Endoplasmic reticulum proteostasis in glioblastoma—From molecular mechanisms to therapeutic perspectives

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Cellular stress induced by the accumulation of misfolded proteins at the endoplasmic reticulum (ER) is a central feature of secretory cells and is observed in many tissues in various diseases, including cancer, diabetes, obesity, and neurodegenerative disorders. Cellular adaptation to ER stress is achieved by the activation of the unfolded protein response (UPR), an integrated signal transduction pathway that transmits information about the protein folding status at the ER to the cytosol and nucleus to restore proteostasis. In the past decade, ER stress has emerged as a major pathway in remodeling gene expression programs that either prevent transformation or provide selective advantage in cancer cells. Controlled by the formation of a dynamic scaffold onto which many regulatory components assemble, UPR signaling is a highly regulated process that leads to an integrated reprogramming of the cell. In this Review, we provide an overview of the regulatory mechanisms underlying UPR signaling and how this pathway modulates cancer progression, particularly the aggressiveness and chemotherapeutic resistance exhibited by glioblastoma, a form of brain cancer. We also discuss the emerging cross-talk between the UPR and related metabolic processes to ensure maintenance of proteostasis, and we highlight possible therapeutic opportunities for targeting the pathway with small molecules.

Gliomas—Clinical, Cellular, and Molecular Issues

Glioblastomas [GBMs; World Health Organization (WHO) grade IV gliomas] represent the most frequent and malignant form of primary brain tumors. Their incidence is thought to be about 3 per 100,000 each year. Standard treatment often includes maximal safe resection, followed by concomitant radiotherapy and chemotherapy with the use of temozolomide (TMZ), an alkylating agent (1). However, the highly infiltrative nature of this tumor, as well as its aggressiveness, leads to systemic failure of current therapeutics. Despite few improvements resulting from the development of second-line treatments such as antiangiogenic agents, the overall prognosis remains dismal and the median survival is 15 to 18 months (2). Furthermore, the neurological dysfunctions induced by tumor progression strongly impair the quality of life of patients (3). Research for new treatments is active in the fields of cell and gene therapy and especially immunotherapy.

The histopathologically defined entity “glioblastoma” covers a very heterogeneous tumoral population. Even if all GBMs share common morphological characteristics (such as proliferation of polymorphic glial cells, endothelial proliferation, necrosis, and vessel thrombosis), their stratification is being refined over the years through the knowledge of underlying pathogenesis (4). A first common distinction is made between so-called primary and secondary GBMs. Primary GBMs are considered to arise de novo as grade IV tumors, whereas secondary GBMs arise from the natural evolution of lower-grade tumors (astrocytomas or oligodendrogliomas; WHO grades II and III). Even if their cellular behavior is ultimately the same, they present with activation of different oncogenic pathways. Primary GBMs commonly show amplification or mutation of EGFR and loss or mutation of NF1, PTEN, RB1, CDKN2A, or CDKN2B or mutations in the TERT promoter (5). The molecular hallmark of secondary GBMs is the presence of mutations in IDH1 or IDH2, a signature for most of the lower-grade gliomas and a good prognostic factor. The progression from low- to high-grade gliomas involves loss of RB1 or CDKN2A (as in primary type) and amplification of PDGFRα, along with alterations related to the original glial cell lineage (mutations in TP53 or ATRX in astrocytomas, codeletion of chromosomes 1p and 19q, or methylation of the TERT promoter in oligodendrogliomas) (5). Along with this classical subdivision, genomic-based clustering has highlighted four subgroups of GBM: proneural (characterized by PDGFRα and IDH mutations, or TP53 mutations), neural (characterized by expression of neuronal markers), classical (characterized by gain of chromosome 7, loss of chromosome 10, or EGFR amplification), and mesenchymal (characterized by mutation of NF1 and expression of YLA0 and CD44). Each shows different clinical and radiological features as well as varied responses to treatment (5). Even if GBMs are nowadays treated in a relatively aspecific manner, these classifications might constitute the basis for more individualized therapeutics.

The individual susceptibility to chemotherapy emerged with the knowledge of the impact of methylation in the promoter of the gene encoding O6-methylguanine-DNA methyltransferase (MGMT). MGMT is a protein that contributes to DNA repair and partially counters the effects of alkylating agents such as TMZ (6). The methylation of its gene promoter, found in the tumors of less than half of GBM patients, is associated with greater chemosensitivity and a better prognosis than in patients whose tumors lack MGMT promoter methylation. Because it has a direct impact on the choice of treatment (radiotherapy versus TMZ), assessment of MGMT promoter methylation has been included...
in clinical practice for patients over 65 years old. Other interesting mutations and targets have been identified, such as BRAF mutations, but their incidence and therapeutic impact are relatively small. In recent years, a growing body of evidence implicates cellular stress response alterations in the pathogenesis and therapeutic resistance of GBM. Altered protein homeostasis (referred to as proteostasis) at the level of the endoplasmic reticulum (ER), the first compartment of the secretory pathway and the site of secretory and transmembrane protein biogenesis, lipid synthesis, and calcium storage, and the signaling pathways engaged to trigger cellular adaptation to ER stress are emerging as relevant drivers of initiation, growth, and chemoresistance in multiple tumor types. Proteostasis pathways are proposed as relevant players in the crossroad between many mutational and metabolic processes, representing a highly promising therapeutic target, the tenets of which are being discussed further in this Review.

