cell viability. PLoS One 2009; 4: e4170.

[60] Lin JH, Li H, Yasumura D, Cohen HR, Zhang C, Panning B, Shokat KM, Lavail MM and Walter P. IRE1 signaling affects cell fate during the unfolded protein response. Science 2007; 318: 944-949.

[61] Han J, Back SH, Hur J, Lin YH, Gildersleeve R, Shan J, Yuan CL, Krokowski D, Wang S, Hatzoglou M, Kilberg MS, Sartor MA and Kaufman RJ. ER-stress-induced transcriptional regulation increases protein synthesis leading to cell death. Nat Cell Biol 2013; 15: 481-490.

[62] Michel S, Canonne M, Arnould T and Renard P. Inhibition of mitochondrial genome expression triggers the activation of CHOP-10 by a cell signaling dependent on the integrated stress response but not the mitochondrial unfolded protein response. Mitochondrion 2015; 21: 58-68.

[63] Sano R and Reed JC. ER stress-induced cell death mechanisms. Biochim Biophys Acta 2013; 1833: 3460-3470.

[64] Cao J, Dai DL, Yao L, Yu HH, Ning B, Zhang Q, Chen J, Cheng WH, Shen W and Yang ZX. Saturated fatty acid induction of endoplasmic reticulum stress and apoptosis in human liver cells via the PERK/ATF4/CHOP signaling pathway. Mol Cell Biochem 2012; 364: 115-129.

[65] Chen Y, Gui D, Chen J, He D, Luo Y and Wang N. Down-regulation of PERK-ATF4-CHOP pathway by Astragaloside IV is associated with the inhibition of endoplasmic reticulum stress-induced podocyte apoptosis in diabetic rats. Cell Physiol Biochem 2014; 33: 1975-1987.

[66] Liu Z, Shi Q, Song X, Wang Y, Wang Y, Song E and Song Y. Activating transcription factor 4 (ATF4)-ATF3-C/EBP homologous protein (CHOP) cascade shows an essential role in the ER stress-induced sensitization of tetrachlorobenzoquinone-challenged PC12 cells to ROS-mediated apoptosis via death receptor 5 (DR5) signaling. Chem Res Toxicol 2016; 29: 1510-1518.

[67] Andruska ND, Zheng X, Yang X, Mao C, Cherian MM, Mahapatra L, Helferich WG and Shapiro DJ. Estrogen receptor α inhibitor activates the unfolded protein response, blocks protein synthesis, and induces tumor regression. Proc Natl Acad Sci U S A 2015; 112: 4737-4742.

[68] Harding HP, Zhang Y and Ron D. Protein translation and folding are coupled by an endoplasmic-reticulum-resident kinase. Nature 1999; 397: 271-274.
[69] Fan P, Tyagi AK, Agboke FA, Mathur R, Pokharel N and Jordan VC. Modulation of nuclear factor-kappa B activation by the endoplasmic reticulum stress sensor PERK to mediate estrogen-induced apoptosis in breast cancer cells. Cell Death Discov 2018; 4: 15.
[70] Taniguchi K and Karin M. NF-κB, inflammation, immunity and cancer: coming of age. Nat Rev Immunol 2018; 18: 309-324.
[71] Peng C, Ouyang Y, Lu N and Li N. The NF-κB signaling pathway, the microbiota, and gastrointestinal tumorigenesis: recent advances. Front Immunol 2020; 11: 1387.
[72] Zhang Q, Lenardo MJ and Baltimore D. 30 Years of NF-κB: a blossoming of relevance to human pathobiology. Cell 2017; 168: 37-57.
[73] Ji Z, He L, Regev A and Struhl K. Inflammatory regulatory network mediated by the joint action of NF-kB, STAT3, and AP-1 factors is involved in many human cancers. Proc Natl Acad Sci U S A 2019; 116: 9453-9462.
[74] Zhu S, Liu H, Sha H, Qi L, Gao DS and Zhang W. PERK and XBP1 differentially regulate CXCL10 and CCL2 production. Exp Eye Res 2017; 155: 1-14.
