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Mini-review

# Endoplasmic reticulum proteostasis control and gastric cancer

Yu Wang[a,1], Kai Wang[b,1], Yang Jin[c], Xia Sheng[a,*]

[a] School of Public Health, Tongji Medical College, Huazhong University of Science and Technology, Wuhan, 430030, China
[b] School of Biological and Pharmaceutical Engineering, Wuhan Polytechnic University, Wuhan, 430023, China
[c] Department of Biosciences, University of Oslo, Oslo, 0371, Norway

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ABSTRACT

The endoplasmic reticulum (ER) is the primary organelle responsible for the synthesis, modification, folding and secretion of proteins, especially in specialized secretory cells. It also contributes to the maintenance of cellular functions, such as $Ca^{2+}$ storage, lipogenesis, gluconeogenesis, and organelle biogenesis. Cellular stress conditions, such as glucose deprivation, hypoxia and disturbance of $Ca^{2+}$ homeostasis, may increase the risk of protein misfolding and perturb proteostasis. This activates ER stress and triggers the unfolded protein response (UPR), leading to either the restoration of homeostasis or cell death. ER stress and UPR have been shown to play crucial roles in the pathogenesis, progression and treatment response of various cancers. In gastric cancer (GC), one of the most aggressive cancer types, critical functions of ER stress signaling have also started to emerge. Herein, we summarize the current knowledge linking ER stress and UPR to GC; we also discuss the possible nodes of therapeutic intervention and propose directions of future research.

## 1. Introduction

### 1.1. Gastric cancer

Gastric cancer (GC) is the fourth most common cancer and the second leading cause of cancer death worldwide, with more than 950,000 new cases yearly and around 720,000 death in 2012 [1]. Interestingly, the global distribution of GC varies substantially across geographical regions: while Asia accounts for more than 70% of the world's cases, the case number in North America and most western European countries is relatively lower [2]. Among the East Asian countries, China contributes ~40% of the world's new cases [3]. Japan exhibits one of the highest incident rates, but the implementation of screening strategies has led to earlier detection and dramatic reduction in mortality rate [4]. Nevertheless, despite an overall decline in incidence and mortality over the past several decades, GC continues to pose a major threat to global health, especially to that of Asian countries.

The variation in epidemiology across the globe demonstrate that a multitude of factors are associated with the pathogenesis of GC, for which *Helicobacter pylori* infection has been generally regarded as a major risk factor [5]. Being classified as Class I human carcinogen, *H. pylori* induces chronic gastritis and a cascade of molecular events that facilitates malignant transformation [6]. Not surprisingly, the *H. pylori* strains that produce oncoproteins such as cytotoxin-associated gene A (CagA) and vacuolating cytotoxin A (VacA) are more likely to cause GC than those that do not [7]. In addition, the infection of Epstein-Barr virus (EBV) also contributes to GC development by altering the expression of various genes, such as *AKT2*, *CCNA1*, *MAP3K4*, and *TGFBR1* [8].

GC is highly heterogeneous in terms of its anatomy, histology and molecular biology. Depending on the anatomical location, GC can be divided into non-cardia and cardia, two types of cancers with distinct epidemiological and pathological features [9]. Histologically, the most common (~95%) GC type is gastric adenocarcinoma (GAC), which can be further divided into intestinal, diffuse and mixed phenotypes according to the Lauren classification [10]. The intestinal GAC is characterized with well to moderately differentiated histology and form glandular structures reminiscent of colorectal adenocarcinoma, hence the type name; while the diffuse type is poorly differentiated without gland formation [10]. On the molecular level, a comprehensive analysis by The Cancer Genome Atlas (TCGA) provided multiplex genomic data on GAC and defined four subclasses: EBV + tumors (9%); microsatellite instability (MSI)-high tumors (22%); tumors with stable genome (20%); and tumors with chromosomal instability (CIN) (50%) [11]. This molecular feature-based classification is expected to become more

* Corresponding author.
*E-mail address:* xiasheng@hust.edu.cn (X. Sheng).
[1] These authors contributed equally to this work.

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frequently used in the future to determine prognosis and to guide treatment. For example, the CIN subtype tumors often display DNA aneuploidy, chromosomal rearrangement, mutations in key oncogenes and tumor suppressor genes, and are more likely to benefit from cisplatin-based neoadjuvant chemotherapy [12]. The fact that MSI-high tumors are prone to mutations due to a deficient DNA repair machinery also potentially confer vulnerability to immune checkpoint inhibitors, corroborated by a recent clinical study [13].

To date, adequate surgical resection is the only curative therapeutic option for GC. Other treatments including endoscopic therapy, radiotherapy and chemotherapy are also used in neoadjuvant, adjuvant, and metastatic settings. With respect to targeted therapies, only two drugs have been approved by the United States Food and Drug Administration so far based on positive clinical trials: ramucirumab, a monoclonal antibody against vascular endothelial growth factor receptor 2, and trastuzumab, a monoclonal antibody that targets human epidermal growth factor receptor 2 (HER2) [2]. Unfortunately, resistance to these drugs will eventually occur via poorly understood mechanisms [14,15].

