Endoplasmic reticulum stress-induced cell death as a potential mechanism for targeted therapy in glioblastoma (Review)

PENGFEI SHI[1*], ZHUOHANG ZHANG[2*], JIE XU[1], LI ZHANG[3] and HONGJUAN CUI[1,4]

[1]State Key Laboratory of Silkworm Genome Biology, Southwest University, Chongqing 400716; [2]Department of Army Occupational Disease, State Key Laboratory of Trauma, Burn and Combined Injury, Daping Hospital, Army Medical University, Chongqing 400042; [3]Department of CT/MRI, The Third Hospital of Hebei Medical University, Shijiazhuang, Hebei 050051; [4]Cancer Center, Reproductive Medicine Center, Medical Research Institute, Southwest University, Chongqing 400716, P.R. China

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Abstract. The endoplasmic reticulum (ER) is an essential organelle for protein synthesis, folding and modification, lipid synthesis, and calcium storage. When endogenous or exogenous stimuli lead to ER-synthesized protein folding dysfunction, numerous unfolded or misfolded proteins accumulate in the ER cavity and cause a series of subsequent responses, referred to as ER stress. If ER stress is continuous, the unfolded protein response (UPR) is not enough to remove the accumulated unfolded and misfolded proteins, and thus, UPR signaling pathways will drive cell apoptosis. Glioblastoma (GBM) is currently the most aggressive and common malignant tumor of the nervous system. Since ER stress may increase the sensitivity of GBM to temozolomide, this article reviews the possible mechanisms of ER stress-induced apoptosis and the factors affecting ER stress, and evaluates the potential of ER stress as a therapeutic target.

Contents

Correspondence to: Professor Hongjuan Cui, State Key Laboratory of Silkworm Genome Biology, Southwest University, 2 Road Tiansheng, Chongqing 400716, P.R. China
E-mail: hcui@swu.edu.cn; hongjuan.cui@gmail.com

*Contributed equally

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1. Introduction

Glioblastoma (GBM) is a common primary malignant brain tumor in the cranial cavity accounting for 45.2% of malignant primary brain and central nervous system tumors (1). Tumors formed by brain glial cells, including astrocytes, oligodendrocytes and ependymal cells, can be referred to as GBM (2). In 2018, the International and European Society for Pediatric Oncology found that GBM grows fast, and 70-80% of patients have a course of 3-6 months, and only 10% of patients have a course of >1 year based on clinical patient data from 10 countries (3,4). Those with a longer course may evolve from low-malignant astrocytomas (5). Due to the rapid growth of GBM, cerebral edema and intracranial pressure are markedly increased, and all patients have symptoms, including headache and vomiting (6). Although excision, radiation and chemotherapy are standard treatments, the prognosis remains poor for patients with GBM (7,8).

The main function of the endoplasmic reticulum (ER) is to synthesize proteins and lipids. In addition to meeting its own needs, the lipids are also provided to the Golgi apparatus, lysosomes, plasma membranes, mitochondria and other membranous cell structures (9). The accumulation of unfolded or misfolded proteins in the ER will cause ER stress, and in turn triggers the unfolded protein response (UPR) to ensure that the protein is folded correctly (10). ER stress can induce the expression of glucose regulatory proteins [78-kDa glucose-regulated protein (GRP78) and GRP94] and other ER molecular chaperones to protect cell proliferation (10). However, ER stress can also independently induce endogenous cell apoptosis and ultimately affect cell fate, such as adaptation, injury or apoptosis (11). Generally, if the ER stress is continuous, the protein kinase R-like endoplasmic reticulum kinase (PERK), inositol-requiring enzyme 1 (IRE1) and activating transcription factor (ATF)6 signaling pathways will be used to transduce the downstream apoptotic pathways (12,13). Therefore, researchers are gradually turning their attention to how to induce GBM cell apoptosis by ER stress. This review discusses the factors that influence the occurrence of ER stress, and the possibility of ER stress as a treatment for GBM.

2. Role of ER stress in cell survival and death

The perception and response to exogenous stress is an important component of cell physiology. Certain studies have demonstrated that the ER can initiate the cell response to exogenous stress (14,15). ER synthetic proteins should be properly folded, glycosylated and disulfide-bonded to form functional proteins (16). Therefore, a quality control mechanism is important for detecting misfolded or unfolded proteins and performing cell functions, such as cell division and cell-to-cell interactions (16,17). Due to the proliferation of cancer cells, the probability of misfolded or unfolded proteins is higher than that of normal cells (18). Therefore, the UPR can prevent the continuous synthesis of misfolded or unfolded proteins to a certain extent, and has a protective effect on GBM cells (19). The UPR has three classic transmembrane ER-resident UPR sensors: IRE1α (20), PERK (21) and ATF6 (22). These sensors can detect misfolded and unfolded proteins, and accelerate the recovery and maintenance of ER homeostasis (17).

Furthermore, the signaling network within the cells is complex. When a signal changes, it must trigger a series of signal changes, suppression or assistance (23). Additionally, sustained ER stress can induce other signaling pathways, such as DNA damage signaling and death receptor-mediated signaling, to promote cell apoptosis (24). The PERK-eIF2α-ATF4-DNA damage inducible transcript 3 (GADD153) signaling pathway is one of the classic signaling pathways of ER stress (25). Therefore, the expression levels of members of this pathway will also cause changes in other genes, which will synergistically promote cell apoptosis (25). p53 is a key player in the DNA damage response (DDR), and its expression is specifically induced by the PERK kinase during the UPR following ER stress (25). p53 activation during the DDR has been well studied (26,27). Once activated, p53 will stimulate and suppress different gene products, which aim to either prevent abnormal proliferation by a reversible arrest of the cell cycle to facilitate the repair processes, or to induce irreversible outcomes, including apoptosis or senescence (25). In addition, PERK expression decreases RNA component of mitochondrial RNA processing endoribonuclease expression, and increases microRNA-206 to inhibit Bcl-2, and consequently induces cleaved caspase3 (28). Cannabidiol (CBD) has the ability to inhibit the proliferation of GBM cells, and CBD can promote the expression of GADD153 to trigger ER stress, and induces mitochondrial dysfunction and lethal mitophagy arrest via the GADD153-tribbles pseudokinase 3-AKT-mTOR axis (29). Salinomycin and its ester derivatives 5-7 increase the levels of phosphorylated (p-)eukaryotic initiation factor (eIF)2α (Ser51) and IRE1α proteins, and also increase the levels of DNA damage indicators, such as γ-H2A histone family member X (γH2AX) protein and modified guanine (8-oxoG), by upregulating the expression levels of GADD153 (30). eIF5B has been demonstrated to serve a critical role in canonical translation, and eIF5B depletion results in the upregulation of DNA damage-inducible protein 34 (GADD34) transcription, and leads to activation of JNK to promote cell death (31). X-box binding protein 1 (XBP1) expression increases DNA damage, protein ATM phosphorylation, and the expression levels of MRE11-RAD50-NBS1 complex and γH2AX (32). In addition, IRE1 can interact with adaptor protein TNF receptor-associated factor 2 (TRAF2) and then initiates JNK, which has been demonstrated to be involved in cell death (33). IRE1 may contribute to apoptosis by activating the RIDD signaling pathway (34).