[75] Mijošek V, Lasitschka F, Warth A, Zabeck H, Dalpke AH and Weitnauer M. Endoplasmic reticulum stress is a danger signal promoting innate inflammatory responses in bronchial epithelial cells. J Innate Immun 2016; 8: 464-478.
[76] Calu V, Ionescu A, Stanca L, Geicu OI, Iordache F, Pisoschi AM, Serban AI and Bilteanu L. Key biomarkers within the colorectal cancer related inflammatory microenvironment. Sci Rep 2021; 11: 7940.
[77] Grivennikov SI and Karin M. Dangerous liaisons: STAT3 and NF-kappaB collaboration and crosstalk in cancer. Cytokine Growth Factor Rev 2010; 21: 11-19.
[78] Hirano T. IL-6 in inflammation, autoimmunity and cancer. Int Immunol 2021; 33: 127-148.
[79] De Simone V, Franzè E, Ronchetti G, Colantoni A, Fantini MC, Di Fusco D, Sica GS, Sileri P, MacDonald TT, Pallone F, Monteleone G and Stolfi C. Th17-type cytokines, IL-6 and TNF-α synergistically activate STAT3 and NF-kB to promote colorectal cancer cell growth. Oncogene 2015; 34: 3493-3503.
[80] Shen J, Chen X, Hendershot L and Prywes R. ER stress regulation of ATF6 localization by dissociation of BiP/GRP78 binding and unmasking of Golgi localization signals. Dev Cell 2002; 3: 99-111.
[81] Haze K, Yoshida H, Yanagi H, Yura T and Mori K. Mammalian transcription factor ATF6 is synthesized as a transmembrane protein and activated by proteolysis in response to endoplasmic reticulum stress. Mol Biol Cell 1999; 10: 3787-3799.
[82] Velho RV, De Pace R, Klünder S, Di Lorenzo G, Schweizer M, Braulke T and Pohl S. Site-1 protease and lysosomal homeostasis. Biochim Biophys Acta Mol Cell Res 2017; 1864: 2162-2168.
[83] Yoshida H, Okada T, Haze K, Yanagi H, Yura T, Negishi M and Mori K. ATF6 activated by proteolysis binds in the presence of NF-Y (CBF) directly to the cis-acting element responsible for the mammalian unfolded protein response. Mol Cell Biol 2000; 20: 6755-6767.
[84] Zeng L, Lu M, Mori K, Luo S, Lee AS, Zhu Y and Shyy JY. ATF6 modulates SREBP2-mediated lipogenesis. EMBO J 2004; 23: 950-958.
[85] Maruyama R, Kamoshida Y, Shimizu M, Inoue J and Sato R. ATF6α stimulates cholesterogenic gene expression and de novo cholesterol synthesis. Biosci Biotechnol Biochem 2013; 77: 1734-1738.
[86] Meng J, Liu K, Shao Y, Feng X, Ji Z, Chang B, Wang Y, Xu L and Yang G. ID1 confers cancer cell chemoresistance through STAT3/ATF6-mediated induction of autophagy. Cell Death Dis 2020; 11: 137.
[87] Hanaoka M, Ishikawa T, Ishiguro M, Tokura M, Yamauchi S, Kikuchi A, Uetake H, Yasuno M and Kawano T. Expression of ATF6 as a marker of pre-cancerous atypical change in ulcerative colitis-associated colorectal cancer: a potential role in the management of dysplasia. J Gastroenterol 2018; 53: 631-641.
[88] Yu S, Hu Q, Fan K, Yang C and Gao Y. CSNK2B contributes to colorectal cancer cell proliferation by activating the mTOR signaling. J Cell Commun Signal 2021; 15: 383-392.
[89] Yu S, Li L, Cai H, He B, Gao Y and Li Y. Overexpression of NELFE contributes to gastric cancer progression via Wnt/β-catenin signaling-mediated activation of CSNK2B expression. J Exp Clin Cancer Res 2021; 40: 54.