### 1.2. The endoplasmic reticulum and unfolded protein response

Tumor cells are constantly challenged by internal stresses (such as oncogenic activation) and external hostile environmental cues (such as hypoxia and nutrient deprivation), which can post a serious threat to their protein homeostasis, also known as 'proteostasis' [16]. Being responsible for the synthesis of more than one third of the proteome in a cell, the endoplasmic reticulum (ER) is the major subcellular compartment for the folding and trafficking of secretory and transmembrane proteins. Besides, ER also plays an essential role in intracellular $Ca^{2+}$ homeostasis and a variety of metabolic processes, such as gluconeogenesis and lipid biogenesis [17]. Stress stimuli, such as accumulation of misfolded or unfolded proteins, imbalance in ER $Ca^{2+}$ levels, glucose deprivation, or hypoxia can all render the ER under stress [18]. To alleviate the stress, the ER initiates a highly integrated signaling network named the unfolded protein response (UPR), which enhances ER protein folding capacity, reduces secretory protein load, and increases unfolded protein clearance via ER-associated degradation (ERAD) and autophagy. On the other hand, upon unresolved stress, the UPR switches from pro-survival to pro-apoptotic signaling and results in cell death [17].

The canonical UPR consists of three ER transmembrane stress sensors: inositol-requiring enzyme 1 (IRE1), protein kinase R-like ER kinase (PERK), and activating transcription factor 6 (ATF6), all of which are bound to the ER chaperone glucose-regulated protein (GRP) 78/BiP under resting conditions and are kept inactive [19]. Under stress conditions, GRP78 dissociates from these UPR sensors, allowing their respective oligomerization and autotransphosphorylation or revealing an ER export motif in ATF6, thereby leading to the activation of UPR and downstream signaling (Fig. 1).

There are two IRE1 isoforms in mammals, IRE1α and IRE1β. IRE1α is ubiquitously expressed, whereas IRE1β is primarily observed in the gastrointestinal and respiratory tracts [20]. IRE1α is a dual enzyme with both endoribonuclease (RNase) and serine/threonine kinase activities. Upon ER stress, the luminal domain of IRE1α goes through self-association, which further leads to its dimerization, oligomerization, and *trans*-autophosphorylation, resulting in a conformational change that activates the RNase domain on its cytosolic face. The highly sequence specific enzyme splices the *X-box binding protein 1* (*XBP1*) mRNA, which is subsequently re-ligated by the tRNA ligase RCTB [21]. This creates a frame shift and facilitates the translation of an active and stable transcription factor termed spliced XBP1 (XBP1s) [22]. XBP1s target genes are involved in the regulation of numerous processes including ER protein folding and secretion capacity, ERAD and lipid synthesis. Under certain conditions, IRE1α may broaden its substrate spectrum and cleave many ER-bound mRNAs, rRNA, and miRNAs through regulated IRE1α-dependent decay (RIDD) [23], which can either preserve ER homeostasis or induce cell death [24]. In response to prolonged stress, IRE1α may initiate a cascade of phosphorylation events that result in the activation of c-Jun N-terminal kinase (JNK) and cell death [25,26], linking IRE1α signaling to apoptosis.

Compared to IRE1α, IRE1β cleaves the *XBP1* mRNA less efficiently [27]. Instead, the IRE1β RNase may have acquired a broader substrate specificity, as it has been shown to mediate the site-specific cleavage of 28S rRNA and various ER-localized mRNAs, resulting in translational attenuation of secretory proteins [28,29]. Considering the tissue-specific expression of IRE1β, this is likely an additional means evolved to maintain ER proteostasis of the highly differentiated secretory cells in the gastrointestinal tract.

PERK has an N-terminal stress-sensing luminal domain and a cytosolic serine/threonine kinase domain. Upon ER stress, PERK goes through dimerization and autophosphorylation, resulting in the activation of its kinase domain that phosphorylates Ser51 in eukaryotic translation initiation factor 2 (eIF2) α-subunit [30]. This halts global translation and relieves the burden of protein overload on the ER [31]. In the meantime, it allows for the translation of several mRNAs with their upstream open reading frames within the 5' region, such as *ATF4* [32]. ATF4 is a key transcription factor promoting adaptive response by regulating the expression of genes involved in protein folding, autophagy and redox homeostasis. Under certain conditions, the pro-apoptotic protein C/EBP homologous protein (CHOP) can be directly activated by ATF4 [33], making PERK signaling another critical switch in cell fate determination.

In addition to PERK, three other kinases converge on the phosphorylation of the same residue in eIF2α, which are general control non-derepressible 2 (GCN2) activated by nutrient deprivation, double-stranded RNA-dependent protein kinase (PKR) activated by viral infections, and heme-regulated eIF2α kinase (HRI) activated by heme deficiency. Together with PERK, these stress kinases, known as the integrated stress response, are responsive to a broad range of physiological and pathological conditions and primarily function as a pro-survival, homeostatic program [34].