ER Proteostasis and Stress Signaling—Generalities
To propagate and activate pro-oncogenic signaling pathways, cancer cells exhibit high demand for protein synthesis and folding compared to nonmalignant cells (7, 8). Moreover, these cells are constantly exposed to both intrinsic stresses (such as genomic instability, increased metabolic burden, and oncogene expression) (9, 10) and extrinsic stresses (including hypoxia, oxidative stress, and nutrient deprivation) (11), which increase the risk of protein misfolding and may perturb proteostasis. In normal and tumor cells, the ER operates as a specialized compartment to control the biogenesis of secretory and transmembrane proteins. Within the ER lumen, a subset of chaperones and foldases ensures the correct protein folding, thus maintaining ER proteostasis (12). However, if the protein folding demand exceeds ER folding and clearance capacities, then misfolded proteins accumulate in this compartment, thereby generating ER stress (13). To restore ER proteostasis, cells trigger an adaptive mechanism, known as unfolded protein response (UPR), through the activation of three ER transmembrane protein sensors: inositol-requiring enzyme 1α (hereafter referred to as IRE1), activating transcription factor 6α (hereafter referred to as ATF6), and protein kinase R–like ER kinase (PERK) (Fig. 1) (14). Under basal conditions, all three sensors (IRE1, ATF6, and PERK) are kept in their inactive state through the association with the ER-resident glucose-regulated protein 78 (GRP78); however, upon ER stress, the association is disrupted and the UPR signal transduction cascade commences (15). Subsequently, IRE1 forms a functional multimer with both serine/threonine kinase and endoribonuclease (RNase) activities in its cytoplasmic domain (16). The RNase domain in IRE1 mediates the cleavage of 26-nucleotide intron from the mRNA encoding X-box binding protein 1 (XBP1) and, with coordinated intervention from the catalytic subunit of the transfer RNA–splicing ligase complex (RTCB), generates a spliced transcript that is translated into a functional transmembrane factor named XBP1s (17). In addition, IRE1 participates in the degradation of various mRNAs and microRNAs (miRNAs) in a process called regulated IRE1-dependent decay (RIDD) (18). ER stress also triggers the translocation of ATF6 from the ER membrane to the Golgi apparatus, where it is cleaved into its active form, ATF6f, by site 1 and 2 proteases (SP1 and SP2) (16). ATF6f is further transported to the nucleus to promote expression of its UPR-related downstream genes (19). Last, after GRP78 disassociation, activated PERK dimerizes, autophosphorylates, and phosphorylates the eukaryotic translation initiation factor 2α (eIF2α), which results in decreased general translation with increased translation of ATF4 and ATF4-dependent transcription of various ER stress regulators (10). Activation of the three UPR branches increases cellular antioxidant capacities, hindering the global protein synthesis and enhancing the expression of chaperones and ER quality control proteins to reinforce protein folding and the ER-associated degradation (ERAD) pathway (20). However, if ER proteostasis cannot be restored, then cell apoptosis is triggered (21).

Constitutive activation of UPR signaling has been observed in many types of human tumors including breast cancers, GBM, lymphoma, myeloma, and various adenocarcinomas (22–28). In addition, activation of all the UPR branches was described in cellular and animal models of BRAF-, RAS-, MYC-, RET-, or HER2-driven tumorigenesis [reviewed in (29)]. Overexpression of the key regulator of ER stress response GRP78 was also frequently reported in tumor tissues and was associated with reduced patient survival (30–32). The concept of ER proteostasis addiction has been proposed as a mechanism supporting tumor growth and malignant cell transformation (33). It is now widely acknowledged that cancer cells may exploit the prosurvival signals of the UPR to cope with both intrinsic and extrinsic stresses and escape apoptosis as well as modulate other disease-associated
processes including migration, invasion, angiogenesis, and inflammation [reviewed in (33, 34)]. Overall, accumulating evidence indicates that UPR signaling modulates almost all hallmarks of cancer (34). In the next section, we will briefly contextualize the contribution of each arm of the UPR to selected cancer hallmarks.

**UPR Signaling and the Hallmarks of Cancer**

**PERK**

Recent data pertaining to tissues and tumors of the gastrointestinal tract suggest that PERK/eIF2α pathway plays a crucial role in cancer initiation through the regulation of cell stemness (35, 36). Moreover, ablation of PERK increases oxidative stress, impairs cell proliferation, and promotes G2/M cell cycle delay in breast cancer models (37). PERK-mediated protection of tumor cells from apoptosis under hypoxia is also observed both in culture and in animal models (29). Through the activation of autophagy and the antioxidant response, PERK facilitates survival of cells experiencing anoxia, a form of programmed cell death induced when they detach from the surrounding extracellular matrix (38). PERK activation is also associated with tumor dormancy and resistance to therapy (39), as well as invasion and metastasis by breast cancer cell lines in culture and in vivo, respectively (40). In breast cancer models, expression of epithelial-to-mesenchymal transition–related genes was found to correlate with that of the PERK downstream target ATF4 (40). Activation of the PERK/eIF2α/ATF4 axis may promote metastasis through the up-regulation of the metastasis-associated LAMP3 gene (41) or induction of matrix metalloproteinases MMP2 and MMP7 (42). Through the direct binding to the VEGFA gene promoter, ATF4 also increases angiogenesis in tumors (43). Moreover, either pharmacological inhibition or engineered knockdown of PERK attenuates tumor growth and significantly reduces blood vessel density in mouse models (43, 44). PERK-mediated inhibition of protein translation also reduces the inhibitor of κB (IκB) to nuclear factor κB (NF-κB) ratio, enabling the translocation of NF-κB to the nucleus and transcription of its downstream inflammatory genes (45).

**IRE1**

The gene encoding the stress sensor IRE1 is sometimes (although not frequently) mutated in cancer and is potentially involved in tumorigenesis (46). Recent data suggest that somatic mutations alter the signaling properties of IRE1 (47). Accumulating evidence links endoplasmic reticulum (ER) IRE1 signaling with various aspects of cancer biology. For instance, combination of an IRE1 RNAse inhibitor with either bortezomib (a proteasome inhibitor) or arsenic trioxide (As2O3) precluded cell survival of acute myeloid leukemia cell growth (48). The IRE1/XBP1 axis has been also implicated in increased sensitivity of transformed cells to hypoxia-induced death (49). Moreover, a direct interaction between XBP1s and hypoxia-inducible factor 1α (HIF1α), a master regulator of tumor cell response to hypoxia, reportedly regulate the expression of aggressiveness-associated genes VEGFA, PDK1, or GLUT1, among others, in triple-negative breast cancers (TNBCs) (50). The role of IRE1 in metastasis remains ambiguous; in normal epithelial cells, IRE1 enhances cell migration (51), whereas in glioma IRE1 inhibits tumor cell invasion (52). Moreover, in TNBC, silencing XBP1 decreased the formation of lung metastases (50). IRE1 signaling is also involved in the regulation of angiogenesis and protumorigenic inflammation. IRE1 interacts with tumor necrosis factor (TNF) receptor–associated factor 2 (TRAF2) to phosphorylate IκB, thus activating NF-κB signaling (53). XBP1s also binds to the VEGFA promoter and regulates its transcription in response to ER stress (43, 54). Furthermore, it was demonstrated that mouse embryonic fibroblasts lacking IRE1 expression were unable to induce VEGFA expression upon ischemia and, when transplanted into immunodeficient mice, generated tumors with reduced vascularization compared to their control counterparts (55). In addition, IRE1 also regulates secretion of vascular endothelial growth factor A (VEGFA), interleukin-6 (IL-6), and IL-1β (52). Thus, IRE1 appears to be an important regulator of tumor progression by regulating several hallmarks of cancer: migration, tolerance to hypoxia, inflammation, and angiogenesis.