[90] Xiao Y, Huang S, Qiu F, Ding X, Sun Y, Wei C, Hu X, Wei K, Long S, Xie L, Xun Y, Chen W, Zhang Z, Liu N and Xiang S. Tumor necrosis factor α-induced protein 1 as a novel tumor suppressor through selective downregulation of CSNK2B blocks nuclear factor-κB activation in hepatocellular carcinoma. EBioMedicine 2020; 51: 102603.
[91] Nakajima S, Hiramatsu N, Hayakawa K, Saito Y, Kato H, Huang T, Yao J, Paton AW, Paton JC and Kitamura M. Selective abrogation of BiP/GRP78 blunts activation of NF-κB through the ATF6 branch of the UPR: involvement of C/EBPβ and mTOR-dependent dephosphorylation of Akt. Mol Cell Biol 2011; 31: 1710-1718.

[92] Cantrell MA, Ebelt ND, Pfefferle AD, Perou CM and Van Den Berg CL. c-Jun N-terminal kinase 2 prevents luminal cell commitment in normal mammary glands and tumors by inhibiting p53/Notch1 and breast cancer gene 1 expression. Oncotarget 2015; 6: 11863-11881.
[93] Portanova P, Notaro A, Pellerito O, Sabella S, Giuliano M and Calvaruso G. Notch inhibition restores TRAIL-mediated apoptosis via AP1-dependent upregulation of DR4 and DR5 TRAIL receptors in MDA-MB-231 breast cancer cells. Int J Oncol 2013; 43: 121-130.
[94] Espinosa L, Cathelin S, D'Altri T, Trimarchi T, Statnikov A, Guiu J, Rodilla V, Inglés-Esteve J, Nomdedeu J, Bellosillo B, Besses C, Abdel-Wahab O, Kucine N, Sun SC, Song G, Mullighan CC, Levine RL, Rajewsky K, Aifantis I and Bigas A. The Notch/Hes1 pathway sustains NF-κB activation through CYLD repression in T cell leukemia. Cancer Cell 2010; 18: 268-281.
[95] Ferrandino F, Grazioli P, Bellavia D, Campese AF, Screpanti I and Felli MP. Notch and NF-κB: coach and players of regulatory T-cell response in cancer. Front Immunol 2018; 9: 2165.
[96] Osipo C, Golde TE, Osborne BA and Miele LA. Off the beaten pathway: the complex cross talk between Notch and NF-kappaB. Lab Invest 2008; 88: 11-17.
[97] Hetz C, Chevet E and Harding HP. Targeting the unfolded protein response in disease. Nat Rev Drug Discov 2013; 12: 703-719.
[98] Atkins C, Liu Q, Minthorn E, Zhang SY, Figueroa DJ, Moss K, Stanley TB, Sanders B, Goetz A, Gaul N, Choudhry AE, Alsaid H, Jucker BM, Axten JM and Kumar R. Characterization of a novel PERK kinase inhibitor with antitumor and antiangiogenic activity. Cancer Res 2013; 73: 1993-2002.
[99] Papandreou I, Denko NC, Olson M, Van Melckebeke H, Lust S, Tam A, Solow-Cordero DE, Bouley DM, Offner F, Niwa M and Koong AC. Identification of an Ire1alpha endonuclease specific inhibitor with cytotoxic activity against human multiple myeloma. Blood 2011; 117: 1311-1314.
[100] Sidrauski C, Acosta-Alvear D, Khoutorsky A, Vedantham P, Hearn BR, Li H, Gamache K, Gallagher CM, Ang KK, Wilson C, Okreglak V, Ashkenazi A, Hann B, Nader K, Arkin MR, Renslo AR, Sonenberg N and Walter P. Pharmacological brake-release of mRNA translation enhances cognitive memory. Elife 2013; 2: e00498.
[101] Das I, Krzyzosiak A, Schneider K, Wrabetz L, D'Antonio M, Barry N, Sigurdardottir A and Bertolotti A. Preventing proteostasis diseases by selective inhibition of a phosphatase regulatory subunit. Science 2015; 348: 239-242.