ATF6 is a basic leucine zipper (bZIP) transcription factor that translocates to the Golgi apparatus when activated. Therein, it is cleaved by the site-1 and site-2 proteases (S1P and S2P), releasing the cytosolic fragment that functions as a transcription factor to regulate gene expression [35]. Many of the ATF6 target genes have been implicated in protein folding and ERAD. ATF6 has also been shown to *trans*-activate key UPR component genes such as *XBP1* and *CHOP* depending on the setting, and form heterodimers with XBP1s that may drive select gene expression programs [36].

In recent years, extensive studies have implicated ER stress and UPR in the hallmarks of cancer, including proliferation, angiogenesis, migration and invasion, tumor microenvironment, and treatment resistance [37]. For example, the functional significance of IRE1α-XBP1s has been demonstrated in multiple myeloma, where targeting *XBP1* splicing with IRE1α RNase inhibitors synergized with the proteasome inhibitor bortezomib in preclinical models [38]. A similar pro-survival role of IRE1α-XBP1s has also been unveiled in prostate cancer cells, in which androgens robustly activated the IRE1α-XBP1s arm while simultaneously inhibited the PERK-eIF2α pathway [39]. PERK-eIF2α-ATF4 signaling mediates the oncogenic effect of c-Myc in lymphoma by promoting cytoprotective autophagy [40], while activation of both IRE1α and PERK arms have been shown to confer survival advantage of different tumor cells under hypoxic conditions [41,42]. Much less is known about the role of ATF6 in cancer, but it has been implicated in tumor cell quiescence and chemoresistance through activation of the Rheb-mTOR signaling [43]. In addition to in cancer cells per se, critical functions for UPR signaling has been established in the modulation of tumor stromal cells, in particular cancer-associated immune cells [44]. For instance, activation of the IRE1α-XBP1s reprograms the tumor-associated dendritic cells and T cells, which results in impaired anti-tumor activity in ovarian cancer [45,46]. With respect to GC, recent

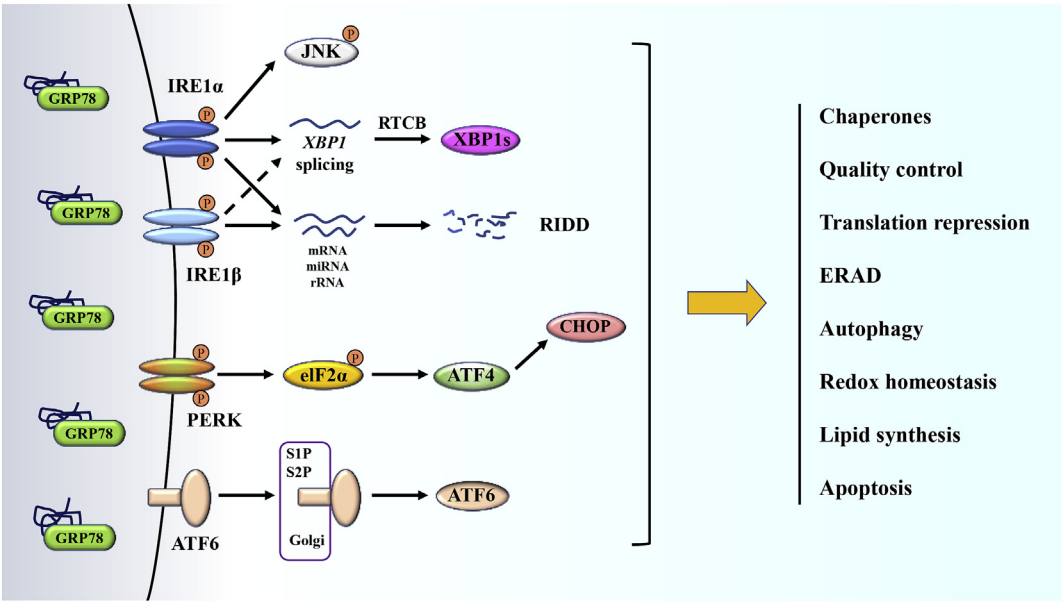


**Fig. 1.** The UPR signaling network. In response to ER stress stimuli, such as the accumulation of unfolded/misfolded proteins, GRP78 dissociates from the three UPR sensors, resulting in their activation. Activated IRE1α splices the *XBP1* mRNA, leading to the generation of XBP1s. XBP1s translocates to the nucleus and induces the expression of UPR target genes. IRE1α activation can also lead to degradation of ER-associated mRNAs through RIDD. Upon unresolved stress, phosphorylated IRE1α induces JNK signaling and apoptosis. IRE1β splices the *XBP1* mRNA less efficiently (denoted as dashed line), but can facilitate cleavage of 28S rRNA, ER-bound mRNAs and miRNAs. Oligomerized PERK phosphorylates eIF2α and inhibits global translation, but concomitantly induces the expression of ATF4. ATF4 can activate CHOP expression under extreme conditions, leading to apoptosis. Activated ATF6 translocates to the Golgi, where it is cleaved by the proteases S1P and S2P, generating an active transcription factor. The UPR target genes are involved in a number of processes that attempt to restore the ER homeostasis.

