Targeting the hallmarks of cancer with therapy-induced endoplasmic reticulum (ER) stress

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The endoplasmic reticulum (ER) is at the center of a number of vital cellular processes such as cell growth, death, and differentiation, crosstalk with immune or stromal cells, and maintenance of proteostasis or homeostasis, and ER functions have implications for various pathologies including cancer. Recently, a number of major hallmarks of cancer have been delineated that are expected to facilitate the development of anticancer therapies. However, therapeutic induction of ER stress as a strategy to broadly target multiple hallmarks of cancer has been seldom discussed despite the fact that several primary or secondary ER stress-inducing therapies have been found to exhibit positive clinical activity in cancer patients. In the present review we provide a brief historical overview of the major discoveries and milestones in the field of ER stress biology with important implications for anticancer therapy. Furthermore, we comprehensively discuss possible strategies enabling the targeting of multiple hallmarks of cancer with therapy-induced ER stress.

From the Endoplasmic Reticulum (ER) to ER stress in a Time Lapse

With the advent of microscopy and optimized staining methods in the 19th century scientists started to identify vital

organelles within the cell; first to be identified was the nucleus, then the mitochondria and chloroplasts, and later on, the Golgi apparatus.[1] Despite being one of the largest structures in the cell, the endoplasmic reticulum (ER) was the last major organelle to be recognized, being identified in 1902 by the Italian scientist Emilio Verratti, a student of Camillo Golgi (**Fig. 1**). However, the *bona fide* existence of the ER as an organelle had to wait for the development of electron microscopy and optimization of centrifugation techniques crucial for fractionation of subcellular components (the latter achieved by Albert Claude, who separated the so-called 'microsomal fraction' in 1945). With the advent of more sophisticated thin-sectioning electron microscopy techniques, the first high-resolution images of the ER were provided by Keith Porter in 1953 and by George Palade in 1956 (**Fig. 1**), marking the beginning of a new era in ER biology research.[2-4] Subsequently, the major functional roles of the ER and/or sarcoplasmic reticulum in Ca^{2+} sequestration during muscle contraction and lipid biosynthesis started to be delineated,[5-7] thus positioning the ER at the center of a number of vital cellular functions ranging from muscle contraction and signaling to cell growth and differentiation.

In the early 1970s, seminal works from Palade (who shared the Nobel prize in Physiology or Medicine in 1974 with Albert Claude and Christian de Duve for their discoveries on the structural and functional organization of the cell) and Günter Blobel provided crucial evidence that ER membranes of secretory cells were studded with ribosomes and that nascent proteins entered the ER to flow through the Golgi on their way to the plasma membrane,[8] thus identifying the crucial role of ER in governing the first step of the secretory pathway (**Fig. 1**).[9] Using elegant cell-free protein synthesis assays, Günter Blobel and David Sabatini started to decipher how newly-synthesized proteins enter the ER as unfolded polypeptides, which led to the suggestion in 1971 of the "signal hypothesis" based on the assumption that a N-terminal sequence motif/signal within the primary sequence
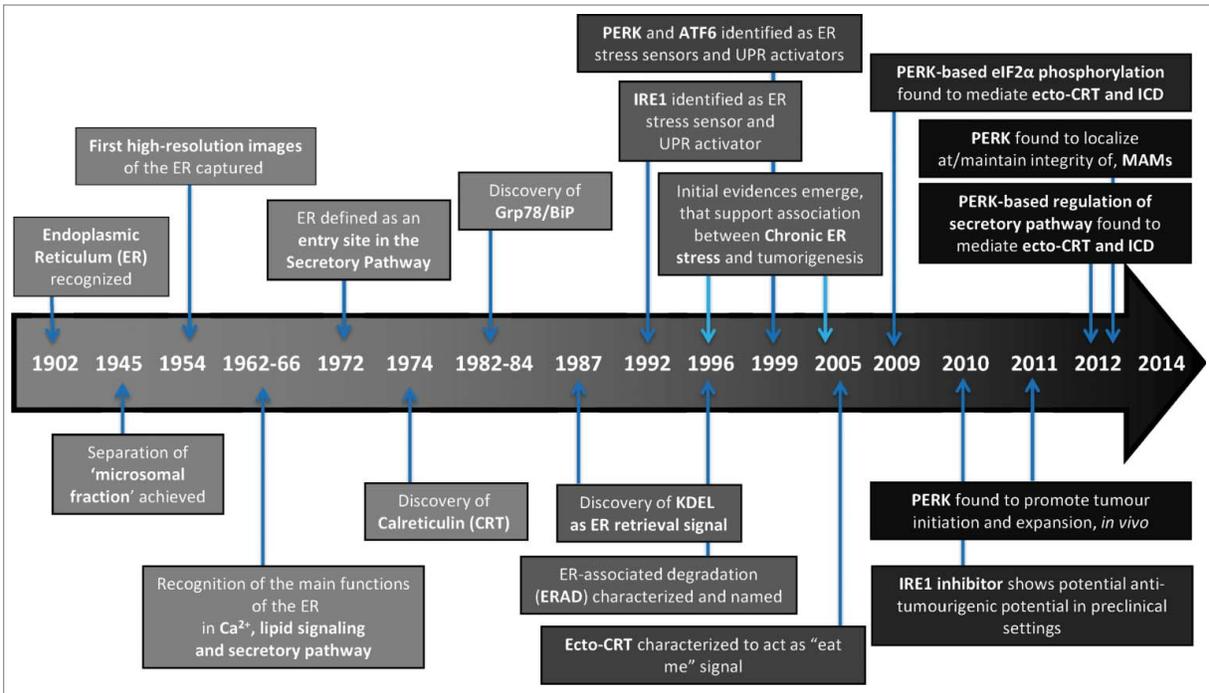
Figure 1. A timeline of major discoveries related to the endoplasmic reticulum (ER) and ER stress that are relevant for therapeutic targeting of cancer. The timeline summarizes 2 different historical facets of ER stress research. The proximal part of the timeline (1902-1987) elucidates the major cell- and molecular biology-based discoveries that paved the way for characterization of the ER as a *bona fide* cell organelle, its major molecular functions, and its role in proteostasis. The distal part of the timeline (1992-2014) elucidates the major discoveries that paved the way for characterization of the unfolded protein response (UPR) as a major ER stress responsive pathway and its therapeutic relevance for cancer, and major events that have recently highlighted the preclinical and clinical relevance of ER stress or UPR components for cancer treatment. Please see the text for details on individual events. CRT, calreticulin; Ecto-, Surface Exposure/Exposed; ICD, immunogenic cell death; MAM, mitochondria-associated membrane.