**ATF6**

Our understanding of the consequence(s) of ATF6 activation in tumors is currently limited. So far, it has been demonstrated that ATF6 is required for the adaptation of dormant squamous carcinoma cells to nutritional stresses and in vivo microenvironment through the up-regulation of RHEB and activation of mTOR signaling (56). Moreover, as shown in the hepatocellular carcinoma model, ATF6 may be involved in the regulation of cell proliferation (57) or in the sensitivity to chemotherapy in leukemia cells (58). Data also suggest ATF6 contribution to cancer progression by shaping tumor microenvironment (59) as well as in the induction of the senescent phenotype (60). In summary, accumulating evidence suggests that activation of the UPR may affect multiple aspects related to cancer progression beyond its classical role in tumor adaptation against hypoxia.

**ER Proteostasis Control in GBM—Molecular and Cellular Impacts**

**UPR-induced transcription factors control cell survival or death**

In situations where ER stress is not alleviated, UPR sensors redirect their downstream signals toward apoptosis (Fig. 2). The C/EBP homologous protein (CHOP) is a major proapoptotic transcription factor triggered by UPR that suppresses antiapoptotic outer mitochondrial membrane protein BCL2 (B cell lymphoma 2) and induces proapoptotic proteins such as death receptor 5 (DR5) and ER oxidoreductin-like protein 1α (ERO1α) (61–64). In GBM cell culture models, numerous anticancer drugs were shown to induce CHOP expression. For instance, CHOP is up-regulated in tumor cell lines exposed to TMZ (22). TMZ also up-regulates the expression of GRP78, which suppresses the proapoptotic activity of CHOP (22). However, combined use of bortezomib and celecoxib [a cyclooxygenase 2 (COX2) inhibitor], both ER stress inducers, up-regulates GRP78 and CHOP expression and activates JNK, caspase-3, caspase-4, caspase-7, and caspase-9, leading to GBM cell death (65). The cisplatin-derived anticancer drug, ruthenium-derivated compound 11 (RDC11), also induces CHOP and GRP78. RDC11-induced CHOP activation is associated with the up-regulation of proapoptotic downstream molecules, Tribbles homolog 3 (TRB3) and ChaC glutathione-specific γ-glutamylcysteine transferase 1 (CHAC1) (66). Nelfinavir (a drug belonging to protease inhibitor class), when combined with TNF-related apoptosis-inducing ligand (TRAIL), increases GBM apoptosis through CHOP and DR5 up-regulation (67). Finally, IRE1 activation is also involved in GBM cell apoptosis induced by a nitric oxide (NO) donor, S-nitroso-N-acetyl penicillamine, leading to the activation of TRAF2 and JNK and the phosphorylation of CREB, a transcription factor involved in NO-mediated cell death (68). Collectively, this shows that, in GBM cells, UPR-induced transcription factors can control both prosurvival and prodeath mechanisms.
UPR-induced transcription factors in cancer-associated signaling

Recent studies underline the complexity of the UPR downstream pathways that also trigger other specific transcription factors, thus regulating tumor survival and growth (Fig. 2). Besides the ability to induce cell death, CHOP activation also triggers the protumoral inflammatory response through caspase-11 activation and release of IL-1β (69). In GBM cells, IRE1-mediated JNK activation induces epieregulin (EREG), a ligand for the epidermal growth factor receptor (EGFR) family member ERBB1, which contributes to an autocrine proliferation loop through EGFR signaling (70). Neovascularization is critical for cancer progression to overcome local changes in tumor microenvironment that limit resources in oxygen and nutrients. A connection between IRE1, PERK, and angiogenesis is observed in several tumor cell types, including breast and brain cancers as well as head and neck squamous and lung carcinomas (43, 55). In GBM, IRE1 appears as a major regulator of invasion and angiogenesis (71). IRE1 RNase activity targets the mRNA of SPARC, a secreted matricellular protein that regulates the interaction between GBM cells and extracellular matrix, promoting GBM cell migration (72). Through oxygen or glucose deprivation–induced ER stress in GBM cells, IRE1 activation also leads to increased expression of VEGFA, which encodes a critical factor of tumor angiogenesis (55). Moreover, IRE1 up-regulates the genes encoding various proangiogenic factors, such as the interleukins IL-1β, IL-6, and IL-8, and down-regulates antiangiogenic factors, such as thrombospondin 1 (THBS1) and decorin, promoting GBM angiogenesis (52). In addition to the activation of the ER stress–induced ATF4 pathway, PERK also supports prosurvival signals under oxidative stress. PERK activation triggers dissociation of the cytoplasmic Kelch-like ECH-associated protein 1 (KEAP1)/NRF2 complex, leading to the release and translocation of NRF2 to the nucleus (73). In GBM, PERK also controls ceramide production that is critical for calcium induction and reactive oxygen species (ROS) generation, which in turn promotes autophagy and cell death (74). PERK-mediated activation of ATF4 leads to the increase of proangiogenic factors such as VEGF, FGF2, and IL-6 and to the decrease in antiangiogenic factors THBS1, DCN, CXCL14, and CXCL10 in a HIF1α-independent manner (43). The PERK and ATF6 arms of the UPR also induce ADAM17, a member of the ADAM (a disintegrin and metalloproteinase) family that is associated with tumor initiation and progression (75). In other brain tumors such as medulloblastoma, PERK activation increases VEGFA expression and is associated with enhanced cell migration through VEGFR2 signaling (76). However, no evidence has been reported so far that PERK promotes GBM angiogenesis and invasion. Recently, the involvement of the ATF6 arm of the UPR has been described in GBM resistance to radiation (77). Irradiation of GBM cells leads to UPR induction with a clear involvement of ATF6-dependent up-regulation of GRP78 and NOTCH1 (77). Moreover, a high-resolution clustered regularly interspaced short palindromic repeats (CRISPR) screen in GBM stem-like cells has also revealed the involvement of ATF6 branch of the UPR in glioma development (78). Together, each UPR arm affects the balance of pro- and antitumor signaling pathways that is integrated by tumor cells and leads to a complete cell adaption to its adverse microenvironment. In summary, the signals triggered by
ER stress also involve major cancer-related transcription factors that in turn control tumor phenotypes.