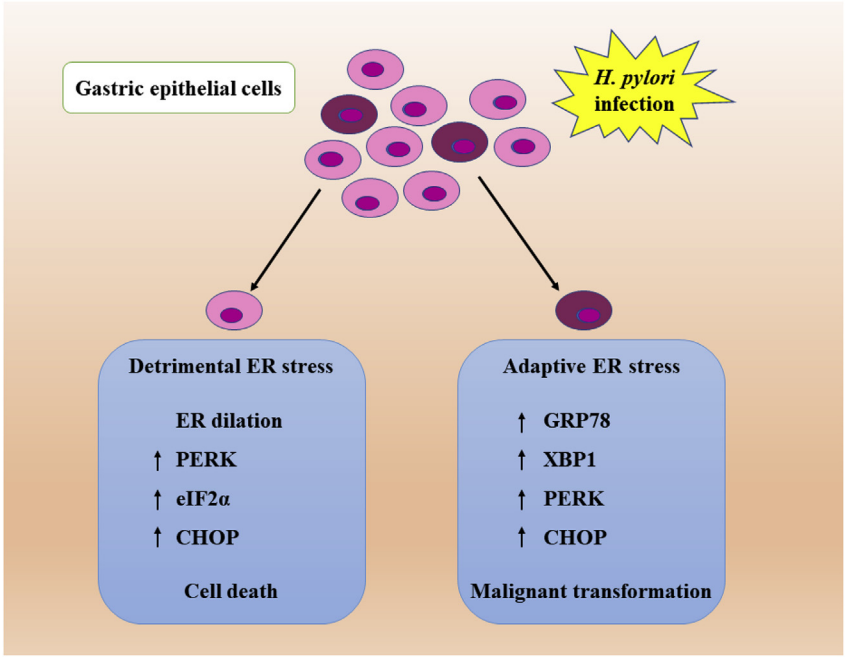


**Fig. 2.** ER stress in *Helicobacter pylori* infection of gastric epithelial cells. In most of the *H. pylori* infected gastric epithelial cells, ER stress mediates a detrimental outcome by activating the PERK-eIF2α branch, resulting in elevated CHOP expression and apoptosis. In contrast, some cells may initiate adaptive ER stress response, activate the expression of GRP78, XBP1, as well as the PERK branch, and obtain malignant characteristics. CHOP upregulation also occurs in this context, but whether it plays a pro-tumorigenic role is not clear.

advances have also started to shed light on the implications of ER stress and UPR signaling in its transformation and development, which is summarized below.

### 1.3. ER stress signaling in gastric cancer

#### 1.3.1. ER stress and Helicobacter pylori infection

*H. pylori* infection is a major risk factor associated with GC development. The transition from normal mucosa to non-atrophic gastritis, triggered primarily by *H. pylori* infection, initiates precancerous lesions which may then progress to atrophic gastritis and intestinal metaplasia [2]. The responses that develop upon *H. pylori* infection are directly mediated through the action of bacterial virulence factors, such as CagA and VacA, which drive the initial molecular events associated with malignant transformation [6].

*H. pylori* alters epithelial cell turnover and promotes cell death in the majority of infected gastric cells, resulting in primary tissue lesions associated with an initial inflammatory response [47]. The cytotoxin ammonia secreted by *H. pylori* disrupts intracellular $Ca^{2+}$ homeostasis in gastric epithelial cells, which likely leads to induction of ER stress

[48]. In line with this report, incubation of gastric epithelial cells with VacA and ammonia activates the PERK-eIF2α branch, and ultimately CHOP expression and apoptosis [49]. Furthermore, in transformed human GC cells, such as SGC-7901, *H. pylori* infection induces vacuolar degeneration, dilated ER, and reduction of organelles [50]. In AGS cells, VacA transfection similarly induces ER dilation, eIF2α phosphorylation, and apoptotic ER stress and autophagy, which could be reversed by genetic inhibition of ATF4 and CHOP [51].

On the other hand, in the remaining gastric epithelial cell population, adaptive responses are induced that increase cell survival and proliferation, resulting in the acquisition of potentially malignant characteristics that may lead to the formation of precancerous lesions [47]. ER stress has also been proposed to play a role in this process, as levels of key UPR components, such as GRP78, CHOP, PERK and XBP1 are significantly correlated with *H. pylori*-positive GC [52]. However, understanding its functional significance and the underpinning mechanisms requires more in-depth studies. The reasons to the divergent ER stress responses induced in these cells that ultimately lead to distinct cell fate are not clear either (Fig. 2).

It is noteworthy to mention that, in addition to *H. pylori*, a diverse microbial community inhabits the stomach and exists in a delicate balance. The potential role of gastric microbiome in GC initiation and progression has been recently summarized elsewhere [53,54]. Yet, little is known about whether and how the gastric microbiome affects the ER homeostasis of the gastric epithelial cells, and the implication of this interaction in GC initiation and progression.