[102] Gallagher CM and Walter P. Ceapins inhibit ATF6α signaling by selectively preventing transport of ATF6α to the Golgi apparatus during ER stress. Elife 2016; 5: e11880.
[103] Wang L, Perera BG, Hari SB, Bhhatarai B, Backes BJ, Seeliger MA, Schürer SC, Oakes SA, Papa FR and Maly DJ. Divergent allosteric control of the IRE1α endoribonuclease using kinase inhibitors. Nat Chem Biol 2012; 8: 982-989.
[104] Ali MM, Bagratuni T, Davenport EL, Nowak PR, Silva-Santisteban MC, Hardcastle A, McAndrews C, Rowlands MG, Morgan GJ, Aherne W, Collins I, Davies FE and Pearl LH. Structure of the Ire1 autophosphorylation complex and implications for the unfolded protein response. EMBO J 2011; 30: 894-905.
[105] Jha BK, Polyakova I, Kessler P, Dong B, Dickerman B, Sen GC and Silverman RH. Inhibition of RNase L and RNA-dependent protein kinase (PKR) by sunitinib impairs antiviral innate immunity. J Biol Chem 2011; 286: 26319-26326.
[106] Liu B, Diaz Arguello OA, Chen D, Chen S, Saber A and Haisma HJ. CRISPR-mediated ablation of overexpressed EGFR in combination with sunitinib significantly suppresses renal cell carcinoma proliferation. PLoS One 2020; 15: e0232985.
[107] Ghosh R, Wang L, Wang ES, Perera BG, Igbaria A, Morita S, Prado K, Thamsen M, Caswell D, Macias H, Weiberth KF, Gliedt MJ, Alavi MV, Hari SB, Mitra AK, Bhhatarai B, Schürer SC, Snapp EL, Gould DB, German MS, Backes BJ, Maly DJ, Oakes SA and Papa FR. Allosteric inhibition of the IRE1α RNase preserves cell viability and function during endoplasmic reticulum stress. Cell 2014; 158: 534-548.
[108] Sanches M, Duffy NM, Talukdar M, Thevakumaran N, Chiovitti D, Canny MD, Lee K, Kurinov I, Uehling D, Al-awar R, Poda G, Prakesch M, Wilson B, Tam V, Schweitzer C, Toro A, Lucas JL, Vuga D, Lehmann L, Durocher D, Zeng Q, Patterson JB and Sicheri F. Structure and mechanism of action of the hydroxy-aryl-aldehyde class of IRE1 endoribonuclease inhibitors. Nat Commun 2014; 5: 4202.
[109] Tang CH, Ranatunga S, Kriss CL, Cubitt CL, Tao J, Pinilla-Ibarz JA, Del Valle JR and Hu CC. Inhibition of ER stress-associated IRE-1/XBP-1 pathway reduces leukemic cell survival. J Clin Invest 2014; 124: 2585-2598.
[110] Tomasio SM, Harding HP, Ron D, Cross BC and Bond PJ. Selective inhibition of the unfolded protein response: targeting catalytic sites for Schiff base modification. Mol Biosyst 2013; 9: 2408-2416.
[111] Mimura N, Fulciniti M, Gorgun G, Tai YT, Cirstea D, Santo L, Hu Y, Fabre C, Minami J, Ohguchi H, Kiziltepe T, Ikeda H, Kawano Y, French M, Blumenthal M, Tam V, Kertesz NL, Malyankar UM, Hokenson M, Pham T, Zeng Q, Patterson JB,

Richardson PG, Munshi NC and Anderson KC. Blockade of XBP1 splicing by inhibition of IRE1α is a promising therapeutic option in multiple myeloma. Blood 2012; 119: 5772-5781.
[112] Volkmann K, Lucas JL, Vuga D, Wang X, Brumm D, Stiles C, Kriebel D, Der-Sarkissian A, Krishnan K, Schweitzer C, Liu Z, Malyankar UM, Chiovitti D, Canny M, Durocher D, Sicheri F and Patterson JB. Potent and selective inhibitors of the inositol-requiring enzyme 1 endoribonuclease. J Biol Chem 2011; 286: 12743-12755.