**UPR-mediated modulation of gene transcription through chromatin structure remodeling**

Very little is known about the role of epigenetic modulation and the UPR in GBM. However, recent studies have shown the existence of functional links between the UPR and epigenetic regulators, thereby leading us to postulate that these links could also play a role in GBM. UPR-mediated gene expression also involves chromatin remodeling by directly acting on histone modifications. For instance, the gene encoding histone demethylase JMJD3 and also known as KAT2A, either act as coactivators of histone acetyltransferases (HATs) or other enzymes that modify the acetylation status of histones, key molecules of the chromatin architecture.

**Posttranscriptional cell reprogramming toward adaptation**

Posttranscriptional regulations induced by the UPR can occur at several levels. First, gene expression can be regulated through modulation of mRNA stability; as such, miRNA can represent effective regulatory tools. The biogenesis and stability of some miRNAs are observed to be under the control of the UPR either at the transcriptional level (95) or at the posttranscriptional level through IRE1-mediated degradation (96). Recent advances in this area have demonstrated that more than 10 miRNAs are regulated at the transcriptional level upon activation of the three branches of the UPR and that these miRNAs exhibited selectivity toward each individual branch (97). This was illustrated in GBM in which three of the four direct targets of IRE1 RNase (96) are deregulated, namely, miR-17, miR-34a, and miR-96. As such, the abundance of miR-17 is increased in irradiated GBM stem cells (98), the abundance of miR-34a, which plays a tumor suppressor role by targeting multiple oncopgenes, is decreased in GBM (99), and the abundance of miR-96 is increased in GBM and promotes tumor growth by contributing to the activation of the WNT/β-catenin pathway (100).

The second level of posttranscriptional regulation is mediated by the direct control of mRNA stability through mechanisms depending on IRE1 and named RIDD (101). RIDD controls mRNA expression profiles through direct cleavage at a conserved site bearing the CUGCGG sequence in a P-loop structure (18). RIDD in GBM has been illustrated in many instances. For example, the stability of both SPARC mRNA (72), whose translation product has been involved in the control of tumor cell migration and invasion, and PERK1 (PER1) mRNA (102), whose translation product is involved in repressing proinflammatory cytokine expression, is decreased. Although many RIDD substrates were identified, the precise mechanisms associated with RIDD selectivity and physiological or pathological relevance remain to be fully elucidated. The third level of posttranscriptional regulation is mediated by translational and posttranslational control. Upon activation of the UPR, both PERK and IRE1 can directly affect (i) protein abundance through inactivation of the translation initiation complex through the phosphorylation of eIF2α or through the degradation of ribosomal RNA, respectively (103), and (ii) protein phosphorylation status. However, both mechanisms have not been linked directly to GBM development and thus require more in-depth investigations.

**ER proteostasis control in glioma stromal cells**

Gliomas represent highly complex tumors consisting of various non-neoplastic stromal cells, such as tumor-associated brain endothelial cells, myeloid dendritic cells (DCs), plasmacytoid DCs, T cells, as well as tumor-associated macrophages and microglia (TAMs) (104, 105). TAMs are predominant glioma-infiltrating immune cells, which may comprise up to 30% of the tumor mass (106). In many types of cancer, increased TAM infiltration correlates with high histological grade and poor patient outcome (107, 108). Two populations of macrophages have been distinguished: classically activated (M1 phenotype) macrophages, which produce inflammatory and immune-stimulating cytokines to elicit the adaptive immune response against transformed cells, and alternatively activated (M2 phenotype) macrophages, which have tumor-supportive properties (109, 110). In established tumors, TAMs resemble M2-like macrophages (111) and they facilitate tumor growth and survival, induce the “angiogenic switch,” suppress the adaptive immune response, and remodel extracellular matrix to promote metastasis [reviewed in (110, 112, 113)]. In line, it was demonstrated that TAMs isolated from postoperative tissue specimens of glioma patients lacked expression of the costimulatory...
molecules CD86, CD80, and CD40 that are critical for T cell activation and hence lost their ability to produce proinflammatory cytokines (including TNFα, IL-1, or IL-6) (104), therefore exhibiting an immunosuppressive phenotype. A large body of evidence demonstrates that the UPR may also contribute to cancer progression by shaping the tumor microenvironment (Fig. 4). Activation of IRE1 or XBP1, PERK, and CHOP in macrophages promotes the production of protumorigenic cytokines IL-6 and TNFα (114, 115), and in DCs, CHOP promotes the production of proinflammatory IL-23, thereby favoring tumor growth (116). Similarly, deletion of ER-resident chaperone GRP96 in macrophages significantly reduced the abundance of IL-17A, IL-17F, IL-23, and TNFα in tumor-bearing mice (117). In addition, Mahadevan and colleagues demonstrated that conditioned media from ER-stressed tumor cells triggered the global ER stress response in the recipient macrophages and DCs, which was manifested by the transcriptional up-regulation of GRP78, XBP1s, and CHOP (118, 119). These cells also up-regulated the transcription of the proinflammatory cytokines IL-6 and IL-23p19 (a subunit of IL-23) and secreted large amounts of IL-6, IL-23, and TNFα, as well as macrophage inflammatory protein 1α (MIP1α), MIP1β, and monocyte chemoattractant protein 1 (MCP1) (118, 119).