#### 1.3.2. ER stress signaling components and gastric cancer

As mentioned above, CHOP is one of the key players linking unresolved ER stress to apoptosis in many cancer types, and a similar role has also been established in GC [55]. Taking cardiac GC for example, CHOP is down-regulated on both mRNA and protein levels in cancer compared with in adjacent non-cancerous tissues. CHOP expression rate is negatively associated with clinical stage, tumor differentiation and lymph node metastasis, while patients with low CHOP level are associated with poor prognosis and short overall survival. Thus, CHOP has been proposed as a potential prognostic biomarker for cardiac GC [56]. To date, much less is known about the key UPR components in GC progression, especially the three canonical stress sensors, IRE1, PERK and ATF6, concerning their expression patterns, functional significance and therapeutic values. Considering the important pro-survival roles of adaptive UPR unmasked in several other cancers, thorough investigations on these aspects in GC will potentially lead to the discovery of novel therapeutic targets.

#### 1.3.3. The ER-resident proteins that promote gastric cancer

The ER is enriched with molecular chaperones to guarantee the correct folding of newly synthesized proteins. As a major ER chaperone, GRP78 is extensively expressed in human neoplasms and has been associated with pathogenesis, aggressiveness and progression of gastric tumors [57], which is recently summarized elsewhere [58]. To exemplify, in early stage GC patients, increased GRP78 expression is identified as an independent biomarker for poor overall survival [59]; while in late stage disease, its expression is also higher in patients with lymph node metastasis than those without [60]. Functionally, GRP78 has been shown to play an important role in GC cell proliferation, anti-apoptosis, invasion, as well as the development to resistance [58]. Its degradation, for instance caused by the interaction with the sodium channel subunit SCNN1B, triggers the activation of UPR including the PERK-ATF4-CHOP branch, and leads to caspase-dependent apoptosis [61].

Similar to GRP78, the ER chaperone GRP94 level is also correlated with the pathogenesis, growth, invasion, and metastasis of GC, and is proposed as a biomarker for the aggressive behavior and poor prognosis [62]. The expression of ERp19, a protein disulfide isomerase (PDI) family member, is higher in gastric tumors than in non-tumor tissues, and associates with tumor size, lymph node involvement and poor prognosis. Furthermore, ERp19 is required for GC cell growth, migration, invasion, partially through promoting the focal adhesion kinase (FAK) signaling [63]. Another PDI family member, anterior gradient 2 (Agr2), is highly expressed in gastric signet-ring cell carcinoma compared to in noncancerous tissue. Secreted Agr2 activates stromal fibroblasts and promotes fibroblast-associated cancer invasion in a paracrine manner, thereby remodeling the tumor microenvironment towards an invasive phenotype [64]. In addition, ER oxidoreductin-1-like (ERO1L), a PDI interaction partner and an important player in hypoxia-induced oxidative protein folding, is highly expressed in GC tissue, and its level is associated with adverse prognosis in patients with GC [65]. Functionally, ERO1L is required for GC cell proliferation, migration, invasion, and chemoresistance in vitro, which is mediated, at least in part, by AKT and JNK signaling [66].

#### 1.3.4. ER-resident proteins that inhibit gastric cancer

In contrast, there are a number of ER chaperones and proteins whose expression is down-regulated in GC. For instance, ERp29 level is significantly lower in GC tissues than in adjacent normal tissues, and is inversely correlated with tumor size, stage and prognosis [67]. Functional analyses have proposed ERp29 as a tumor suppressor in various GC model systems by repressing the PI3K-AKT pathway [68]. Likewise, ERp57 expression is dramatically decreased in cancer and metastases compared with in normal gastric mucosa, while loss of ERp57 expression is positively linked with disease aggressiveness [69].

Meanwhile, several ER membrane-associated proteins have also been implicated in this regard. For example, the expression of ER membrane protein complex subunit 6 (EMC6) is also lost or reduced in glandular cells of GC patients compared to normal stomach mucosa. Overexpression of EMC6 in GC cells inhibits cell growth, migration, invasion, and induces apoptosis and cell cycle arrest [70]. The level of ER Golgi intermediate compartment 1 (ERGIC1) gradually decreases from normal gastric mucosal tissues, to dysplastic tissues, and to GC tissues; while ectopic expression of ERGIC1 suppresses proliferation and enhances apoptosis in different GC cell lines, demonstrating an inhibitory effect in GC cell survival [71]. Junctophilin (JPH) proteins stabilize junctional membrane complexes between ER and the plasma membrane. The *JPH3* gene is found frequently silenced in GC due to promoter CpG methylation. Ectopic expression of JPH3 induces UPR gene expression upon ER stress, promotes mitochondrial mediated-apoptosis, and inhibits tumor cell growth in vitro and in vivo, indicating a tumor suppressive function [72]. Lastly, the expression of oxysterol-binding protein-related protein 8 (ORP8), a sterol sensor, is significantly lower in GC tissues than in normal tissues. Ectopic expression of ORP8 markedly induces the levels of GRP78, phospho-PERK and CHOP, and concurrently decreases Wnt3a and β-catenin expression, resulting in impeded GC cell proliferation in vitro and in vivo [73].