of secretory proteins functions to target them to the ER membrane.[10] About 10 years later, in 1982, further studies led to the discovery of the machinery deputed for the translocation of unfolded polypeptides in the ER lumen, which was named the signal recognition particle (SRP).[11,12] With increasing knowledge of the biochemical mechanisms underlying secretion and trafficking, it also became clear that the ER imposes a stringent quality control on its products, enabling only correctly folded and post-translationally modified proteins to leave the ER and traffic to the Golgi in order to reach their final destination. This is an outstanding task considering that approximately one-third of the polypeptides synthesized by a cell enter the ER, where they are folded and modified and then trafficked across the cell, in part through the secretory pathway (**Fig. 1**).

Research conducted from the mid-70s to mid-80s revealed the main mechanisms regulating oxidative folding, disulfide bridge formation, and glycosylation as signals of a protein's folding state, and led to the identification of several crucial molecular chaperones such as calreticulin (CRT; discovered in 1974 as a Ca^{2+} binding protein of the sarcoplasmic reticulum in skeletal muscle cells)[13] and the glucose-sensitive glucose regulated protein 78 (GRP78, also known as immunoglobulin binding protein or BiP), which act to prevent aberrant interactions and aggregation of protein-folding intermediates (**Fig. 1**).[1]

With increasing understanding of the major function of the ER in folding and secretion, scientists plowed into the molecular

mechanisms that allow retention and exit of proteins in and from the ER and the cellular consequences of disturbing these processes. In 1987, Munro and Pelham provided evidence for the concept of ER protein retrieval (i.e., avoidance of "ER escape" by ER-resident proteins) by showing that a number of ER luminal proteins contain the sequence KDEL at their C-terminus, which governs their retention in the ER (**Fig. 1**).[14] Deletion of this sequence from ER resident proteins drives their export to the Golgi and their "escape" through secretion. Subsequently, the 90s were marked by exciting findings that paved the way for 2 major discoveries in the field; namely the machineries deputed for the recognition and retrotranslocation of misfolded proteins from the ER to the cytosol for degradation (ER-associated degradation or ERAD) and the signal transduction mechanisms that play a role in sensing and decoding the luminal status of the ER (the unfolded protein response or UPR). The existence of a lysosome-independent mechanism for degradation of ER-associated misfolded proteins was already hinted at by research published in the late 1980s and early 1990s.[15,16] However, it was not until 1996 that the term ERAD was coined by McCracken and Brodsky to delineate the process through which misfolded proteins are eventually retrotranslocated to the cytosol to be degraded by the 26S proteasome (**Fig. 1**).[17]

At approximately the same time, the expression of GRP78 (encoded by the *KAR2* gene in yeast), was shown to be transcriptionally induced by the accumulation of unfolded

proteins in the ER, leading to the designation of this pathway as the UPR.[18] Using a genetic screen for mutations that block the activation of a UPR-inducible reporter in yeast, the groups of Walter and Sambrook independently identified the gene encoding an ER transmembrane Ser/Thr protein kinase called inositol requiring-1 (IRE1, also known as ERN1), a proximal ER stress sensor in the UPR pathway (**Fig. 1**).[19,20] Further investigations into IRE1 led to the recognition of its site-specific endoribonuclease (RNase) activity that is crucial for its conserved function as an ER stress sensor and mediator of the transcriptional induction of prosurvival UPR genes in yeast and mammals.[19,20] Soon after the discovery of IRE1, 2 other UPR effectors were identified in higher eukaryotes: the Ser/Thr kinase protein kinase RNA-like endoplasmic reticulum kinase (PERK, also known as EIF2AK3)[21-23] and the transcription factor activating transcription factor 6 (ATF6) (**Fig. 1**).[24]

These discoveries triggered an avalanche of elegant biochemical and genetic investigations from different laboratories[16,25-28] that greatly advanced our understanding of how these UPR effectors sense disturbances in the protein folding status of the ER and transmit this information via the activation of 3 key transcription factors (XBP1, ATF4, and ATF6) in the nucleus to switch on the vast gene expression program of the UPR (readers are referred to recent extensive reviews in this subject).[25-27,29]

In the last decades, several studies using different model systems have outlined the intrinsic prosurvival and adaptive role of the UPR, which is primarily engaged to rescue proteostasis, redox balance, and the secretory capacity of the ER under conditions of manageable stress. However, they also made it clear that in the case of unmitigated ER stress, effector mechanisms emanating from the stressed ER can elicit and propagate danger signaling in order to communicate the stressed status of the cell to its environment and/or induce cell death (further discussed in later sections). The molecular mechanisms underlying the latter functions of the UPR are somewhat elusive but include the following: (1) the spatiotemporal coordination of the 3 different signaling branches of the UPR, with the requirement for sustained PERK signaling to mount an apoptotic threshold level of CHOP expression, thus resulting in transcription of its proapoptotic targets,[27] (2) the activity of the UPRosome as a dynamic signaling platform regulating both the amplitude and duration of IRE1 signaling and the UPR effector responses,[27] and, discovered more recently, (3) the CHOP-mediated exacerbation of protein translation and protein oxidation in the ER.[30] It has also become apparent that ER stress can evoke various caspase-dependent and caspase-dispensable mechanisms of cell death,[28] thus highlighting that when the stress is too severe and adaptive mechanisms, including the induction of autophagy,[31,32] have failed to rescue ER homeostasis, permanent ER stress leads to cell death.