Evidence also suggests that the UPR may blunt the antitumor immune response by affecting antigen presentation and antigen-presenting cells per se. Perturbation of the secretory pathway or ER stress decreases the presentation of high-affinity peptides by major histocompatibility complex (MHC) classes I and II (120, 121). Moreover, UPR-dependent products that transfer from cancer cells to DCs trigger arginase activation (an enzyme that suppresses T cell function) (122) and hinder the ability of DCs to cross-present antigen and cross-prime CD8⁺ T cells (119). Those CD8⁺ T cells also up-regulated the abundance of IL-2, IL-10, and FOXP3 and concomitantly down-regulated that of CD28, which indicates a suppressive phenotype (119). Notably, in DCs, IRE1 is constitutively activated and its downstream target XBP1s is abundant, even in the absence of ER stress (123). Further, loss of XBP1 promotes defects in DC phenotype and antigen presentation, which was mediated by RIDD of mRNAs encoding CD18 integrins and components of MHC class I machinery, such as tapasin (123). XBP1 reportedly promotes the development and survival of DCs (124).

The UPR is also involved in the cross-talk between tumor cells and endothelial cells. Upon binding to VEGFR on endothelial cells, VEGF activates the UPR sensors through the phospholipase Cγ (PLCγ) pathway without accumulation of misfolded proteins in the ER (59). This, in turn, promotes endothelial cell survival in an AKT-dependent manner and induces angiogenesis in mouse models (59). In addition, more recent work showing that signal transducer and activator of transcription 3 (STAT3)- or STAT6-activating cytokines yield predominantly IRE1-mediated cathepsin expression and secretion suggests that UPR activation in TAMs contributes to cancer invasion (125). So far, very little has been described in gliomas except for the role of IRE1 in controlling the production of the proinflammatory chemokines, such as IL-6, IL-8, or CXCL3 (52, 102). Nonetheless, UPR activation may contribute to cancer progression by the reciprocal communication between the tumor and surrounding cells, and therefore, targeting glioma stromal cells through UPR modulation may pose a promising treatment strategy.

**ER Proteostasis Control and Response to Chemotherapy and Radiotherapy in GBM**

**ER proteostasis and current treatments**

Modulating the protein folding capacity of the ER by interfering with protein trafficking, synthesis, quality control, or degradation offers attractive strategies for developing new anticancer drugs. The current therapeutic and pharmacological strategies that target ER proteostasis in cancer focus either on exacerbating ER stress to a level with which tumor cells cannot cope and therefore die or on decreasing the adaptative capacity of the tumor cells, leading to loss of selective advantage and tumor death. Over the past 5 years, several inhibitors of the three UPR sensors have been developed (Table 1) (44, 58, 126–140). Some new drugs are now tested to specifically target particular UPR sensors to kill cancer cells or sensitize them to commonly used treatments. To date, four compounds reportedly modulate ATF6 signaling. The protein disulfide isomerase PDIA5 is critical for ATF6 activation, enabling its export from ER under stress conditions; genetic or pharmacological inhibition of the PDIA5/ATF6 axis (using the PD1 inhibitor 16F16) sensitizes leukemia cells to imatinib treatment (58). Similarly, in a

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**Fig. 3. Epigenetic regulation in ER stress signaling.** Histone deacetylases (HDACs) and HAT-mediated regulation of ER stress signaling through chromatin remodeling in the nucleus and through posttranslational modification of select proteins in the cytosol. The pathways in black have been described in human brain tumors. CBX7, chromobox 7; EGR1, early growth response 1; SIRT1, sirtuin 1. **
more recent work, it was demonstrated that ceapins, a class of pyrazole amides, blocked ATF6 signaling in response to ER stress by trapping it in the ER (126, 127). On the other hand, Plate et al. identified two non-toxic small molecules, compounds 147 and 263, which selectively activated the ATF6 branch of the UPR (128). They further demonstrate that those compounds reduced secretion and extracellular aggregation of destabilized amyloidogenic proteins (128). Both approaches, either blocking ATF6 activation or promoting it, may therefore represent useful strategies for controlling ER proteostasis in various human diseases, including cancers.

Most of the IRE1 modulators target the nucleotide-binding pocket to control IRE1 RNase activity. IRE1 RNase inhibitors from the salicylaldehyde family include 4m8C, ManKindCorp (MKC) analogs, 3-methoxy-6-bromosalicylaldehyde, and STF-083010 (Table 1). 4m8C binds the catalytic site in IRE1 to block XBP1s cleavage and RIDD (141). 3-Methoxy-6-bromosalicylaldehyde also blocks XBP1s cleavage and subsequent RIDD in a reversible way (130). STF-083010 and MKC-3946 inhibit tumor growth in a mouse model of human multiple myeloma (130, 131, 135). MKC-3946 also shows synergistic effects in combination with the proteasome inhibitor bortezomib in multiple myeloma (131). From screening of small molecules in an XBP1 splicing reporter system, toyocamycin was identified as a specific RNase inhibitor and affected neither IRE1 phosphorylation nor the other UPR arms (142). Toyocamycin also shows synergistic effects with bortezomib in inducing multiple myeloma apoptosis (142). In the same screen, trierixin and quinotrierixin were also identified, although their mechanisms of action were not elucidated (143, 144). Other IRE1 modulators interact with the adenosine triphosphate (ATP)–binding pocket to stabilize an active form of the kinase domain. The type I ATP-competitive broad kinase inhibitors sunitinib and APY29 activate IRE1 RNase activity in cultured insulinoma (INS-1) cells (145). In contrast, the type II ATP kinase inhibitor compound 3 prevents the kinase activity, oligomerization, and RNase activity of IRE1 in INS-1 cells (136). Finally, ATP-competitive IRE1 kinase-inhibiting RNase attenuators (KIRAs), which allosterically inhibit IRE1 RNase activity by breaking oligomers, were recently discovered. KIRA6, an optimized KIRA, inhibits IRE1 in mouse models and promotes cell survival under ER stress (134). Finally, IRE1-derived peptides modulate IRE1
Table 1. Drugs targeting the UPR. Names, structures, and target of molecules identified to target directly the ATF6 (green), IRE1 (pink), or PERK (yellow) pathways. All the molecules indicated are inhibitors except for compounds 147 and 263 that activate ATF6.