[113] Cross BC, Bond PJ, Sadowski PG, Jha BK, Zak J, Goodman JM, Silverman RH, Neubert TA, Baxendale IR, Ron D and Harding HP. The molecular basis for selective inhibition of unconventional mRNA splicing by an IRE1-binding small molecule. Proc Natl Acad Sci U S A 2012; 109: E869-878.
[114] Qiu Q, Zheng Z, Chang L, Zhao YS, Tan C, Dandekar A, Zhang Z, Lin Z, Gui M, Li X, Zhang T, Kong Q, Li H, Chen S, Chen A, Kaufman RJ, Yang WL, Lin HK, Zhang D, Perlman H, Thorp E, Zhang K and Fang D. Toll-like receptor-mediated IRE1α activation as a therapeutic target for inflammatory arthritis. EMBO J 2013; 32: 2477-2490.
[115] Logue SE, McGrath EP, Cleary P, Greene S, Mnich K, Almanza A, Chevet E, Dwyer RM, Oommen A, Legembre P, Godey F, Madden EC, Leuzzi B, Obacz J, Zeng Q, Patterson JB, Jäger R, Gorman AM and Samali A. Inhibition of IRE1 RNase activity modulates the tumor cell secretome and enhances response to chemotherapy. Nat Commun 2018; 9: 3267.
[116] Le Reste PJ, Pineau R, Voutetakis K, Samal J, Jégou G, Lhomond S, Gorman AM, Samali A, Patterson JB, Zeng Q, Pandit A, Aubry M, Soriano N, Etcheverry A, Chatziioannou A, Mosser J, Avril T and Chevet E. Local intracerebral inhibition of IRE1 by MKC8866 sensitizes glioblastoma to irradiation/chemotherapy in vivo. Cancer Lett 2020; 494: 73-83.
[117] Feldman HC, Tong M, Wang L, Meza-Acevedo R, Gobillot TA, Lebedev I, Gliedt MJ, Hari SB, Mitra AK, Backes BJ, Papa FR, Seeliger MA and Maly DJ. Structural and functional analysis of the allosteric inhibition of IRE1α with ATP-Competitive ligands. ACS Chem Biol 2016; 11: 2195-2205.
[118] Bouchecareilh M, Caruso ME, Roby P, Parent S, Rouleau N, Taouji S, Pluquet O, Bossé R, Moenner M and Chevet E. AlphaScreen-based characterization of the bifunctional kinase/RNase IRE1alpha: a novel and atypical drug target. J Biomol Screen 2010; 15: 406-417.
[119] Bouchecareilh M, Higa A, Fribourg S, Moenner M and Chevet E. Peptides derived from the bifunctional kinase/RNase enzyme IRE1α modulate IRE1α activity and protect cells from endoplasmic reticulum stress. FASEB J 2011; 25: 3115-3129.
[120] Doultsinos D, Carlesso A, Chintha C, Paton JC, Paton AW, Samali A, Chevet E and Eriksson LA. Peptidomimetic-based identification of FDA-approved compounds inhibiting IRE1 activity. FEBS J 2021; 288: 945-960.
[121] Axten JM, Medina JR, Feng Y, Shu A, Romeril SP, Grant SW, Li WH, Heerding DA, Minthorn E, Mencken T, Atkins C, Liu Q, Rabindran S, Kumar R, Hong X, Goetz A, Stanley T, Taylor JD, Sigethy SD, Tomberlin GH, Hassell AM, Kahler KM, Shewchuk LM and Gampe RT. Discovery of 7-methyl-5-(1-{[3-(trifluoromethyl)phenyl]acetyl}-2,3-dihydro-1H-indol-5-yl)-7H-pyrrolo[2,3-d]pyrimidin-4-amine (GSK2606414), a potent and selective first-in-class inhibitor of protein kinase R (PKR)-like endoplasmic reticulum kinase (PERK). J Med Chem 2012; 55: 7193-7207.