The last decade has also witnessed an increase in studies investigating the ER–mitochondria interface, with several elegant reports documenting the relevance of this interorganellar communication, which is facilitated by proteinaceous ER subdomains juxtaposed to mitochondria, in shaping a variety of crucial cellular processes including cell death signals during ER stress (reviewed elsewhere).[33,34] These subdomains were first isolated as specific structural entities in 1990 by Jean Vance, who called them mitochondria-associated membranes (MAMs), and were further shown to favor the exchange of lipids and second messengers such as Ca^{2+} between the ER and mitochondria.[33,34] The recent discovery that the ER stress sensor PERK is a MAM component[35] (together with other known ER resident proteins) and performs UPR-independent functions at these contact sites reveals newly emerging facets of ER functions that will certainly be a focus of various future studies (**Fig. 1**).

It has also become increasingly evident that deregulation of UPR signaling linked to chronic ER stress is implicated in a variety of pathologies, including cancer. The period spanning the beginning of the new millennium (the mid-1990s to early 2000s) was hallmarked by a number of important studies providing evidence of activated ER stress signaling (accompanied by altered ER morphology) in solid tumors, leading to the proposal that the UPR may serve either a protumorigenic role through its cytoprotective function, or an antitumorigenic function, mainly by inducing dormancy or increasing apoptotic vulnerability of the cancer cells (first proposed and discussed in the review by Ma and Hendershot in 2004).[36-39] An increasing number of recent *in vivo* studies have further validated the double-edged sword role of the UPR in cancer, delineating its reliance on oncogenic drivers, tumor stages, and/or therapeutic context (reviewed in[26-28,40,41]). This is perhaps not surprising, given that cues that alter ER functions and disturb the folding environment, such as glucose or oxygen deprivation and oxidative stress, are predominant hallmarks of the tumor microenvironment (as discussed further below). Also, the heightened metabolic and proliferation rates, as well as the increased pace at which cancer cells secrete factors to dynamically modulate and communicate with their fluctuating environment, impose an increased folding and secretory load on the ER, resulting in constitutive activation of the UPR.[42]

More recently, constitutive activation of the prosurvival function of the UPR, coupled to the upregulation of ER chaperones, has been shown to assist in processes such as angiogenesis, invasion, and dissemination, in addition to increasing resistance to oxidative stress, especially in hypoxic tumors.[43-49] Moreover, an increasing number of reports delineate an important extracellular role of ER resident proteins such as CRT, GRP78, GRP94, and PDIs as prosurvival or protumorigenic signals, with the notable exception of surface exposed (ecto-)CRT. In 2005, a seminal study of Gardai and Henson provided the first evidence that ecto-CRT acts as an "eat me" signal in response to cellular stress inducing apoptosis, inciting removal of the dying cells by phagocytes (**Fig. 1**).[50] A series of important studies from Guido Kroemer's laboratory[51-53] and our group[54-56] followed up on this observation and underscored that the ability of certain anticancer agents to elicit cancer cell-based ecto-CRT is reliant on the induction of oxidative ER stress and the presence of a functional PERK-modulated secretory pathway or UPR module (**Fig. 1**).[56,57] The spatiotemporally-defined surface exposure of this specific ER-resident protein was discovered to be of vital importance for the induction of immunogenic cell death (described in more detail later) and has been found to be an

essential step in the cascade of events triggering antitumor immunity, a guiding component of successful anticancer therapy.

The concerted efforts of many laboratories all over the world to address the role of ER stress in cancer are revealing the broad nature of this stress response. The recent development of novel inhibitors for ER stress sensors or UPR effectors such as IRE1 and PERK might prove instrumental in revealing new facets of proximal UPR function in cancer. For example, a first-in-class PERK inhibitor (GSK2606414) that selectively binds the kinase domain of PERK and is able to trap the kinase in its inactive conformation was shown to slow tumor growth in a xenograft pancreatic tumor model. However, a preclinical study using GSK2656157, a related and optimized PERK inhibitor with decreased lipophilicity, showed gradual but reversible degeneration of the pancreas, but retained its antitumor effect in a variety of tumor xenograft models.[58,59] This is in line with observations that PERK promotes tumor initiation and expansion *in vivo*, probably by favoring angiogenesis (**Fig. 1**).[46] Interestingly, the identification of an IRE1 endonuclease-specific inhibitor has shown that attenuating the adaptive branch of the UPR also has the potential to halt tumor progression, as treatment with this inhibitor showed significant antimyeloma activity in a xenograft model (**Fig. 1**).[60,61]

Although the development of small molecule inhibitors of the main branches of the UPR has generated promising results, it currently remains unclear how suppression of these UPR signals and the consequent loss of cell autonomous proteostasis affects crucial cancer cell–tumor stroma interactions defining the major hallmarks of cancer.

Whereas targeting the UPR effectors is a relatively novel strategy with potential clinical implications, durable progress has already been achieved at the level of lethal ER stress induction in cancer cells using novel inhibitors of ER function; for example, bortezomib, a selective proteasome inhibitor (**Table 1**), has exhibited significant success in the treatment of patients with advanced refractory myeloma.[62] Considering the central role of ER and ER stress in a cell, we envisage that induction of lethal ER stress could be one of the best therapeutic strategies for simultaneous targeting multiple cancer cell autonomous and non-autonomous functions.