With respect to metastasis, germline mutations of *CDH1* (encoding the invasion suppressor E-cadherin) are the only known genetic cause of hereditary diffuse GC [74]. The ER chaperone DnaJ Heat Shock Protein Family Member B4 (DNAJB4) directly interacts with and stabilizes wildtype E-cadherin, while promotes premature degradation of unfolded E-cadherin mutants through ERAD. Therefore, DNAJB4 functions as a sensor of E-cadherin structural features and may restrain the invasion and metastasis of hereditary diffuse GC [75].

#### 1.3.5. ER calcium-related factors and gastric cancer

The sarco/endoplasmic reticulum $Ca^{2+}$-ATPases (SERCAs) pump cytosolic $Ca^{2+}$ into the ER lumen, thereby modulating the $Ca^{2+}$ concentration to regulate various cellular processes including gene transcription, cell growth, differentiation, and apoptosis [76]. In GC cells, gene expression of SERCA3 is found to be transcriptionally regulated by transcription factors Sp1, Sp3, and Klf-4 [77]. In patients, SERCA3 expression is reduced in GC, and is negatively related to depth of invasion,

distant metastasis, and tumor node metastasis staging. High SERCA3 level is associated with a favorable prognosis in GC patients [78]. In contrast, stromal interacting molecule 1 (STIM1), an ER $Ca^{2+}$ sensor and activator of store-operated channel entry, contributed to SGC7901 cell proliferation, viability and migration in vitro [79]. In addition, the key $Ca^{2+}$-buffering chaperone calreticulin is found over-expressed in gastric tumors, and its level is significantly associated with lymph node and distant metastasis as well as poor prognosis [80].

#### 1.3.6. Crosstalk with other signaling in gastric cancer

Several previous studies have investigated the impact of ER stress on crucial kinase signaling in GC cells, shedding light on the possible interactions between ER stress signaling and other critical pathways. When GC cells are under mild ER stress (3 μM tunicamycin), both GRP78 and ERK1/2 are rapidly activated, which may protect the cells from apoptosis [81]. However, prolonged challenge with the same stimulus results in apoptosis by activating PERK branch and concomitantly repressing AKT Ser473 phosphorylation, an effect that can be counteracted by estrogen treatment (1 nM 17β-estradiol) [82]. Importantly, if the cells are exposed to chemotherapeutic agents, enhanced ER stress alleviates the apoptotic rate by activating the p38 MAP kinase pathway, thereby conferring resistance to chemotherapy [83]. These results indicate that ER stress may determine the cell fate by participating in the modulation of cellular signaling network in GC cells. All the ER stress-related proteins described here are also summarized in Table 1.

### 1.4. Targeting the ER stress signaling in gastric cancer

Although extensive efforts have been made in recent decades to treat GC with various anticancer drugs, effective therapeutics to cure the disease are still lacking in the clinics. Given the significance of ER function in cancer cells, targeting the ER homeostasis is emerging as a new therapeutic strategy [84]. A number of IRE1 inhibitors modulating its RNase activity, kinase activity, or both, have been developed; many of them have demonstrated significant anticancer effect in various cancer models [85], highlighting IRE1α-XBP1s as a promising therapeutic target. Moreover, IRE1α RNase repression may also synergize with existing clinical drugs or enhance response to chemotherapy [86–88]. In the meantime, PERK kinase inhibitors have shown potent inhibitory effect in the growth of multiple human tumor xenografts in mice [89]. A variety of small molecule drugs and chemical extracts that disrupt ER homeostasis have also demonstrated antitumor effect in GC model systems, suggesting that ER proteostasis and adaptive UPR may represent an Achilles' heel in GC.

Thus far, two major UPR signaling have been established to facilitate the detrimental ER stress response, the PERK-eIF2α activated ATF4-CHOP signaling and the IRE1-JNK pathway [90]. In GC models, most of the compounds that activate the lethal ER stress are through the up-regulation of CHOP, this includes 7-acetylsinumaximol B (a bioactive cembranoid from *Sinularia sandensis*) [91], dehydroeffusol (extracted from the medicinal herb *Juncus effuses*) [92], Tanshinone IIA (from *Salviae Miltiorrhizae Radix*) [93], and the recombinant Lz-8 protein from the fungus *Ganoderma lucidum* [94]. In the meantime, activation of IRE1-JNK pathway has been observed to mediate the anti-proliferative and apoptotic effect of bufalin (extracted from Chan Su) [95], as well as the iron-chelators deferoxamine and deferasirox [96].