3. Apoptosis mechanism of ER stress

GRP78 is a key regulator of the UPR (35). As a $Ca2^{+}$-binding molecular chaperone in the ER, GRP78 maintains ER homeostasis, suppresses stress-induced apoptosis and controls UPR signaling (35). In the case of protein folding, GRP78 will inhibit the activation of these sensors (PERK, IRE1α and ATF6) (36). When misfolded and unfolded proteins exceed critical thresholds, GRP78 separates from the three sensors, leading to the activation of three distinct but partially functionally overlapping signaling pathways (37-39) (Fig. 1).

PERK, located at the ER membrane, is a type I transmembrane Ser/Thr kinase (40). PERK has a luminal stress-sensing domain and a cytosolic kinase domain (41). PERK is activated through a homo-oligomerization process leading to PERK trans-autophosphorylation and phosphorylation of its main substrate (42). During the early phase of ER stress, PERK activity can promote survival by inducing translational arrest, upregulating chaperones and enhancing the expression of the antioxidant gene, such as quinone oxidoreductase 2 and heme oxygenase 1 (43). Activated PERK induces the phosphorylation of serine 51 of the eukaryotic translation initiation factor 2α (eIF2α) and inhibits the synthesis of misfolded proteins (40). eIF2α can activate activating transcription factor 4 (ATF4), a transcription factor controlling the expression of certain genes involved in folding, autophagy, amino acid metabolism, antioxidant response, apoptosis and DNA damage, such as GADD153 (42). Under normal physiological conditions, GADD153 is present in the cytoplasm; however, continuous ER stress can promote GADD153 activation and transfer to the nucleus (44,45). Additionally, GADD153 has been reported to result in the decrease of Bcl-2 protein and the translocation of the pro-apoptotic molecule Bax from the cytosol to the mitochondria, which in turn induces the mitochondrial apoptotic pathway (46). Cytochrome'C can cause the activation of the caspase adapter apoptotic peptidase activating factor 1 and pro-caspase-9 by forming an enzyme complex with them. This complex is referred to as 'apoptotic bodies' (46). Additionally, caspase-9 further activates caspase-3/7 (46). The inhibitor of apoptosis protein inhibits activation of caspase-3; however, the release of second mitochondria-derived activator of caspase can remove the inhibitory effect (47).

Although a few studies have demonstrated that the existence of IRE1α is beneficial to the neovascularization of GBM, IRE1α also induces cell death and serves a unique role in ER stress (48-50). GRP78 can bind the luminal domain of IRE1α (49). Under ER stress, IRE1α dissociates from GRP78 and promotes the separation of TRAF2, and also induces cleavage of XBP1 into a splicing variant of XBP1 and transcription of GADD153 (51,52). TRAF2 forms a complex with TNF receptor superfamily member 1A-associated death domain protein, transforming growth factor β-activated kinase 1 and receptor-interacting protein 1 (53). This complex can activate apoptosis signal-regulating kinase 1 (ASK1), and then activate mitogen-activated protein kinase 4/7 (54-56) and the JNK apoptosis signaling pathway (57).

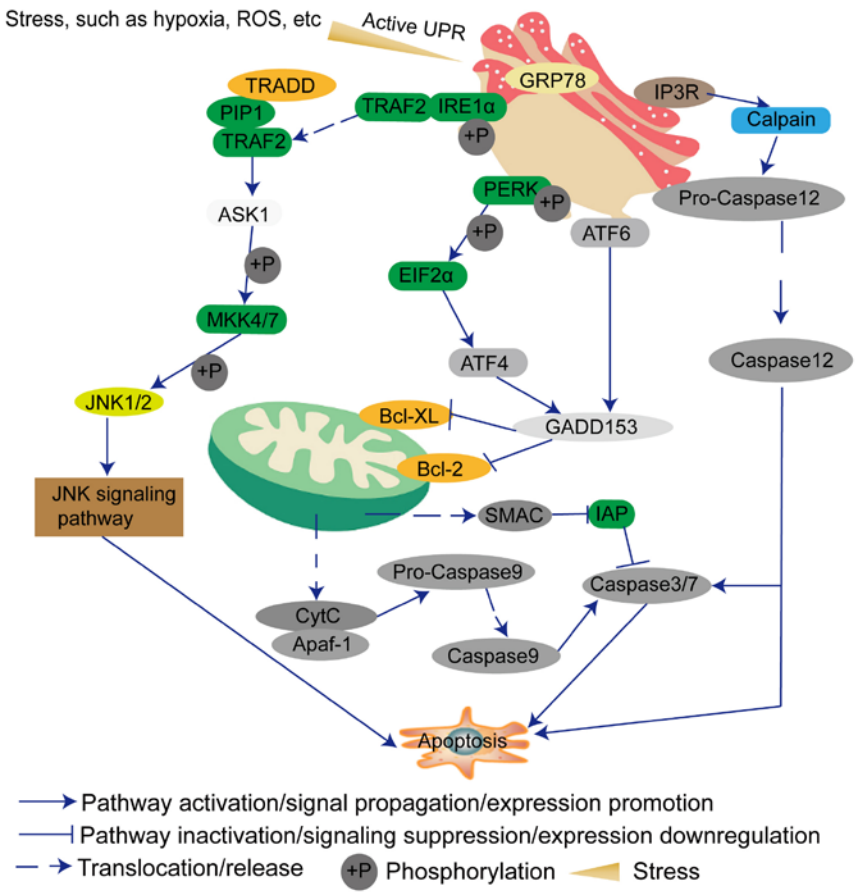

Figure 1. Apoptotic pathway caused by ER stress in glioblastoma. The UPR signaling pathway has three classic transmembrane endoplasmic reticulum-resident universal periodic response sensors, namely IRE1α, PERK and ATF6. Following ER stress, IRE1α, PERK and ATF6 can dissociate from GRP78 and initiate apoptosis signals. ER, endoplasmic reticulum; ROS, reactive oxygen species; UPR, unfolded protein response.