Hallmarks of Cancer and Therapy-Induced ER Stress: a Bird's Eye View

Early studies (mainly anatomical and pathological in nature) largely described cancer in a rather simplistic manner as an insular mass of highly proliferating cancer cells.[63] However, studies performed over the last 2 decades have drastically changed our understanding of this complex disease to a level where a tumor is now regarded more as a "pseudo-organ" rather than an insular mass.[29,64] A cancerous tumor is composed of multiple distinct cell types (tumor cells, immune cells, stromal cells, and vasculature-related cells) that come together to perform and/or respond to heterotypic interactions and autocrine/paracrine signaling amongst each other and create a distinctive yet dynamic tumor microenvironment.[63] The progression of a tumor is thus regulated by multiple processes derived not only from the cancer cells

but also from the stromal, vasculature-related, and/or immune cells.[63] The physiological nature of this "pseudo-organ" (i.e., tumor) resembles that of a "wound that never heals"[65] and remains in a chronic state of disequilibrium between proliferation and cell death (causing exaggerated growth of the tumor mass) with the co-existence of antitumor immunity and protumorigenic inflammation that interferes with resolution of inflammation or the healing process and thus prolongs the "wounded" state.[65]

Over the years it became necessary to understand the major signatures or hallmarks that define the state of being cancerous for prognostic, diagnostic, and therapeutic reasons. These hallmarks and the major "umbrella processes" associated with them are summarized in **Fig. 2**. It is clear from these hallmarks that cancer represents an "evolving disease" capable of exploiting everything at its disposal (autonomous signaling as well as non-autonomous interactions or paracrine signaling) for its own growth and progression. Based on these hallmarks, approximately 10 classes of therapeutics capable of targeting them have been proposed—epidermal growth factor receptor (EGFR) inhibitors, cyclin-dependent kinase inhibitors, immune activating anti-CTLA4 antibodies, telomerase inhibitors, selective anti-inflammatory drugs, inhibitors of HGF/c-MET, inhibitors of vascular endothelial growth factor (VEGF) signaling, PARP inhibitors, proapoptotic BH3 mimetics, and aerobic glycolysis inhibitors.[63]

However, in line with the enigmatic complexity of cancer these hallmarks,[63] although comprehensive, do not exhaustively explain the "state of cancer" thereby leaving ample gaps for further exploration of the tumor microenvironment and dissection of signaling pathways for effective therapeutic targeting.[66,67] Thus, there is a need to target broad stress-responsive cellular processes that govern both cancer cell autonomous signaling as well as non-autonomous crosstalk—a strategy that should prove instrumental in the pursuit of targeting multiple hallmarks of cancer simultaneously.

Therapeutic induction of ER stress as a strategy to broadly target various hallmarks of cancer has seldom been discussed. This is despite the fact that several therapies that primarily target the ER have shown clinical promise in cancer patients (**Table 1**) and several "seasoned" or well-established clinically applied cancer therapeutics have been shown to have ER stress-inducing effects associated with positive outcome (at least in preclinical studies; discussed in later sections and summarized in **Table 1**). Interestingly, it seems that the success of therapy-induced ER stress may rely not only on direct induction of cancer cell death[27] (a cell autonomous feature) but also on the ability to modulate or even "reset" the tumor microenvironment by modifying the signals derived from cancer cells and/or tumor stromal/immune cells (cell non-autonomous features). It is very important to note here that therapy-induced ER stress strongly differs from the ER stress associated with basal conditions[27] for a tumor cell or for that matter for the tumor microenvironment in general.[26,29,40] A basal, non-therapy exposed, tumor is associated with a predominantly chronic type of ER stress induced by various physiological stressors, as discussed earlier, which can be largely protumorigenic.[25,26,29,40]

In the present review we will discuss possible strategies enabling targeting of the various hallmarks of cancer with therapy-induced ER

Table 1. Endoplasmic reticulum (ER) stress-inducing therapeutics, their targets or ER stress-inducing mechanisms, and clinical or preclinical applications

Drug or Therapy	Main Target	Mechanism of ER stress induction	Clinical application/trials or pre-clinical trials	Refs.
Therapeutics/Drugs that have ER or ER associated proteins as primary or direct selective targets				
Epidermal growth factor (EGF)-SubA	ER lumen protein, GRP78-targeting cytotoxin SubA	SubA targets GRP78, compromises its function, and affects proteostasis in ER	—	156
Oncolytic viruses	ER lumen	Oncolytic viruses stress the ER through viral protein overload	Clinically applied for treatment of various cancers such as glioma, glioblastoma, lung cancer, bladder carcinoma, melanoma, mesothelioma, sarcoma, breast cancer, multiple myeloma, pancreatic cancer, prostate cancer, reproductive tract tumors, astrocytoma, hepatocellular carcinoma, head and neck cancer, neuroblastoma.	157
Protein disulphide isomerase (PDI) inhibitors	ER lumen protein - PDI	PDI inhibition causes rapid accumulation of misfolded or unfolded proteins in the ER	—	158
Photodynamic therapy (PDT) with ER-localizing photosensitive drugs such as hypericin or mTHPC	ER membranes	ER membrane associated photosensitive drugs are light-activated, causing massive production of ROS and ROS-based ER stress	Hypericin–based PDT (Hyp-PDT) is currently being tested in preclinical trials for the production of dendritic cell (DC)-based vaccines against glioblastoma and ovarian cancer (Garg et al. unpublished results; Immunotherapy Platform Leuven/ITPL); Hyp-PDT has been clinically applied for the treatment of non-melanoma skin cancer, cutaneous T-cell lymphoma, mesothelioma and basal/squamous cell carcinoma; m-THPC-PDT has been clinically approved for treatment of head and neck cancer, lung cancer, brain cancer, skin cancer, and bile duct cancer.	54,159
Thapsigargin or thapsigargin-based prodrug (G202)	ER sessile protein - SERCA	SERCA2 inhibition causes ER Ca^{2+} imbalance; G202 is thapsigargin fused with masking peptide that inhibits its activity until the peptide is cleaved at tumor site	Thapsigargin-based pro-drug G202 is currently being applied in clinical trials for castrate-resistant prostate cancer therapy (NCT01056029).	160,161
Tunicamycin	N-glycosylation in the ER	Lack of N-glycosylation causes accumulation or overload of misprocessed proteins in the ER	Preclinical studies for tunicamycin-based treatment of breast cancer have shown promise without palpable toxicity.	99
Versipelostatin; *****Epigallocatechin gallate (derived from green tea extract);	ER lumen protein - GRP78	Inhibition of GRP78 chaperone function compromises ER protein folding	BiP inhibitors have shown good promise in preclinical studies and are potential candidates for combinatorial therapies; Epigallocatechin gallate (as part or source of extracts) has recently been used for various clinical trials for treatment of colorectal cancer (NCT01360320), breast cancer (NCT00949923), urothelial cancer (NCT01993966), superficial skin cancer (NCT02029352) and multiple myeloma (NCT00942422).	106,162
Therapeutics/Drugs that have ER or ER associated proteins as secondary or indirect non-selective targets				
2-Deoxyglucose	Glucose metabolism	Interference with glucose metabolism causes ER stress	Clinical dose escalation studies and Phase I/II clinical trials have been carried out with 2-DG for various cancers (NCT00096707 and NCT00633087).	163
7A7, anti-EGFR antibody	EGFR	Induces ER stress through an unknown mechanism	7A7 is an antibody against murine EGFR, used extensively for preclinical studies.	164
Anthracyclines;*****Mitoxantrone				165