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oligomeric status upon ER stress and uncouple XBP1 mRNA splicing from RIDD both in cultured HuH7 human hepatoma cells and in Caenorhabditis elegans (146). IRE1 inhibitors are suitable specific drugs to kill cancer cells or sensitize them to common chemo-or radiotherapies.

PERK phosphorylation is inhibited by compound 38 (GSK2606414). This compound decreases pancreatic tumor growth in a mouse model (147). The related drug GSK2656157 is also efficient in vivo and reduces cell metabolism and tumor-associated angiogenesis (44). Small molecules also attenuate PERK-dependent signaling by targeting downstream elf2α complexes. ISRIB reverses the effects mediated by elf2α phosphorylation without directly affecting PERK phosphorylation (137) but rather inhibits the exchange factor elf2β (148). Salubrinal blocks the protein phosphatase 1 (PP1) in complex with either CreP or the growth arrest and DNA damage 34 (GADD34) proteins that dephosphorylate elf2α either constitutively or under ER stress, respectively, leading to the retardation of mRNA translation (138). In contrast, guanabenz was described to inhibit only the PP1-GADD34 complex under conditions of ER stress (139, 141). Prolonged elf2α phosphorylation also leads to increased expression of proapoptotic genes (141). A novel inhibitor of the PP1c-GADD34 pathway, Sephin, was recently discovered and was shown to improve the condition of Charcot-Marie-Tooth disease in mice (140). Thus, the discovery of multiple small molecules that target the UPR with positive outcomes in preclinical models of various diseases highlights the fact that UPR signaling modules are suitable therapeutic targets; further work will reveal whether these drugs have potential for treating brain cancer.

### Induced imbalance in ER proteostasis in GBM as a therapeutic approach

Over the past 20 years, the perturbation of ER homeostasis leading to an increased proteotoxic burden has been proposed as a novel strategy to kill cancer cells. As such, a large number (>55) of small molecules have been tested on GBM cell lines and induced cell death by a mechanism that indirectly perturbs ER proteostasis, hence highlighting their potential use as therapeutic agents (149, 150) [Table 2 (22, 65–67, 151–211)]. The impact of these molecules on ER proteostasis imbalance was in most cases (85%) inferred by the up-regulation of GRP78 and/or CHOP mRNA, but generally, the causality of ER stress in the cell death process was not demonstrated. Currently, the standard treatment for GBM comprises surgical resection of the tumor, followed by radiotherapy and exposure to the alkylating agent TMZ (212). As a stand-alone treatment, TMZ has been shown to induce ER proteostasis imbalance in GBM cells, and its effects toward inducing cell death are potentiated by GRP78 mRNA silencing (22). Moreover, TMZ treatment of U87 cells (a GBM cell line) promotes the activation of the PERK pathway (213). To date, no clear link between TMZ and the IRE1 arm of the UPR is available, although several links between radiation therapy and the machinery controlling ER proteostasis have been established. The presence of a single-nucleotide polymorphism (rs12435998) in suppressor of Lin12-likelike protein 1 (SEL1L), an ERAD E3 ubiquitin ligation adaptor subunit, predicts better response of patients to radio-chemotherapy and is associated with longer survival (214). Similarly, the ER-resident lectin-like chaperone calreticulin modulates radiosensitivity of the U251MG cell line.
Table 2. UPR modulating drugs in GBM. Molecules used in GBM models and reported to act through the modulation of ER proteostasis. HSP72, heat shock protein 72; Hsc70, heat shock cognate 70.