ATF6 is a type II transmembrane protein. ATF6 has a cytosolic bZIP transcription factor domain (58). During ER stress, ATF6 translocates to the Golgi where it is cleaved by proteases (59). The cleaved ATF6 cytosolic fragment can then act as a transcription factor (59). Prior to that, ATF6 needs to be modified, such as by reduction and glycosylation (60). ATF6 also induces GADD153 expression (61,62).

4. Factors inducing ER stress in GBM

Abnormal gene expression and ER stress. Normal tissue cells need to undergo a series of changes before they can become cancer cells, such as genetic changes, or activation or inactivation of certain signaling pathways (8). For example, stearoyl CoA desaturase (SCD1) and proto-oncogene SEC61 translocon subunit γ can promote ER homeostasis, avoid the production of misfolded proteins and inhibit the occurrence of tumors (63). Paraoxonase 2 (PON2), a paraoxonase protein, consists of lactone hydrolases with different substrate specificities (64). When PON2 is located on the nuclear membrane and ER, it can increase the stability of the ER and protect cancer cells from adverse environmental conditions and chemotherapy (64). Hypoxia-stimulated galectin-1 (Gal1) is an effective regulator of GBM cell migration and an angiogenic molecule (65). Additionally, the reduction of Gal1 weakens the expression levels of seven genes related to chemical resistance: ORP150, BNIP3L, HERP, TRA1, GADD45B, GRP78 and CYR61 (65). The absence of cytochrome P450 17A1 can induce the occurrence of ER stress and reactive oxygen species (ROS) generation by regulating secretion-associated Ras-related GTPase 1 (66). Furthermore, heat-shock protein 27 and 90 can decrease the levels of cytochrome C, caspase3, caspase9 and caspase12 in GBM cells (67,68). Additionally, cyclophilin B is a prolyl isomerase residing in the ER, and its absence can damage the ER structure (69).

In addition, knockdown of cAMP-responsive element-binding protein 3 induces cell apoptosis by increasing p-PERK, p-eIF2α, ATF4, Bax and caspase3 (70). Reversion inducing cysteine rich protein with kazal motifs (RECK) is a key suppressor gene in regulating cancer cell invasion and metastasis (71). Highly expressive RECK can modulate ER stress by binding to or sequestering GRP78 to activate p-eIF2α (71). Tumor necrosis factor receptor-associated protein 1 can markedly induce the occurrence of ER stress by activating ATF4 (72). In addition, neural precursor cells can migrate to advanced astrocytoma via the release of the vanillin receptor [transient receptor potential vanillin subfamily member 1 (TRPV1)] (73). TRPV1 induces GBM cell death via ER stress (73). Therefore, drugs that target these proteins located on the ER membrane or stabilizing the structure of the ER can be developed.

ROS and ER stress. The redox environment of the ER determines the fate of proteins entering the ER, and the level of

redox signaling mediators also regulates the level of ROS (74). ROS can induce the occurrence of ER stress through redox signaling mediators, such as NADPH-P450 reductase, protein disulfide isomerase-endoplasmic reticulum oxidoreductase 1, NADPH oxidase 4, glutathione/glutathione disulfide and calcium (74,75).

In addition, ROS-mediated hypoxia-inducible factor 1α serves an important role in promoting tumor microenvironment, anti-apoptosis and drug resistance in GBM (76). Mitochondrial PTEN-induced kinase 1 (PINK1), a regulator of the Warburg effect, is a negative regulator of proliferation in GBM cells (77). PINK1 can inhibit ROS generation and cell proliferation through FOXO3a (77). This finding highlights the importance of the balance between PINK1 and ROS in normal cells and cancer cells (77). Additionally, luteolin, a common dietary flavonoid, can induce a lethal ER stress pathway and mitochondrial dysfunction by increasing the intracellular ROS levels (78). Dihydroartemisinin (DHA) induces cell apoptosis through mitochondrial membrane depolarization, cytochrome'C and caspase 9 (79). Furthermore, the cytotoxicity of DHA can increase the expression levels of GRP78, GADD153, eIF2α and caspase12 (79).

Hypoxia and ER stress. One of the main obstacles for tumor progression is that cancer cells grow in a low-oxygen environment (80). Hypoxia can stimulate the adaptive response to promote cell proliferation and survival, as well as angiogenesis (81). However, some researchers have illustrated that hypoxia can also cause cell apoptosis or necrosis (81,82). Consequently, under hypoxic conditions, understanding the decision-making process that regulates cell death, adaptation and resistance for treatment is crucial. Hypoxia has been demonstrated to induce ER stress (83). Additionally, hypoxia can induce the cell surface exposure of calreticulin, a hallmark of immunogenic cell death (84,85).

Studies have demonstrated that after knock out of the gene encoding endothelin-1, the expression levels of endothelin receptor type B, endothelin 1, endothelin converting enzyme 1 and endothelin receptor type A are upregulated, which will increase the sensitivity of GBM cells to hypoxia-induced ER stress (86,87). Furthermore, under hypoxic conditions, the expression levels of snail family transcriptional repressor 2 and mesoderm specific transcript are upregulated, which will amplify the inhibitory effect of IRE1 on various genes (88). Hypoxia also leads to upregulation of IGFBP6, IGFBP7, IGFBP10/CYR61, WISP1 and WISP2, and downregulation of IGFBP9/NOV at the mRNA level (89). IRE1 markedly downregulates IGFBP7, IGFBP10/CYR61, WISP1 and WISP2, and upregulates IGFBP9/NOV, which shows that ER stress is an essential part of malignant GBM cell proliferation (90).

Low glucose and ER stress. The glucose metabolism allows energy to be oxidized by its carbon bonds and then used in the form of ATP. The final product of glucose can be lactate or carbon dioxide (91). In the 1920s, Otto Warburg and his colleagues found that tumors were absorbing a lot of glucose compared with surrounding tissues (92). Furthermore, in the presence of oxygen, glucose can also be fermented to produce lactic acid through aerobic glycolysis (92). Subsequently, in 1929, the British biochemist Herbert Crabtree confirmed Warburg's findings and further revealed that the respiratory intensity of tumors was variable, and numerous tumors exhibited this phenomenon (93). Additionally, Racker developed his theory of the origin of the Warburg effect in terms of intracellular pH imbalance and ATPase activity defects (94). Research on genetics and pharmacology demonstrated that the Warburg effect is necessary for cancer cell proliferation (95). Studies have demonstrated that the direct and indirect result of cancer-causing mutations is the reprogramming of cancer cell metabolism (96,97). Obtaining the necessary nutrients from the nutrient-deficient environment is a common feature of tumor metabolism (98). Cancer cells can use these nutrients to maintain viability and build new biomass (98). Therefore, tumors are considered to be a metabolic disease (99).