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Table 1. Endoplasmic reticulum (ER) stress-inducing therapeutics, their targets or ER stress-inducing mechanisms, and clinical or preclinical applications (*Continued*)

Drug or Therapy	Main Target	Mechanism of ER stress induction	Clinical application/trials or pre-clinical trials	Refs.
	DNA or proteins of DNA replication machinery	Associate with cellular membranes in general including ER membranes and cause ROS production leading to ROS-based ER stress	Anthracyclines/mitoxantrone have been used for more than 40 years for treatment of various cancers including pediatric malignancies, sarcomas, leukemia, lymphomas, Kaposi's sarcoma, uterine cancer, ovarian cancer and breast cancer.	166
Bleomycin	DNA	Induces ER stress through an unknown mechanism	Bleomycin is frequently used for the treatment of Hodgkin's lymphoma and germ cell tumors. It is also used for the treatment of Kaposi's sarcoma, cervical cancer, and squamous cell carcinomas of head and neck.	167
Bortezomib;*****Nelfinavir; *****Atazanavir;*****MG132; *****Salinosporamide A; *****Carfilzomib;*****CEP-18770; *****Ritonavir;	26S Proteasome	Proteasome inhibition cripples the ERAD system, indirectly causing protein overload in the ER	Bortezomib was the first proteasome inhibitor to enter the clinic; it is approved for the treatment of multiple myeloma and mantle cell lymphoma; Carfilzomib and CEP-18770 have been applied in clinical trials for multiple myeloma and certain other leukaemias; Ritonavir has been applied in clinical trials for breast cancer (NCT01009437) and glioma (NCT01095094); Nelfinavir has been applied in clinical trials for cervical cancer (NCT01485731), various solid tumors or malignancies (NCT01445106, NCT00436735), rectal cancer (NCT00704600).	168
BRAF inhibitor (BRAFi) e.g., vemurafenib	Inhibits BRAF^{V600E} kinase	Possibly interferes with cytosolic Ca^{2+} homeostasis causing ER stress	Vemurafenib was first approved for the treatment of melanoma; It has also been applied in clinical trials for thyroid cancer (NCT01709292), gliomas (NCT01748149), leukemia (NCT01711632), colorectal cancer (NCT02164916), multiple myeloma (NCT01524978).	40
Brefeldin A or brefeldin A-based pro-drug (breflate)	ADP-ribosylation factor	Inhibition of anterograde ER-to-Golgi transfer causes "Golgi collapse" into the ER	Breflate is a water-soluble and stable pro-drug derivative of brefeldin A that has shown good preclinical promise.	118,169
Cannabinoids	Bind respective cannabinoid receptors	Cause ER stress through ceramide accumulation and eIF2α phosphorylation	Cannabinoids have recently reached clinical trials for the treatment of glioblastoma and various advanced cancers (NCT00316563).	170
Carboplatin	DNA replication or repair machinery	Carboplatin produces ROS that induce ER stress	Carboplatin is used as standard treatment for various epithelial cancers such as lung cancers, endometrial cancer, and head and neck cancer.	171
Cardiac glycosides e.g, bufalin; digoxin; digitoxin;	Na$^+$/K$^+$ ATPase in plasma membrane	Increases intracellular Na$^+$, causing blockade of antiporter function of Na$^+$/Ca^{2+} exchanger thereby causing Ca^{2+} homeostasis imbalance leading to ER stress;	Cardiac glycosides have been clinically applied in cancer patients (breast, head and neck, hepatocellular, colorectal, lung, and prostate) with underlying cardiac disorder; Their presence has been shown to augment patient survival.	172
Celecoxib	COX-2 inhibitor	Causes leakage of Ca^{2+} from the ER into the cytosol	Celecoxib has been used in the clinic either alone or in combination with other therapeutics for treatment of lung cancer (NCT00030407), prostate cancer (NCT00136487), colorectal cancer (NCT00087256),	