<table>
<thead>
<tr>
<th>Model</th>
<th>Drug name</th>
<th>Link to ER stress</th>
<th>Cellular impact</th>
<th>Clinical trial (yes/no)</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>In vivo Human cell lines</strong></td>
<td>2,5-Dimethyl-celecoxib</td>
<td>GRP78 and CHOP induction</td>
<td>Apoptosis induction</td>
<td>No (151)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Δ9-Tetrahydrocannabinol</td>
<td>ATF4, CHOP, and TRB3 induction and eIF2α phosphorylation</td>
<td>Apoptosis induction, reduced tumor growth, and autophagy</td>
<td>Yes (152, 153)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Asiatic acid (2,3,23-trihydroxy-12-ursen-28-oic acid, C39H48O3)</td>
<td>GRP78 and calpain induction, calnexin and IRE1α down-regulation</td>
<td>Cell death induction</td>
<td>No (154)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Epigallocatechin 3-gallate + TMZ</td>
<td>GRP78 down-regulation</td>
<td>Increased mice survival and increased glioma cell sensitivity to TMZ</td>
<td>No (22, 155)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>NEO212 (TMZ conjugated to perillyl alcohol)</td>
<td>CHOP induction</td>
<td>Cell death induction</td>
<td>No (156)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Perillyl alcohol</td>
<td>GRP78, ATF3, and CHOP induction</td>
<td>Cytotoxicity and decreased invasion</td>
<td>Yes (157, 158)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Piperlongumine</td>
<td>CHOP, eIF2α, ATF4, GADD34, and GRP78 induction</td>
<td>ROS-induced cell death</td>
<td>No (159)</td>
<td></td>
</tr>
<tr>
<td><strong>In vitro Primaries</strong></td>
<td>RDC11</td>
<td>GRP78 and CHOP induction, and XBP1 splicing</td>
<td>DNA damage and apoptosis induction, and cell growth inhibition</td>
<td>No (66)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>TMZ + chloroquine</td>
<td>CHOP induction</td>
<td>Autophagy inhibition and apoptosis induction</td>
<td>No (160)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>2-Amino-N-(4-(5-(2-phenanthrenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl)-phenyl)acetamide (OSU-03012)</td>
<td>Involvement of GRP78 and PERK pathways</td>
<td>Cell death induction</td>
<td>No (161)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Celecoxib + sildenafil</td>
<td>eIF2α phosphorylation and activation of ATF4/CHOP pathway</td>
<td>Autophagy and cell death induction</td>
<td>No (162)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Terpyridineplatinum(II) complexes</td>
<td>GRP78 induction</td>
<td>Perturbation of redox metabolism and cell cycle arrest</td>
<td>No (163)</td>
<td></td>
</tr>
<tr>
<td><strong>Human cell lines</strong></td>
<td>TMZ + SKI-II (4-((4-(4-chlorophenyl)-2-thiazolyl)amino)phenol)</td>
<td>GRP78 and CHOP induction</td>
<td>ROS-induced cell death</td>
<td>No (164)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Withaferin A</td>
<td>GRP78, IRE1, and CHOP induction</td>
<td>ROS production and apoptosis induction</td>
<td>No (165)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>2-Deoxy-α-glucose</td>
<td>ER stress response gene signature</td>
<td>IL-8 induction</td>
<td>No (166)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>2-Hydroxyoleic acid</td>
<td>IRE1α, CHOP, and ATF4 induction, XBP1 splicing, and eIF2α phosphorylation</td>
<td>Cell cycle arrest and autophagy induction</td>
<td>No (168)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>5-Androstene 3β,17α diol (17α-AED)</td>
<td>GRP78 and CHOP induction, and activation of PERK/eIF2α signaling</td>
<td>Autophagy induction</td>
<td>No (169)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Amiodarone + TRAIL</td>
<td>CHOP induction</td>
<td>Apoptosis induction</td>
<td>No (170)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Antp-TPR hybrid peptide</td>
<td>GRP78 and CHOP induction</td>
<td>Cell death and cytotoxicity induction</td>
<td>No (171)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Berberine</td>
<td>GRP78, CHOP, and PERK induction, and eIF2α phosphorylation</td>
<td>Apoptosis induction and ROS generation</td>
<td>No (172, 173)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Bufalin</td>
<td>GRP78 and CHOP induction, and PERK and eIF2α phosphorylation</td>
<td>Apoptosis and autophagy induction</td>
<td>No (174)</td>
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<table>
<thead>
<tr>
<th>Model</th>
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<th>Link to ER stress</th>
<th>Cellular impact</th>
<th>Clinical trial (yes/no)</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Candidaspongiolide (CAN)</td>
<td>Activation of PERK/eIF2α signaling</td>
<td>Apoptosis induction and protein synthesis inhibition in normal cells</td>
<td>No</td>
<td>(175)</td>
<td></td>
</tr>
<tr>
<td>Celastral</td>
<td>HSP72 and HSP90 induction</td>
<td>Autophagy induction and accumulation of protein aggregates</td>
<td>No</td>
<td>(176)</td>
<td></td>
</tr>
<tr>
<td>Celecoxib + γ-irradiation</td>
<td>CHOP induction</td>
<td>Cell cycle arrest and autophagy induction under hypoxia</td>
<td>Yes</td>
<td>(177)</td>
<td></td>
</tr>
<tr>
<td>Celecoxib/2,5-dimethyl-celecoxib + bortezomib</td>
<td>GRP78 and CHOP induction</td>
<td>Apoptosis induction</td>
<td>No</td>
<td>(65)</td>
<td></td>
</tr>
<tr>
<td>Copper (Cu)</td>
<td>GRP78 induction and aggregation</td>
<td>ROS generation</td>
<td>No</td>
<td>(178)</td>
<td></td>
</tr>
<tr>
<td>Cyano enone of methyl boswellates</td>
<td>Activation of IRE1α and PERK</td>
<td>Apoptosis induction</td>
<td>No</td>
<td>(179)</td>
<td></td>
</tr>
<tr>
<td>Fatsioside A</td>
<td>PERK and eIF2α phosphorylation, and CHOP induction</td>
<td>Apoptosis induction</td>
<td>No</td>
<td>(180)</td>
<td></td>
</tr>
<tr>
<td>Fluoxetine</td>
<td>Activation of PERK/eIF2α/ATF4 and ATF6/CHOP signaling</td>
<td>Apoptosis induction</td>
<td>No</td>
<td>(181)</td>
<td></td>
</tr>
<tr>
<td>Glucosamine</td>
<td>GRP78, IRE1α, and eIF2α induction</td>
<td>Autophagic cell death induction</td>
<td>No</td>
<td>(182)</td>
<td></td>
</tr>
<tr>
<td>Nelfinavir/atazanavir</td>
<td>Induction of GRP78, CHOP, and PERK/eIF2α/ATF4 activation</td>
<td>Cell death induction and accumulation of protein aggregates (misfolding)</td>
<td>Yes</td>
<td>(22, 67)</td>
<td></td>
</tr>
<tr>
<td>Minocycline (7-dimethylamino-6-desoxotetracycline; Mino)</td>
<td>PERK/eIF2α/CHOP and IRE1 activation, XBP1 splicing, and GRP78 induction</td>
<td>Apoptosis and autophagy induction</td>
<td>No</td>
<td>(184)</td>
<td></td>
</tr>
<tr>
<td>Phenethyl isothiocyanate</td>
<td>GRP78, CHOP, XBP1, IRE1α, and calpain 1 and 2 induction</td>
<td>Apoptosis induction, decreased migration and invasion, and cell cycle arrest</td>
<td>No</td>
<td>(185–187)</td>
<td></td>
</tr>
<tr>
<td>Polyether ionophore antibiotics (monensin, salinomycin, nigericin, narasin, and lasalocid A)</td>
<td>CHOP and ATF4 induction, and eIF2α phosphorylation</td>
<td>TRAIL-mediated apoptosis</td>
<td>No</td>
<td>(188)</td>
<td></td>
</tr>
<tr>
<td>Quinine, quinacrine, melfoquine, and hydroxychloroquine</td>
<td>GRP78, GRP94, IRE1, and CHOP induction, and eIF2α phosphorylation</td>
<td>ROS generation and apoptosis induction</td>
<td>No</td>
<td>(189)</td>
<td></td>
</tr>
<tr>
<td>S1 (BH3 mimetics)</td>
<td>GRP78 and CHOP induction, and IRE1 activation</td>
<td>Apoptosis and autophagy induction</td>
<td>No</td>
<td>(191)</td>
<td></td>
</tr>
<tr>
<td>Schweinfurthin analogs</td>
<td>eIF2α phosphorylation and GRP78 induction</td>
<td>Inhibition of cancer growth and apoptosis induction</td>
<td>No</td>
<td>(192)</td>
<td></td>
</tr>
<tr>
<td>Sulindac sulfide</td>
<td>GRP78 induction</td>
<td>Cell death induction</td>
<td>No</td>
<td>(193)</td>
<td></td>
</tr>
<tr>
<td>TMZ</td>
<td>CHOP induction</td>
<td>No</td>
<td>(22)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Unsaturated fatty acids + irradiation</td>
<td>GRP78 induction</td>
<td>Increased radiosensitivity and cell death induction</td>
<td>No</td>
<td>(194)</td>
<td></td>
</tr>
<tr>
<td>Zoledronic acid</td>
<td>IRE1 induction</td>
<td>Apoptosis induction</td>
<td>No</td>
<td>(195)</td>
<td></td>
</tr>
<tr>
<td>Other cell lines</td>
<td>Ursolic acid</td>
<td>Activation of PERK/eIF2α/CHOP and IRE1/JNK pathway</td>
<td>Apoptosis and autophagy induction</td>
<td>No</td>
<td>(196)</td>
</tr>
<tr>
<td>Valproate</td>
<td>GRP78, GRP94, calreticulin, and CHOP induction</td>
<td>Inhibition of proliferation</td>
<td>No</td>
<td>(197, 198)</td>
<td></td>
</tr>
<tr>
<td>Wogonin</td>
<td>GRP78 induction and eIF2α phosphorylation, and XBP1 splicing</td>
<td>ROS production and apoptosis induction</td>
<td>No</td>
<td>(199)</td>
<td></td>
</tr>
<tr>
<td>Yessotoxin</td>
<td>eIF2α and PERK phosphorylation, and XBP1 splicing</td>
<td>Cell cycle arrest and protein synthesis inhibition</td>
<td>No</td>
<td>(200)</td>
<td></td>
</tr>
</tbody>
</table>