Disruption of $Ca^{2+}$ homeostasis is a bona fide inducer of ER stress and UPR. Several molecules have been reported to affect ER $Ca^{2+}$ homeostasis, leading to detrimental outcomes in GC cells. For example, E platinum enhances ER $Ca^{2+}$ outflow by increasing inositol trisphosphate receptor type 1 expression and decreasing ERp44 expression, resulting in ER stress and the activation of PERK branch [97]. Celecoxib, a non-steroidal anti-inflammatory drug, increases intracellular $Ca^{2+}$ level, up-regulates ER chaperones GRP78, ERdj3, ERdj4, and 150-kDa oxygen-regulated protein (ORP150), and activates PERK and ATF6 branches [98–100]. Other molecules that interfere with ER $Ca^{2+}$ homeostasis and induce apoptosis include vitamin E succinate [101], caffeic acid [102], and apogossypolone [103].

Reactive oxygen species (ROS) and ER stress are closely interrelated, with the activation of one frequently leads to the induction of the other [104]. A number of refined curcumin analogs have shown promising antitumor activities in GC experimental models by inducing ROS generation and the subsequent activation of lethal ER stress, thereby impairing GC cell survival [105–109]. Other molecules reported to give rise to ROS and ER stress comprise the rheumatic arthritis drug auranofin [110], chemotherapeutic agent E platinum [97], AKT inhibitor MK-2206 [111], mTOR inhibitor rapamycin [112], vitamin E [113], a natural alkaloid [114], wogonin (5,7-dihydroxy-8-methoxyflavone) [115] and iron-chelating agents deferoxamine and deferasirox [96]. One of the possible mechanisms is that these compounds may interact with and inhibit the activity of thioredoxin reductase 1, a key antioxidant enzyme, thus leading to increased intracellular ROS level [108,114].

Tumor necrosis factor-related apoptosis-inducing ligand (TRAIL) is one of the most effective cancer treatments owing to its ability to selectively kill cancer cells, without affecting normal cells [116]. However, several GC cells display resistance to TRAIL due to deficient death receptor 5 (DR5) expression. Cyclopamine induces ROS and ER stress, and the activation of CHOP regulates the proteasome degradation of survivin, which hampers the existence of DR5. Therefore, cyclopamine can elevate DR5 expression and sensitize GC cells to TRAIL-induced

**Table 1**
Implications of ER stress proteins in gastric cancer.

| Protein | Expression (tumor vs normal) | Function | Reference |
|---|---|---|---|
| GRP78 | Up-regulated | Promotes proliferation, anti-apoptosis, invasion, chemoresistance | [58] |
| GRP94 | Up-regulated | TBD | [62] |
| Calreticulin | Up-regulated | Promotes EMT and metastasis | [80] |
| ERp19 | Up-regulated | Promotes cell growth, migration, invasion | [63] |
| ERO1L | Up-regulated | Promotes proliferation, migration, invasion, chemoresistance | [65] |
| Agr2 | Up-regulated | Promotes stromal fibroblasts and invasion | [64] |
| STIM1 | TBD | Promotes viability, migration | [79] |
| CHOP | Down-regulated | Promotes apoptosis | [55,56] |
| ERp29 | Down-regulated | Tumor suppressor, repress PI3K-AKT signaling | [67,68] |
| ERp57 | Down-regulated | TBD | [69] |
| ERGIC1 | Down-regulated | Inhibits proliferation and induces apoptosis | [71] |
| JPH3 | Down-regulated | Induces UPR and mitochondrial mediated-apoptosis, and inhibits cell growth | [72] |
| EMC6 | Down-regulated | Inhibits cell growth, cell cycle, migration, invasion, and induces apoptosis | [70] |
| ORP8 | Down-regulated | Induces GRP78, p-PERK and CHOP, and decreases Wnt3a and β-catenin expression | [73] |
| SERCA3 | Down-regulated | TBD | [77] |
| DNAJB4 | TBD | Stabilizes E-cadherin, inhibits EMT | [75] |

EMT, epithelial-to-mesenchymal transition. TBD, to be determined.