Low glucose means that cancer cells collect less energy. GRP78 can be upregulated in a low-glycemic state, and enables GBM cells to survive by inducing autophagy (100). Additionally, in the low-glycemic stage, p-PERK and cleavage of ATF6 are upregulated, which indicates that low glucose can lead to ER stress, activation of caspase, cell dysfunction, cell arrest and cell death (101-103). Metformin is the first-line drug for type 2 diabetes, and it can induce cancer cell death via the ASK1/phorbol-12-myristate-13-acetate-induced protein 1 and ROS/ASK1/JNK signaling pathways (104). The aforementioned can also indicate that the ketogenic diet can partially inhibit cancer cell proliferation.

pH and ER stress. In tumor tissues, due to increased glycolytic activity, slow blood circulation and insufficient blood supply of cancer cells, the pH of certain tumors (astrocytoma and squamous cell carcinoma) is <6.0, while the normal physiological pH is 7.3 (105). The low outflow of potentially toxic metabolic waste and a low influx of metabolites further enhance acidic conditions where cancer cells are located (106). The metastasis of solid tumors to acidic sites can promote tumor growth, invasion, angiogenesis, immunosuppression and chemotherapy resistance (107). However, there are conflicting reports on the effects of the acidic environment on cancer cell physiology. For example, low pH can promote tumor development; however, certain studies have demonstrated that low pH can also induce cancer cell apoptosis (108,109). For example, acidic stress may lead to upregulation of Src activity, VEGF and MMPs, which is conducive to cancer cell survival and metastasis (110,111). Acid-mediated apoptosis is considered to be the result of caspase activation (109). The acidic environment can regulate GBM cell proliferation and radiosensitivity (112). Additionally, acidity induces the expression of eIF2α, IRE1α, ATF6, GADD153 and caspase12 (113,114). This indicates that, in the brain tissue, the acidic environment may kill cancer cells via the ER stress pathway.

Calcium activator or inhibitor and ER stress. Certain drugs that affect ER calcium balance, such as the thapsigargin (115), calcium ionophore A23187 (116) and calcium ion chelator EGTA (117), can lead to ER stress. Calcitonin C (Cal-C) is a photoactivated inhibitor (118). Cal-C binds to protein kinase C and other protein regulatory domains with diacylglycerol/phorbol ester binding sites (118). It may damage calcium imbalance in GBM cells, and then result in ER stress (119). 2,9-diazaspiro[5.5]undecane depletes intracellular Ca^{2+}

stores (120). Cyclophilin/calcineurin inhibitor Cyclosporine A has certain apoptotic characteristics, causes numerous cytoplasmic vacuoles, and increases immunizing ER stress and autophagy markers, such as PERK, IRE1α, GRP78, GADD153 and LC3-II (118). Salinomycin is a polyether ionophore antibiotic and induces cell apoptosis through ER stress and autophagy (121). Nonsteroidal anti-inflammatory drugs can release additional Ca^{2+} to induce ER stress, thereby preventing cell transformation and slowing proliferation (122). Monensin can destroy calcium homeostasis and overcome TNF-related apoptosis-inducing ligand (TRAIL) resistance in GBM cells via ER stress, and thus it is currently considered an anticancer drug (123). Additionally, other polyether antibiotics, such as narasin, salinomycin, lasalocid A and nigericin, can also overcome TRAIL resistance in GBM cells via ER stress (123).

Lipid stress and ER stress. ER stress can give rise to changes in lipid metabolism; however, certain evidence suggests that dysfunctional lipid metabolism may activate UPR, regardless of whether there is a misfolded protein in the ER lumen (124). Subsequently, after UPR, genes involved in lipid metabolism will be upregulated (125). The brain is generally considered to be one of the most fat-rich organs, and the lipid content itself can affect various clinically relevant behavioral indicators (126). These bioactive lipids include steroids, diacyl glycerol, sphingolipids, phosphatidylinositol phosphate, phosphatidylcholine and polyunsaturated fatty acids (126). Furthermore, saturated fatty acids have the effect of promoting ER stress, while unsaturated fatty acids counteract this effect (126). Saturated fatty acids, such as palmitic acid and stearic acid, are known inducers of ER stress in various cell types, such as liver and breast cancer cells, and can regulate cell survival and apoptosis signals (126). SCD1, a downstream gene of sterol regulatory element-binding protein (SREBP), mediates lipid desaturation, which has also been found to be a critical determinant of cancer cell survival (127). SREBPs have important roles in regulating lipid metabolism and mediate lipid synthesis in GBM cells (127). Loss of SREBP and lipid synthesis can block GBM cell proliferation in xenograft models (128). In addition, SREBP ablation is also accompanied by the activation of IRE1α and PERK (129). These findings indicate that proliferating cells need to establish a balance between their proliferation rate and unsaturated lipid supply to prevent ER stress. Normal cells can regulate their proliferation rate in response to nutrient availability and retain a pool of unsaturated lipid, which allows cells to maintain homeostasis and avoid ER stress (129). However, with the rapid proliferation of cancer cells, if the exogenous unsaturated lipids are limited, the cancer cells will experience ER stress, eventually leading to cell death (129).

5. Potential targeted therapy for GBM via ER stress pathway

Due to the rapid proliferation of cancer cells, cancer cells need to synthesize a large amount of protein to support their own needs, resulting in misfolded proteins occurring in cancer cells. According to the ClinicalTrials.gov database (https://www.clinicaltrials.gov/), some studies have been carried out on the effect of ER stress on tumor treatment. Among them, a project investigating TN-TC11G (9-tetrahydrocannabinol + CBD) in combination with temozolomide (TMZ) and radiotherapy in patients with newly-diagnosed GBM is recruiting patients.

TMZ is the first-line drug for clinical glioma chemotherapy. It is an oral alkylated chemotherapy drug and effectively crosses the blood-brain barrier. However, over time, some GBM can gradually resist TMZ-induced damage. This resistance may be associated with the DNA repair pathway (O6-methylguanine DNA methyltransferase, DNA mismatch repair, base excision repair system), EGFR, MDM2 proto-oncogene, p53 mutation and PTEN (130). Therefore, researchers pay increasing attention to natural compounds, small molecules, viruses, bacteria, and calcium activators or inhibitors, and conduct basic research, aiming to one day treat glioma in clinical settings.