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Curcumin	ER sessile protein - SERCA2 (among other targets)	SERCA2 inhibition causes ER Ca^{2+} imbalance	Applied in the clinic recently, largely (but not always) as preventive therapy for multiple myeloma, rectal cancer, colorectal cancer, pancreatic cancer, osteosarcoma, cutaneous T-cell lymphoma. head and neck cancer (NCT00527982), breast cancer (NCT01695226), bladder cancer (NCT00006124), ovarian cancer (NCT01124435), uterine cancer (NCT00231829).	173,174
Cyclophosphamide	DNA	Induces ER stress through an unknown mechanism	Cyclophosphamide is routinely applied for the treatment of a number of malignancies including lymphomas, breast cancer, bone and soft tissue sarcomas, ovarian cancer.	175
Edelfosine	Incorporates into the lipid rafts in cell membranes	Targets ER membrane-associated lipid rafts to induce ER stress	Clinically evaluated in Phase I and II studies for the treatment of lung cancer and glioblastoma.	176
Eeyarestatin,*****ML240; *****DBeQ;	p97/VCP	Accumulation of ubiquitylated proteins	p97/VCP-targeting drugs have shown promising preclinical results for various cancers including cervical cancer and lung cancer.	26,177
HDAC Inhibitors (HDACi) e.g. Vorinostat	Histone deacetylase	Causes GRP78 acetylation, which in turn inhibits GRP78 function and compromises ER protein folding, causing ER stress	HDACi have been clinically applied or are being currently clinically tested for the treatment of various solid cancers, lymphomas, and leukemias.	178,179
High hydrostatic pressure (HHP)	Cellular proteins and cellular aqueous homeostasis	Induces ER stress due to major effects on cellular aqueous homeostasis and protein homeostasis	HHP-treated cancer cells fed to dendritic cells (DCs) have been used for DC-based immunotherapy that has recently entered clinical trials for treatment of prostate cancer (NCT02107404), ovarian cancer (NCT02107937); cannot be applied for direct tumor treatment in patients.	180
HSP90 inhibitors (HSP90i)*****e.g., 17-AAG,*****Geldanamycin; *****Alvespimycin; *****Retaspimycin;*****PU-H71; *****SNX-2112;	HSP90	Inhibition of HSP90 chaperone function compromises ER protein folding	HSP90i have shown encouraging results in the clinic for the treatment of melanoma, leukemia, prostate cancer, lung cancer, multiple myeloma, and breast cancer.	181
Ionomycin	Ca^{2+}	Interferes with Ca^{2+} balance thereby causing ER stress as one of the consequences	-	
MAL3-101	HSP70	Inhibition of HSP70 chaperone function compromises ER protein folding	Used for preclinical research into the treatment of multiple myeloma with some promise.	26
Melphalan	DNA	Induces ER stress through an unknown mechanism (Dudek et al. Unpublished results)	Melphalan is routinely used for isolated-limb perfusion based treatment of extremities-confined melanoma; It is also used for locoregional treatment of extremities-associated soft tissue sarcoma, hepatocellular carcinoma, liver metastasis of cancers such as ocular melanoma and colorectal cancer.	182-185
Microtubule-binding chemotherapeutics e.g. vincas, taxanes	Microtubule	Cause ER stress due to alteration of ER movement/morphology, hyperploidy induction, BiP upregulation, and/or P-body formation*	Microtubule-binding chemotherapeutics are routinely used for clinical treatment of various tumor types including lymphomas, breast cancer, lung cancer, bladder cancer, leukemias, melanoma, myeloma,	186,187

Table 1. Endoplasmic reticulum (ER) stress-inducing therapeutics, their targets or ER stress-inducing mechanisms, and clinical or preclinical applications (*Continued*)

Drug or Therapy	Main Target	Mechanism of ER stress induction	Clinical application/trials or pre-clinical trials	Refs.
			sarcoma, ovarian cancer, mesothelioma, pancreatic cancer, colorectal cancer, prostate cancer.	
Oxaliplatin	DNA	Associated with cellular membranes in general including ER membranes and causes ROS production leading to ROS-based ER stress	Oxaliplatin is clinically approved for the treatment of colorectal cancer patients; It is also in the clinic for treatment of various solid tumors (NCT01233505).	188
Photodynamic therapy (PDT) with photofrin	Cellular Membranes	Partial contact	Photofrin-PDT has been clinically approved for treatment of lung cancer, esophagus cancer, brain cancer, bladder cancer, ovarian cancer and bile duct cancer; Photofrin-PDT treated cancer cell-based vaccines have shown promising preclinical results.	54,159
Radiotherapy	DNA	Causes ROS production in the vicinity of cellular membranes including the ER membranes thereby causing ER stress	Radiotherapy is widely used for the clinical treatment of various solid malignancies, carcinomas, lymphomas, sarcomas, and pediatric tumors.	189
Shikonin	Tumor-specific pyruvate kinase-M2 protein, 20S subunit of proteasome	Causes ER stress through ROS mainly derived from the mitochondria	A small clinical study has shown that a shikonin mixture can be effective for treatment of patients of lung cancer; Shikonin in general has shown promising preclinical results.	190
Sorafenib	Multiple Kinases	Induction of p97/VCP phosphorylation	Sorafenib has been clinically applied for the treatment of renal carcinoma, liver cancer, thyroid cancer, prostate cancer, breast cancer, head and neck cancer, sarcoma, lung cancer, and mesothelioma.	191
UV irradiation	DNA	Causes ROS production in vicinity of cellular membranes including the ER membranes thereby causing ER stress	-	
Wogonin	Mitochondria	Causes ER stress through ROS mainly derived from the mitochondria	-	