**Table 2**
Molecules that target ER homeostasis in gastric cancer.

| Molecule | Origin | Settings | Effect | Reference |
|---|---|---|---|---|
| Clinical drugs | | | | |
| Celecoxib | NSAID | Various in vitro models | Increased intracellular $Ca^{2+}$, activation of GRP78 and UPR | [98–100] |
| Deferoxamine and deferasirox | Iron chelator | Various in vitro models | Induction of ROS, ER stress, activation of JNK | [96] |
| Platinum | Chemotherapeutic agent | In vitro and in vivo, BGC-823, MGC803, SGC-7901 | Disruption of $Ca^{2+}$ homeostasis, activation of GRP78, p-PERK, *p*-eIF2α, ATF4, and CHOP | [97] |
| Rapamycin | mTOR inhibitor | In vitro and in vivo, SGC-7901 and BGC-823 | Induction of ROS, ER stress, activation of JNK signaling | [112] |
| Other chemicals and compounds | | | | |
| MK-2206 | AKT inhibitor | In vitro and in vivo, SGC-7901 and BGC-823 | Induction of ROS, ER stress, and mitochondrial dysfunction | [111] |
| Cyclopamine | Sonic hedgehog signaling antagonist | Various cell lines | Induction of ROS, ER stress, and DR5 | [117] |
| α-Tocopheryl succinate | Vitamin E | In vitro, SGC-7901 | Induction of ROS and ER stress, activation of CHOP | [101,113] |
| Apogossypolone | Bcl-2 family inhibitor | In vitro and in vivo, SGC-7901 | Induction of ER stress and CHOP | [103] |
| Curcumin analogs | Turmeric | Various in vitro and in vivo models | Induction of ROS and ER stress | [105–109] |
| 7-Acetylsinumaximol B | *Sinularia sandensis* | In vitro, NCI-N87 | Activation of PERK-elF2α-ATF4-CHOP signaling | [91] |
| Kangfuxin | *Periplaneta americana* | In vitro, SGC-7901 | Induction of ER stress and autophagy | [127] |
| Bufalin | Chan Su extract | In vitro, SGC-7901 and BGC823 | Induction of ER stress and autophagy | [95] |
| Piperlongumine | Long pepper | Various in vitro and in vivo models | Induction of ROS and ER stress | [114] |
| Dehydroeffusol | *Juncus effusus* | Various in vitro and in vivo models | Activation of ATF4-CHOP and suppression of ATF6 and GRP78 | [92] |
| Auranofin | Clinical drug for rheumatic arthritis | Various in vitro and in vivo models | Induction of ROS, ER stress and mitochondrial dysfunction | [110] |
| 3,3′-diindolylmethane | Cruciferous vegetables | In vitro, BGC-823 and SGC-7901 | Up-regulated GRP78, CHOP and DR5 | [119] |
| Tanshinone IIA | *Salviae Miltiorrhizae* | In vitro, AGS | Up-regulated CHOP and down-regulated GRP78 | [93] |
| Caffeic acid | Coffee and fruits | In vitro, SCM1 | Disrupted $Ca^{2+}$ homeostasis | [102] |
| Casticin | *Fructus Viticis* | Various In vitro models | Induction of ROS, and ER stress, activation of CHOP and DR5 | [120] |
| Wogonin | *Scutellaria baicalensis* | In vitro and in vivo, MKN-45 and MFC | Induction of ROS and ER stress, activation of PI3K-AKT pathway | [115] |
| Recombinant Lz-8 | *Ganoderma lucidum* | In vitro, SGC-7901 | Induction of ER stress and ERAD, activation of ATF4-CHOP pathway | [94] |
| Ultrafine particles | *Ulmus davidiana* var. *japonica* | Various in vitro models | Up-regulated GRP78 and induction of apoptosis | [128] |

NSAID, non-steroidal anti-inflammatory drug.

apoptosis [117]. Fuligocandin B compounds interact with and inhibit the activity of valosin-containing protein (VCP/p97), an AAA ATPase, leading to ER stress and CHOP expression, thus also result in DR5 expression and TRAIL sensitivity [118]. 3,3′-diindolylmethane (from cruciferous vegetables) and casticin (from *Fructus Viticis*) also sensitize GC cells to TRAIL via a similar mechanism of action [119,120].

Lastly, the lethal ER stress may also reverse epithelial-mesenchymal transition (EMT) process, thereby thwarting peritoneal dissemination. Compounds function in this aspect include honokiol (from *Magnolia officinalis*) [80,121,122], biseugenol (an aryl hydrocarbon receptor inhibitor) [123], and melatonin [124]. Molecules identified to date that target ER homeostasis in GC are summarized in Table 2. However, most of the studies have been conducted using either cell culture or limited preclinical models; thus, more comprehensive studies investigating the in vivo effects of these compounds are needed to facilitate their clinical translation. In the meantime, inhibitors of the UPR, such as the IRE1α Kinase Inhibiting RNase Attenuators (KIRAs), IRE1α RNase inhibitor MKC compounds, as well as the PERK kinase inhibitors, have seen considerable antitumor effects in multiple cancer models [125,126]. It would be interesting to investigate whether these compounds function in a similar manner in GC models.

## 2. Conclusion and perspectives

In recent years, the implication of ER proteostasis and UPR signaling in GC has become a topic of increasing interest. This review is the first to summarize the literature studying the involvement of ER proteins, UPR components, and compounds that target ER stress-related pathways in this disease. Despite the encouraging progress, huge gaps in our knowledge of ER stress signaling in GC remain. The major questions to be answered are the expression pattern and regulation of key UPR components and ER chaperones in GC patients; the functional significance and the underlying mechanisms of the canonical UPR signaling in GC transformation, progression, metastasis and treatment resistance. With respect to GC treatment, the efficacy of either inducing the terminal ER stress or targeting the adaptive UPR by using the inhibitors of IRE1, PERK and ATF6 remains to be evaluated in experimental models, while exploring the potential combinatorial strategies with ramucirumab or trastuzumab are also of great interest. Future research addressing these issues will pave the way to finding novel therapeutic avenues in this malignant disease.

## Conflicts of interest

The authors declare no conflicts of interest that pertain to this work.

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