Natural compounds. GRP78 predominantly resides in the ER lumen within normal cells, and most of the research on GRP78 has focused on cytosolic or total GRP78 (131,132). However, in tumor microenvironments where GRP78 expression is upregulated, GRP78 also localizes to the surface of GBM cell membranes (133). GRP78 may influence not only GBM cells, but also the surrounding microenvironmental vasculature (133). Therefore, it has been gradually revealed that some compounds, such as epigallocatechin 3-gallate (EGCG), honokiol, celecoxib and bortemozib, can inhibit the growth of glioma by inhibiting GRP78 (133). IRE1 is the main mediator of the UPR (134). When cancer cells trigger ER stress in an unfavorable environment, the IRE1 signal can be an adaptive mechanism (135). However, the Food and Drug Administration-approved compounds methotrexate, cefoperazone, folinic acid and fludarabine phosphate, as inhibitors of IRE1, hinder the adaptation mechanism (135). In addition, flavokawain B, a natural kava chalcone, exhibits potent antitumor activity in various cancer types, such as lung cancer cells (136) and gastric cancer cells (134). It induces protective autophagy by targeting the ATF4-GADD153-AKT-mTOR signaling pathway (137). Piperlongumine preferentially kills high-grade glioma (HGG) cells but has little effect on normal brain cells (138). It induces ROS generation and disrupts protein folding in the ER by increasing the oxidative deactivation of peroxide reduction 4 to activate the ER stress pathway in HGG cells (138). Therefore, piperlongumine can be regarded as an effective drug for the treatment of GBM.

There are still numerous compounds that can induce cell apoptosis via the ER stress pathway in GBM cells. For example, Isochaihulactone, a natural compound extracted from the Chinese traditional herb Nan-Chai-Hu, can disrupt ER homeostasis in GBM cells (139). The novel resorcinol derivatives [2,4-bis (4-fluorophenylacetyl) resorcinol (BFP)] can increase some characteristic ER stress markers, such as GRP78, IRE1, eIF2α and GADD153, in human GBM cell lines (U251 and U87), and a mouse GBM cell line (C6 cells) (140). In addition, treatment with BFP can increase ROS generation and downstream caspase activation, such as caspase12, caspase9 and caspase7 (140). Cannabinoids can inhibit the epithelial-mesenchymal transition of several tumors in rats and mice, and enhance tumor immune surveillance (141). Therefore, cannabinoids may be considered as potential anticancer drugs. In 2003, cannabinoids were used to explore the anticancer mechanism (142). The results

demonstrated that the main mediator of cannabinoid is the stress-regulating protein p8 (also designated as a candidate for metastasis 1) (142). Further research revealed that p8 has an apoptotic effect by upregulating ER stress-related genes ATF4 and GADD153 (142). Additionally, Shikonin (one of the main active ingredients of Chinese herbal medicine *Lithospermum erythrorhizon*) (143), fatsioside A (a novel baccharane-type triterpene glycoside) (144), garlic compounds (diallyl sulfide and diallyl disulfide) (145), apigenin, (-)-epigallocatechin, and genistein (146,147), desipramine (a tricyclic antidepressant) (148), curcumin (149,150), xanthatin (a natural sesquiterpene lactone purified from *Xanthium strumarium* L.) (151), honokiol (a cell-wall component of *M. grandiflora*) (152), sinomenine hydrochloride (the main biologically active alkaloid isolated from *Leymus chinensis*) (152), radicol (a novel trinorguaiane type sesquiterpene) (153), phenyl isothiocyanate (a member of the isothiocyanate family) (154,155), redox organoruthenium compound 11 (RDC11; one of the most active compounds among the novel ruthenium-derived compounds) (156) and obtusaquinone [OBT; a natural compound from the heartwood of *Dalbergia retusa* (cocobolo)] (157) have also been reported to induce ER stress (Table I). Among them, after injecting GBM cells into the mouse cranial cavity, RDC11 and OBT can reduce tumor progression, and improve the survival rate of the mouse (156,157). Therefore, whether other natural compounds can pass through the blood-brain barrier at the individual level requires in-depth research. In addition, there are also numerous reports on other tumors, which suggest that natural compounds can induce cell apoptosis through ER stress. For example, aspirin can induce multiple myeloma (MM) cell apoptosis by inhibiting Blimp1, activating the ATF4/CHOP apoptotic pathway (158). Valosin containing protein (p97/VCP) is an ER-associated protein, and novel p97/VCP inhibitor induces ER stress and apoptosis in both bortezomib-sensitive and -resistant MM cells (159). Furthermore, there are numerous other compounds that can also affect cancer cell proliferation through ER stress in other tumors, such as 18βH (a semisynthetic derivative of -glycyrrhetinic acid) in breast cancer cells (MCF-7 and MDA-MBA-231) (160), resveratrol (a natural polyphenol compound) (161) and 2-pyrazine-PPD (a novel dammarane derivative) (162) in gastric cancer, sothiocyanates (natural compounds abundant in cruciferous vegetables) in non-small cell lung cancer cells (163), and honokiol (a hydroxylated biphenyl natural product) in prostate cancer, melanoma, lung cancer, leukemia and colorectal cancer (164). Therefore, whether these natural compounds can induce ER stress and be used for the treatment of GBM *in vivo* still requires basic verification and clinical trials.