continued on next page
current treatments. Therefore represent interesting therapeutic avenues as adjuvants to the treatment of GBM patients. In this context, molecules that directly cause proteostasis imbalance in tumor stroma might play significant roles in the therapeutic response that control of ER proteostasis and the UPR tumor cells and in the contribution of the three arms of the UPR in GBM progression is still unknown.

TMZ-mediated toxicity through the DNA damage pathway may influence the selection of an adapted cell population that is resistant to the treatment. Drugs inducing further ER stress (such as salinomycin) induce ER proteostasis imbalance and thereby may ultimately confer selective advantage and aggressiveness to tumor cells (216), as previously shown in the case of oncogene-induced cell transformation (218). In this context, tumor cells exhibiting high basal ER stress signaling activity could represent good targets for drugs that selectively impair UPR adaptive signaling (as described in Table 1), and hence, resistance to treatments (most likely caused by either high adaptive capacity or hormesis—adaption through low-dose exposure) (219) observed in the cancer cells could be dampened through selective inhibition of the three arms of the UPR. We speculate that the use of IRE1 inhibitors or ATF6 activation inhibitors in GBMs may therefore affect tumor cell sensitivity to TMZ and irradiation. To achieve such a goal, it becomes evident that the systematic analysis of UPR activation in human tumors could be used as a stratification tool and, as a consequence, could predict better responsiveness of tumor cells to adjuvant therapies.

Conclusions and Perspectives

On the basis of the aforementioned evidence, it has become clear that control of ER proteostasis through the UPR is an essential player in cancer in general and in GBM in particular. The role of the UPR in GBM has been mostly investigated using cultured cells and animal (mouse) models, but data from human GBM tumors remain scarce to confirm the relevance of this pathway in real patients. As previously shown for other cancers, such as TNBCs, in which the constitutive activation of one branch of the UPR, namely, the IRE1/XBP1 axis, confers selective advantage and aggressiveness to tumor cells (50), it might be conceivable that GBM tumors (or a subset) exhibit increased UPR activation that, in turn, correlates with tumor aggressiveness. For instance, preliminary analysis of publicly available transcriptomes (216) reveals that a subset of GBM tumors (between 15 and 20%) exhibits a signature resembling high IRE1 activity, and this signature correlated with shorter survival of the patients. Similar observations are available for a few types of cancer, and therefore, such hypothesis could be tested systematically. The current treatments applied to GBM induce ER proteostasis imbalance and thereby may ultimately contribute to the selection of an adapted cell population that is resistant to the initial treatment. Drugs inducing further ER stress (such as salinomycin) sensitize glioma cells to TMZ treatment through the down-regulation of MGMT, N-methylpurine DNA glycosylase (MPG), and RAD51, three gene products involved in DNA repair (217), indicating that TMZ-mediated toxicity through the DNA damage pathway may interfere with the ER stress response, although the precise underlying molecular mechanisms remain unclear. Another approach would be to classify cancer cells as showing a selective advantage on the basis of high basal ER stress signaling activity, as previously shown in the case of oncogene-induced cell transformation (218). In this context, tumor cells exhibiting high basal ER stress signaling activity could represent good targets for drugs that selectively impair UPR adaptive signaling (as described in Table 1), and hence, resistance to treatments (most likely caused by either high adaptive capacity or hormesis—adaption through low-dose exposure) (219) observed in the cancer cells could be dampened through selective inhibition of the three arms of the UPR. We speculate that the use of IRE1 inhibitors or ATF6 activation inhibitors in GBMs may therefore affect tumor cell sensitivity to TMZ and irradiation. To achieve such a goal, it becomes evident that the systematic analysis of UPR activation in human tumors could be used as a stratification tool and, as a consequence, could predict better responsiveness of tumor cells to adjuvant therapies.

REFERENCES AND NOTES


12 of 18


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Endoplasmic reticulum proteostasis in glioblastoma—From molecular mechanisms to therapeutic perspectives

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