* P-bodies are cytoplasmic regions where mRNA translation is inhibited

Abbreviations: COX, cyclo-oxygenase; DC, dendritic cell; EGFR, epidermal growth factor receptor; eIF2α, eukaryotic initiation factor 2 α; ER, endoplasmic reticulum; ERAD, endoplasmic reticulum-associated protein degradation; GRP, glucose-regulated protein; HHP, high hydrostatic pressure; HSP, heat shock protein; Hyp, hypericin; mTHPC, m-tetrahydroxyphenylchlorin; PDT, photodynamic therapy; ROS, reactive oxygen species; SERCA, sarcoendoplasmic reticulum calcium transport ATPase; p97/VCP, valosin-containing protein.
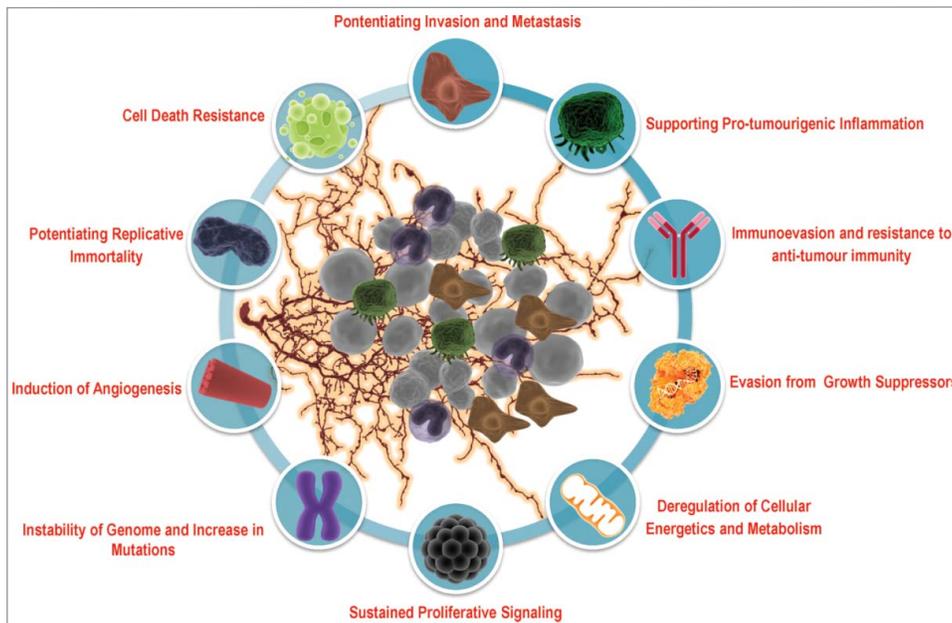
Figure 2. Schematic representation of the main hallmarks of cancer. A number of major hallmarks of cancer that are utilized by a malignant tumor for further progression and tumorigenesis have been characterized. These include **potentiating invasion and metastasis** (the ability to undergo epithelial-to-mesenchymal transition [EMT] for invasion or metastasis and MET at the site of colonization; support from tumor stroma or immune cells through certain chemokines or cytokines; extracellular matrix [ECM]-degrading enzymes); **supporting protumorigenic inflammation** (the ability to exploit certain chemokines, cytokines, and other factors that are secreted by immune cells as growth factors; certain immune cell-derived factors can also facilitate angiogenesis, invasion, and metastasis); **immunoevasion and resistance to antitumor immunity** (the ability to evade immunosurveillance; resistance to danger signaling; ability to cause T cell exhaustion/apoptosis, and suppression of dendritic cell [DC], natural killer [NK], and macrophage function); **evasion from growth suppressors** (loss-of-function of tumor suppressor genes; evasion of contact inhibition); **deregulation of cellular energetics and metabolism** (the ability to perform "aerobic glycolysis" or "Warburg effect"-like metabolism; executing energy metabolite-based intratumoral symbiosis; involvement of gain-in-function mutations in metabolism-related enzymes); **sustained proliferative signaling** (defective gain-in-function by several components of mitogenic growth signaling); **cell death resistance** (deregulation of proapoptotic signaling and/or increased antiapoptotic signaling; autophagy-based cell death suppression); **potentiating replicative immortality** (increased telomere maintenance; resistance to senescence; potentiation of telomerase activity); **induction of angiogenesis** (aberrant increase in proangiogenic factors/signaling, further supported by pericytes, inflammation-inciting immune cells and bone marrow-derived cells); and **instability of genome and increase in mutations** (defects in DNA maintenance and repair machinery; loss of telomeric DNA; increased hyperploidy).

Research has shown that therapy-induced ER stress has the ability to modulate a number of growth-promoting signaling pathways (basally or in response to stress), including the p38MAPK pathway, PI3K pathway, Akt-mTOR pathway, and Raf/MEK/ERK pathway (**Fig. 3**); depending on the tumor or therapeutic context, ER stress-inducing agents may either suppress or activate these pro-growth pathways.[69] For example, various ER stress-inducing therapies have been shown to activate growth-promoting pathways (**Table 1**), including anthracyclines,[70,71] tunicamycin,[71,72] microtubule-targeting chemotherapeutics,[73] and thapsigargin.[72,73] On the other hand, various ER stress-inducing modalities have shown the ability to suppress this hallmark of cancer. For example, Newcastle disease virus can trigger a p38 MAPK-mediated cell death pathway[74] although it is not clear whether this is achieved through CHOP phosphorylation, a recently described mode of p38MAPK-mediated cell death.[69] Moreover, Hypericin-based photodynamic therapy (Hyp-PDT) (**Table 1**) can cause immediate inhibition of Akt-mTOR and ERK signaling pathways.[75,76] In fact, it has been reported that Hypericin on its own is capable of inhibiting the pro-growth pathways originating from EGFR and CK2.[77,78] Similarly, an association between BiP/GRP78 and Raf-1[79] or its mutated form BRAF$^{(V600E)80}$ is associated with the ability to either evade ER stress-induced cell death or induce cytoprotective ER stress, respectively. This raises the prospect of using BiP/GRP78 inhibitors (**Table 1**) to target proliferative signaling of cancer (**Fig. 3**).