Small molecule compounds. GBM stem cells (GSCs) can be considered key drivers of tumor growth, aggressiveness and therapy resistance in GBM (8). PERK is a well-characterized switch between survival and death during persistent ER stress and mediates cell death through induction of GADD153 (165). A previous study has demonstrated that ER stress aggravation targets GSCs, and PERK directly regulates SOX2 downregulation at the protein level to induce GSC differentiation, independent from eIF2α/ATF4 signaling (165). Furthermore, ionizing radiation potentiates ER stress, which reduces proliferation in a PERK-dependent manner (166). Adding PERK inhibitor, ER stress inducer (2DG) and GADD34 phosphatase inhibitor (Sal003) to irradiated GBM cells can reduce cell viability (166). In addition, other highly selective PERK inhibitors may provide a ground-breaking, anticancer treatment strategy in a PERK-dependent manner. 7-Methyl-5-(1-2,3-dihydro-1H-indo l-5-yl)-7H-pyrrolo[2,3-d]pyrimidin-4-amine (GSK2606414) is an oral, effective and selective PERK inhibitor, which inhibited the growth of a human tumor xenograft in mice by inducing ER stress (167). Therefore, GSK2606414 treatment may be considered as an effective drug therapy for GBM. Small-molecule inhibitor 42215 of PERK can markedly induce apoptosis after treatment of cancer cells (168). ATF4 is the master regulator of the cellular stress response and the core regulator of the PERK-eIF2α signaling pathway (169). Kurarinone (Extract of *S. flavescens* Roots) activates ATF4 to induce cancer cell apoptosis (169). A mixture of sixteen previously selected small molecules ('active mixture'; AM16: l-arginine, l-tyrosine, l-histidine, l-tryptophan, l-methionine, l-phenylalanine, adenine, l-(-)-malic acid, 2-deoxy-d-ribose, orotic acid, d-(+)-mannose, hippuric acid, pyridoxine, d-biotin, (-)-riboflavin and l-ascorbic acid) can upregulate ATF4 and GADD153 to induce cell apoptosis (170). Furthermore, salicylaldehyde analogs (MK0186893) and umbelliferones (4 μ8c) can be used as IRE1 RNase inhibitors, and have shown promise as a potential therapeutic strategy to counteract disease pathogenesis associated with overactive IRE1 signaling (171,172). Palmitoylation inhibitors (2-bromopalmitate, cerulenin and tunicamycin) induce cell death by promoting the accumulation of XBP1 (173). In addition, >10,000 non-toxic compounds that may activate IRE1-dependent XBP1 splicing through a mechanism independent of binding the IRE1 kinase active site have been identified by a high-throughput screening approach in July 2020 (174). This undoubtedly provides more drugs for the treatment of tumors via ER stress and requires in-depth exploration and screening.

In addition to specific small molecule modulators of UPR pathways and their potential use in developing anticancer therapies, numerous small molecule compounds have been demonstrated to induce GBM cell apoptosis (Table I). For example, NEO214 (rolipram-perillyl alcohol conjugate) is produced by the covalent linkage of carbamate linkage and cyclopropanol (175). It can cross the blood-brain barrier, and induce cell death via ER stress and the death receptor 5/TRAIL/TNF superfamily member 10 signaling pathway (175). Therefore, NEO214 may be considered as a potential clinical antitumor drug. Asiatic acid (AsA) is a natural small molecule, and it is widely used to cure various neurological disorders. AsA also induces ER stress by increasing GRP78, IRE1α and calpain, to damage a cellular organization in human GBM cells (LN18, U87MG and U118MG) (176). Notably, AsA can cross the blood-brain barrier (12). Therefore, AsA may be considered as a potential clinical antitumor drug. In addition, 2-amino-N-acetamide (176), NEO212 (a combination of TMZ and perillyl alcohol) (177), NEO100 (a high-purity and high-quality polychlorohydrin) (178), Compound-7g (179), platinum thiopyridine (II) complex (180), endothelial monocyte activating polypeptide II (181), berberine (an isoquinoline quaternary alkaloid isolated from a variety of medicinal plants) (182), N-methyl-4-isoleucine-cyclosporine (a small molecule cyclophilin binding inhibitor) (183), celecoxib (a non-steroidal anti-inflammatory drug) (184), the silent mating type information regulation 2 homolog activator

Table I. Potential compounds for the treatment of glioblastoma.

Author, year	Compounds	Impact on UPR members	Efficacy for glioblastoma	(Refs.)
Lu *et al*, 2012	BFP	GRP78, GRP94, IRE1, eIF-2α, GADD153	ROS generation; pro-apoptosis	(140)
Guzman *et al*, 2003; Carracedo *et al*, 2006	Cannabinoids	GRP78, ATF4, GADD153	Pro-apoptosis; decreases the mitochondrial membrane potential	(141,142)
Pan *et al*, 2015	Fatsioside A	PERK, eIF-2α, GADD153	Induces apoptosis and death	(144)
Das *et al*, 2007	BFP	Calpain	ROS generation; pro-apoptosis; increases in intracellular free [Ca^{2+}]; release of cytochrome C	(145)
Das *et al*, 2010	Apigenin	PARP	Reduces cell viability; pro-apoptosis	(146)
Das *et al*, 2010; Djerir *et al*, 2018	EGCG; Genistein	GRP78	ROS generation; increase in intracellular free [Ca^{2+}]; induces apoptosis; release of cytochrome C	(146,147)
Ma *et al*, 2011	DMI	GADD153, GADD34	Pro-apoptosis	(148)
Garrido-Armas *et al*, 2018; Sansalone *et al*, 2019	Curcumin	IRE1, ATF6	Induces apoptosis; decreases mitochondrial membrane potential	(149,150)
Ma *et al*, 2019	Xanthatin	GRP78, PERK, IRE1, eIF-2α, GADD153, ATF4, ATF6, XBP1s	Pro-apoptosis; inhibits cell proliferation	(151)
Martin *et al*, 2013	Honokiol	GRP78, ATF4	Pro-apoptosis	(152)
Li *et al*, 2017	RAD	GRP78	Induces apoptosis; blocks autophagy	(153)
Chou *et al*, 2015; Chou *et al*, 2017	PEITC	GRP78, GADD153, XBP-1, IRE1α, calpain I, calpain II	Induces cell arrest and apoptosis; ROS generation; increases intracellular free [Ca^{2+}]	(154,155)
Kim *et al*, 2014	Piperlongumine	eIF-2α, GADD153	Increases ROS levels	(138)
Meng *et al*, 2009	RDC11	GRP78, XBP1, GADD153	Induces DNA damage; inhibits cell proliferation	(156)
Badr *et al*, 2013	Obtusaquinone	C-jun	Induces DNA damage; pro-apoptosis; ROS generation	(157)
Cho *et al*, 2019	NEO214	GRP78, GADD153	Induces apoptosis; decreases glioma progression	(175)
Cho *et al*, 2017	NEO212	GRP78, GADD153	Induces cell death; blocks autophagy	(177)
Marin-Ramos *et al*, 2019	NEO100	Calpain-1	RhoA activation; induces apoptosis; reduces GSC invasion	(178)
McCubrey *et al*, 2006	2-amino-N-acetamide	GRP78	Induces apoptosis	(176)
Lin *et al*, 2019	Airaterone	IRE1α	ROS generation; inhibits cell proliferation	(66)
Chen *et al*, 2019	Compound-7g	GRP78, eIF2α, Ire1α, GADD153	Suppresses cell proliferation and viability; induces apoptosis	(179)
Koncarevic *et al*, 2009	TPC	GADD45	Induces cell arrest	(180)
Li *et al*, 2017	EMAP II	GRP78, GADD153	Induces apoptosis; decreases GBM-induced angiogenesis	(181)
Eom *et al*, 2010	Berberine	GRP78, PERK, eIF2α, GADD153	ROS generation; pro-apoptosis; increases intracellular free [Ca^{2+}]	(182)

Table I. Continued.