[122] Yi S, Chen K, Zhang L, Shi W, Zhang Y, Niu S, Jia M, Cong B and Li Y. Endoplasmic reticulum stress is involved in stress-induced hypothalamic neuronal injury in rats via the PERK-ATF4-CHOP and IRE1-ASK1-JNK pathways. Front Cell Neurosci 2019; 13: 190.
[123] Guo J, Ren R, Sun K, Yao X, Lin J, Wang G, Guo Z, Xu T and Guo F. PERK controls bone homeostasis through the regulation of osteoclast differentiation and function. Cell Death Dis 2020; 11: 847.
[124] Axten JM, Romeril SP, Shu A, Ralph J, Medina JR, Feng Y, Li WH, Grant SW, Heerding DA, Minthorn E, Mencken T, Gaul N, Goetz A, Stanley T, Hassell AM, Gampe RT, Atkins C and Kumar R. Discovery of GSK2656157: an optimized PERK inhibitor selected for preclinical development. ACS Med Chem Lett 2013; 4: 964-968.
[125] Krishnamoorthy J, Rajesh K, Mirzajani F, Kesoglidou P, Papadakis AI and Koromilas AE. Evidence for eIF2α phosphorylation-independent effects of GSK2656157, a novel catalytic inhibitor of PERK with clinical implications. Cell Cycle 2014; 13: 801-806.
[126] Robert F, Kapp LD, Khan SN, Acker MG, Kolitz S, Kazemi S, Kaufman RJ, Merrick WC, Koromilas AE, Lorsch JR and Pelletier J. Initiation of protein synthesis by hepatitis C virus is refractory to reduced eIF2.GTP.Met-tRNA(i)(Met) ternary complex availability. Mol Biol Cell 2006; 17: 4632-4644.
[127] Boyce M, Bryant KF, Jousse C, Long K, Harding HP, Scheuner D, Kaufman RJ, Ma D, Coen DM, Ron D and Yuan J. A selective inhibitor of eIF2alpha dephosphorylation protects cells from ER stress. Science 2005; 307: 935-939.
[128] Dadey DYA, Kapoor V, Khudanyan A, Thotala D and Hallahan DE. PERK regulates glioblasto-

ma sensitivity to ER stress although promoting radiation resistance. Mol Cancer Res 2018; 16: 1447-1453.
[129] Sidrauski C, McGeachy AM, Ingolia NT and Walter P. The small molecule ISRIB reverses the effects of eIF2α phosphorylation on translation and stress granule assembly. Elife 2015; 4: e05033.
[130] Nguyen HG, Conn CS, Kye Y, Xue L, Forester CM, Cowan JE, Hsieh AC, Cunningham JT, Truillet C, Tameire F, Evans MJ, Evans CP, Yang JC, Hann B, Koumenis C, Walter P, Carroll PR and Ruggero D. Development of a stress response therapy targeting aggressive prostate cancer. Sci Transl Med 2018; 10: eaar2036.
[131] Smith AL, Andrews KL, Beckmann H, Bellon SF, Beltran PJ, Booker S, Chen H, Chung YA, D'Angelo ND, Dao J, Dellamaggiore KR, Jaeckel P, Kendall R, Labitzke K, Long AM, Materna-Reichelt S, Mitchell P, Norman MH, Powers D, Rose M, Shaffer PL, Wu MM and Lipford JR. Discovery of 1H-pyrazol-3(2H)-ones as potent and selective inhibitors of protein kinase R-like endoplasmic reticulum kinase (PERK). J Med Chem 2015; 58: 1426-1441.
[132] Lee AS. Glucose-regulated proteins in cancer: molecular mechanisms and therapeutic potential. Nat Rev Cancer 2014; 14: 263-276.
[133] Virrey JJ, Dong D, Stiles C, Patterson JB, Pen L, Ni M, Schönthal AH, Chen TC, Hofman FM and Lee AS. Stress chaperone GRP78/BiP confers chemoresistance to tumor-associated endothelial cells. Mol Cancer Res 2008; 6: 1268-1275.