Author, year	Compounds	Impact on UPR members	Efficacy for glioblastoma	(Refs.)
Wang *et al*, 2017	NIM811	ATF4, eIF2α	Blocks autophagy; promotes cell death	(183)
Suzuki *et al*, 2013	Celecoxib	GRP78, GADD153	Induces cell autophagy and cell arrest; delays cell proliferation; pro-apoptosis	(184)
Ye *et al*, 2019	SRT2183	GRP78, PERK, IRE1α, eIF2α, GADD153	Inhibits cell proliferation; induces cell arrest; pro-apoptosis	(185)
Jia *et al*, 2010	17α-AED	GRP78, eIF2α, XBP1, ATF6, GADD153	Induces autophagy and apoptosis	(186)
Liu *et al*, 2013	Minocycline	GRP78, eIF2α, GADD153	Induces autophagy and apoptosis	(187)
Shen *et al*, 2014				
Bown *et al*, 2000				
Park *et al*, 2019	UA	GRP78, GRP94, PERK, ATF6, eIF2α, GADD153, IRE1	Increases intracellular free [Ca2+]; induces autophagy and apoptosis; loss of the mitochondrial membrane potential	(188-190)
Kavitha *et al*, 2015	AsA	GRP78, calpain, IRE1α, calnexin	Induces apoptosis; increases intracellular free [Ca^{2+}]	(12)

B, Viruses, bacteria, calcium activators or inhibitors

Author, year	Compounds	Impact on UPR members	Efficacy for glioblastoma	(Refs.)
Kim *et al*, 2017	OP-A	GADD153	Induces apoptosis	(191)
Qaisiya *et al*, 2017	UCB	GADD153	Induces inflammation and apoptosis	(192)
Mahoney *et al*, 2011	Rhabdovirus	IRE1α	Promotes cell death	(193)
Abraham *et al*, 2013	CHIKV	XBP1, eIF2α	DNA fragmentation; PARP cleavage; loss of mitochondrial membrane potential	(194)
Kusaczuk *et al*, 2018	SiNPs	GRP78, GRP94	Impaired mitochondria function; proinflammatory response	(195)
Rubiolo *et al*, 2014	Yessotoxin	PERK, eIF2α, XBP1	Induces autophagy, apoptosis and cell arrest	(196)
Kim *et al*, 2011	Amiodarone	GADD153	Increases intracellular free [Ca^{2+}]	(197)

BFP, 2,4-bis (4-fluorophenylacetyl) resorcinol; DAS, diallyl sulfide; DADS, diallyl disulfide; EGCG, epigallocatechin 3-gallate; DMI, desipramine; SH, sinomenine hydrochloride; RAD, radicol; PEITC, phenyl isothiocyanate; RDC11, ruthenium-derived compounds 11; OSU-03012, 2-amino-N-acetamide; NEO214, rolipram-perillyl alcohol conjugate; NEO212, perillyl alcohol conjugate; NEO100, enriched perillyl alcohol manufactured under cGMP conditions; TPC, platinum thiopyridine(II) complex; EMAP II, endothelial monocyte activating polypeptide II; NIM811, N-methyl-4-isoleucine-cyclosporine; SRT2183, (R)-N-(2-(3-((3-hydroxypyrrolidin-1-yl)Methyl)iMidazo[2,1-b]thiazol-6-yl)phenyl)-2-naphthaMide; 17α-AED, neuro-steroid, 5-androstene 3β,17α diol; UA, ursolic acid; AsA, asiatic acid; OP-A, ovitriol A; UCB, unconjugated bilirubin; CHIKV, Chikungunya virus; SiNPs, silica nanoparticles; ROS, reactive oxygen species; GSC, glioblastoma stem cell; GBM, glioblastoma.

(R)-N-(2-(3-((3-Hydroxypyrrolidin-1-yl)methyl)imidazo[2,1-b] thiazol-6-yl)phenyl)-2-naphthamide (185), neuro-steroid, 5-androstene 3β,17α diol (186), minocycline (187) and ursolic acid (188-190) can also induce GBM cell apoptosis via the ER stress pathway. Whether these small molecules can be used in clinical trials needs to be examined in animal models to ensure that they can cross the blood-brain barrier and reduce damage to normal cells.

Viruses, bacteria, and calcium activators or inhibitors. In addition to compounds, some viruses, bacteria, and calcium activators or inhibitors have been reported to induce GBM cell apoptosis via ER stress (Table I). For instance, ovitriol A (a fungal sesterterpene from *Bipolaris oryzae*) can induce paralysis-like cell death in human glioma cell lines (T98G, U251MG, U343, U373MG and A172), accompanied by the expansion of the ER (191). Unconjugated bilirubin may cause bilirubin neurotoxicity (192). It can also cause cell death t by increasing GADD153 in U87MG cells (192). Rhabdovirus is an important regulator of rhabdovirus-mediated cytotoxicity and mediates the ER stress response pathway to induce cell apoptosis (193). Chikungunya virus (CHIKV), an old-world alphavirus, can induce DNA fragmentation, loss of mitochondrial membrane potential, poly(ADP-ribose) polymerase (PARP) cleavage, nuclear enrichment and visible cytopathic effects in a dose- and time-dependent manner (194).

The focus of tumor research has always been the optimization of treatment strategies for malignant tumors. Silica nanoparticles (SiNPs) are such a strategy, which is rapidly developing into a promising tool for cancer diagnosis, imaging and treatment (195). SiNPs lead to impaired mitochondrial function, ROS generation and cell death by elevating levels of ER stress genes, including GRP94, GRP78, GADD153 and cyclooxygenase-2 (COX2) (195). Yessotoxin (YTX) is a polycyclic ether compound produced by dinoflagellate and accumulates in filter-fed shellfish (196). YTX can upregulate p-PERK, p-eIF2α, s-XBP1 and GADD153 in human glioma cell lines (SF539, SF295 and SNB75) (196). Additionally, YTX induces cell cycle arrest and increases cholesterol and polar lipid content in glioma cells (196). In addition, amiodarone is a widely used antiarrhythmic drug (197). Amiodarone can inhibit a variety of ion channels, including Na^+/Ca^{2+} exchangers, L-type Ca^{2+} channels and Na^+ channels, and increases the intracellular Ca(2+) level and GADD153 expression (197). Although viruses, bacteria, and calcium activators or inhibitors can induce cancer cell apoptosis through ER stress, their safety still needs to be considered.

Combined application. Various studies on GRP78 have also demonstrated that GRP78 has an important role in recurrent GBM and tumor progression after initial treatment (198,199). Of particular importance is TMZ, the standard-of-care chemotherapeutic treatment for GBM. TMZ has been demonstrated to result in activation of the UPR in GBM cells, inducing increased levels of UPR markers, GRP78 and GADD153 (100). Therefore, certain drugs can be used in combination with TMZ to enhance the sensitivity of GBM to TMZ by increasing ER stress (Table II). For example, bufothionine is extracted from the skins and parotid venom glands of the toad *Bufo bufo gargarizans Cantor* (200). Bufothionine can synergize with TMZ to exert an anti-growth effect by triggering ER

Table II. Potential treatments for glioblastoma in combination with TMZ.

Author, year	Combined drugs	Impact on UPR members	Efficacy for glioblastoma	(Refs.)
Sun *et al*, 2019	Bufothionine	GADD153, PERK, eIF2α, ATF6	Pro-apoptosis; inhibiting cell proliferation	(200)
Zhao *et al*, 2019	XL765	PERK, eIF2α, GADD153	Pro-apoptosis; inhibiting cell viability	(201)
Ma *et al*, 2016	Fluoxetine	PERK, eIF2α, ATF4, ATF6	Pro-apoptosis	(202)
Sun *et al*, 2013	P4HB inhibition	ATF4, GADD34	Pro-apoptosis	(203)
Golden *et al*, 2014; Golden *et al*, 2015; Shteingauz *et al*, 2018	Chloroquine	GRP78, GADD153	Block autophagy	(198,204,205)
Weatherbee *et al*, 2016	JLK1486	GRP78, ATF4, GADD153	Decreasing cell proliferation; inducing cell death and the formation of DNA DSBs	(206)
Kardosh *et al*, 2013	DMC	GRP78, GADD153	Pro-apoptosis	(207)

XL765, voxtalisib; P4HB, prolyl 4-hydroxylase-β polypeptide; JLK1486, N,N-[(8-hydroxyquinoline)methyl]-substituted benzylamine; DMC, 2,5-dimethyl-celecoxib; DNA DSBs, DNA double stranded breaks.

stress (200). PI3K/mTOR signaling is ubiquitous in GBM (201). XL765 (Voxtalisib/SAR245409), an effective dual inhibitor of PI3Ks and mTOR, inhibits the proliferation of GBM cells by inducing ER stress-dependent apoptosis (201). The combination of XL765 and TMZ can achieve improved therapeutic effects in A172, U87MG and T98G cells (201). Fluoxetine (FLT), as a drug widely used in cancer-related depression, has strong anticancer effects in different types of cancer cells, such as human ovarian granulosa tumor COV434 cells, and SKBR3 and MCF-7 breast cancer cells (202). The combination of FLT and TMZ can also induce the activation of ATF6, PERK, eIF2α, ATF4 and GADD153 (202). The upregulation of prolyl 4-hydroxylase-β polypeptide (P4HB) expression is associated with the increase of the IC_{50} of TMZ, and is relatively upregulated in resistant GBM cells (203). Targeting P4HB blocks its protective function and makes GBM cells sensitive to TMZ (203). Chloroquine (CQ), a quinoline-based antimalarial drug, can kill the plasmodium falciparum parasite in the red blood cell stage by blocking the acidic food vacuole heme to detoxify (198). Under physiological pH conditions, CQ has unique chemical properties and is a weak base that easily crosses the lipid bilayer of cells (198). The combination of TMZ and CQ can trigger cell death by enhancing the formation of LC3B-II, the accumulation of polyubiquitinated proteins, GADD153 and the cleavage of PARP (198,204,205). N,N-[(8-hydroxyquinoline)methyl]-substituted benzylamine (JLK1486) is a novel type of ER stress inducer (206). The combined use of TMZ and JLK1486 can cause long-term ER stress in human GBM cell lines (U87MG, A172 and T98G) by increasing the levels of GRP78, ATF4 and GADD153 (206). In addition, celecoxib is a selective inhibitor of COX2. Increasing reports have described that this drug has powerful anti-proliferation and pro-apoptotic effects without the obvious involvement of COX2 (207,208). Celecoxib causes ER stress by leaking calcium from the ER into the cytoplasm (207). The combination of bortezomib and celecoxib can increase the expression levels of ER stress markers GRP78 and GADD153, and cause the activation of c-jun (207). In addition, whether other compounds enhance the sensitivity of GBM to TMZ by enhancing ER stress needs to be verified.

6. Conclusions and perspectives

The resistance of GBM to TMZ treatment is the bottleneck of clinical treatment of this disease. Numerous cellular processes, including inflammation, autophagy and apoptosis, are regulated by the ER stress pathway. Furthermore, ER stress is a key regulator of TMZ sensitivity and is more likely to function in a cell-specific manner. Under low-dose and short-term TMZ treatment, ER stress may have cytoprotective effects. However, persistent ER stress can induce cell apoptosis. Therefore, numerous external factors and internal changes can induce ER stress in GBM cells. Although internal factors cannot be directly influenced, external factors can be used to delay GBM cell proliferation. For example, in a daily diet, patients with glioma can eat foods with less sugar and saturated fatty acids to inhibit cancer cell proliferation.

In addition, this review also summarizes some natural compounds and small molecule compounds, which are expected to treat GBM via ER stress. These compounds are also expected to be combined with TMZ. Additionally, there are numerous reports on other tumors that certain specific small-molecule regulators and natural compounds can specifically induce ER stress (165,209,210). Whether they can cross the blood-brain barrier and induce GBM cell apoptosis still requires verification. Additionally, the safety of the drug should also be worthy of consideration. Overall, although limited research has explored the pro-apoptosis function of ER stress for GBM cells, it has demonstrated that induced ER stress appears to be a potential treatment for GBM in the future.

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Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Authors' contributions

PS and ZZ wrote this manuscript. JX prepared the table and figure. LZ revised grammar and polished vocabulary after the first review. HC drafted the manuscript. Data authentication is not applicable. All authors read and approved the final manuscript.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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