[134] Ermakova SP, Kang BS, Choi BY, Choi HS, Schuster TF, Ma WY, Bode AM and Dong Z. (-)-Epigallocatechin gallate overcomes resistance to etoposide-induced cell death by targeting the molecular chaperone glucose-regulated protein 78. Cancer Res 2006; 66: 9260-9269.
[135] Stuart EC, Scandlyn MJ and Rosengren RJ. Role of epigallocatechin gallate (EGCG) in the treatment of breast and prostate cancer. Life Sci 2006; 79: 2329-2336.
[136] Mhaidat NM, Al-Balas QA, Alzoubi KH and AlEjielat RF. Potassium-3-beta-hydroxy-20-oxo-pregn-5-en-17-alpha-yl sulfate: a novel inhibitor of 78 kDa glucose-regulated protein. Onco Targets Ther 2016; 9: 627-634.
[137] Schoenhacker-Alte B, Mohr T, Pirker C, Kryeziu K, Kuhn PS, Buck A, Hofmann T, Gerner C, Hermann G, Koellensperger G, Keppler BK, Berger W and Heffeter P. Sensitivity towards the GRP78 inhibitor KP1339/IT-139 is characterized by apoptosis induction via caspase 8 upon disruption of ER homeostasis. Cancer Lett 2017; 404: 79-88.
[138] Cerezo M, Lehraiki A, Millet A, Rouaud F, Plaisant M, Jaune E, Botton T, Ronco C, Abbe P, Amdouni H, Passeron T, Hofman V, Mograbi B, Dabert-Gay AS, Debayle D, Alcor D, Rabhi N, Annicotte JS, Héliot L, Gonzalez-Pisfil M, Robert C, Moréra S, Vigouroux A, Gual P, Ali MMU, Bertolotto C, Hofman P, Ballotti R, Benhida R and Rocchi S. Compounds triggering ER stress exert anti-melanoma effects and overcome BRAF inhibitor resistance. Cancer Cell 2016; 30: 183.
[139] Ruggiero C, Doghman-Bouguerra M, Ronco C, Benhida R, Rocchi S and Lalli E. The GRP78/BiP inhibitor HA15 synergizes with mitotane action against adrenocortical carcinoma cells through convergent activation of ER stress pathways. Mol Cell Endocrinol 2018; 474: 57-64.
[140] Wu J, Wu Y and Lian X. Targeted inhibition of GRP78 by HA15 promotes apoptosis of lung cancer cells accompanied by ER stress and autophagy. Biol Open 2020; 9: bio053298.
[141] Taghizadeh S, Soheili ZS, Sadeghi M, Samiei S, Ranaei Pirmardan E, Kashanian A, Zakeri F, Latifi-Navid H and Shams Najafabadi H. sFLT01 modulates invasion and metastasis in prostate cancer DU145 cells by inhibition of VEGF/GRP78/MMP2&9 axis. BMC Mol Cell Biol 2021; 22: 30.
[142] Pechan P, Rubin H, Lukason M, Ardinger J, DuFresne E, Hauswirth WW, Wadsworth SC and Scaria A. Novel anti-VEGF chimeric molecules delivered by AAV vectors for inhibition of retinal neovascularization. Gene Ther 2009; 16: 10-16.
[143] Bagley RG, Kurtzberg L, Weber W, Nguyen TH, Roth S, Krumbholz R, Yao M, Richards B, Zhang M, Pechan P, Schmid S, Scaria A, Kaplan J and Teicher BA. sFLT01: a novel fusion protein with antiangiogenic activity. Mol Cancer Ther 2011; 10: 404-415.
[144] Walczak A, Gradzik K, Kabzinski J, Przybylowska-Sygut K and Majsterek I. The role of the ER-induced UPR pathway and the efficacy of its inhibitors and inducers in the inhibition of tumor progression. Oxid Med Cell Longev 2019; 2019: 5729710.
[145] White-Gilbertson S, Hua Y and Liu B. The role of endoplasmic reticulum stress in maintaining and targeting multiple myeloma: a double-edged sword of adaptation and apoptosis. Front Genet 2013; 4: 109.