From the above discussion it is clear that many ER stress-inducing therapies have the ability to suppress growth-promoting pathways, and that therapies incapable of doing this alone can be combined with inhibitors of mitogenic or growth signaling pathways to ameliorate this deficiency (**Fig. 3**).

stress. We will also try to provide a rationale for proposing which types of ER stress-inducing therapeutics have the highest capability to target as many cancer hallmarks as possible (**Fig. 3**).[67,68]

Targeting Proliferative Signaling and Resistance to Growth Suppression in Cancer

Chronic proliferation is an "innate" property of tumor cells (**Fig. 2**). Cancer cells tend to deregulate the normally stringently controlled growth-promoting and/or mitogenic signaling pathways (e.g., Raf-associated signaling, mitogen-activated protein (MAP)-kinase pathway, phosphoinositide 3-kinase [PI3K] pathway) and cell cycle progression (controlled by prototypical tumor suppressor proteins such as retinoblastoma protein [RB1] and TP53 protein), thereby gaining the capacity to proliferate uncontrollably (**Fig. 2**).[63]

Targeting Replicative Immortality and Genomic or Mutational Instability in Cancer

Unlimited replicative potential is an important property of immortalized cancer cells (**Fig. 2**). Increased expression of telomerase (a specialized DNA polymerase) in cancer cells increases
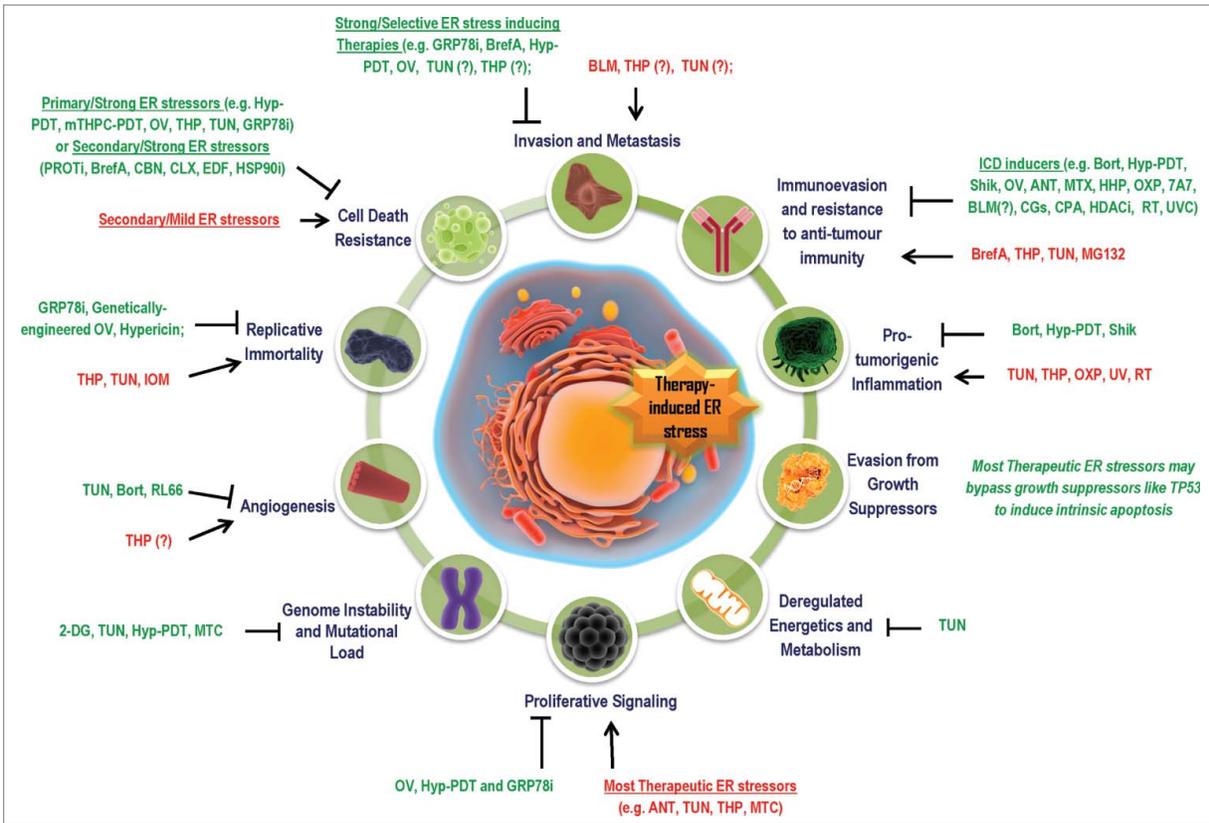
Figure 3. An overview of therapeutic ER stress-based targeting of the main hallmarks of cancer. Respective therapy-based ER stress inducers (see **Table 1**) have been segregated into 2 categories (wherever possible) based on their ability to target each of the hallmarks of cancer; such that therapies or drugs labeled with green inhibit the hallmark (thereby inhibiting or suppressing tumorigenesis) whereas those labeled with red support the hallmark (thereby enabling or supporting tumorigenesis). The question mark in parenthesis (?) indicates that data supporting the ability of the given therapy or drug to target or support a hallmark of cancer are not conclusive but are evidenced by either contradictory or incomplete observations. Please see the text for further details. 2-DG, 2-deoxyglucose; 7A7, murine anti-EGFR antibody; ANT, anthracycline; BLM, bleomycin; Bort, bortezomib; BrefA, brefeldin A; CBN, cannabinoids; CG, cardiac glycoside; CLX, celecoxib; CPA, cyclophosphamide; EDF, edelfosine; GRP78i, BiP/GRP78 inhibitor; HDACi, HDAC inhibitor; HHP, high hydrostatic pressure; HSP90i, HSP90 inhibitor; Hyp-PDT, hypericin-based photodynamic therapy; ICD, immunogenic cell death; IOM, ionomycin; MTC, microtubule-targeting chemotherapy; MTX, mitoxantrone; OV, oncolytic viruses; OXP, oxaliplatin; PROTi, proteasome inhibitor; RL66, an analog of curcumin; RT, radiotherapy; Shik, shikonin; THP, thapsigargin; TUN, tunicamycin; UVC, UV irradiation of C-band wavelength.

the stability of telomeric DNA (instability of telomeric DNA is a barrier to unlimited proliferation)—a phenomenon that has been found to correlate with resistance to cellular senescence (i.e., natural cellular proliferation arrest) and cell death or apoptosis.[63] The high replicative potential of cancer cells is further supported by increased mutational load and genomic instability that is characterized by defects in DNA or chromosomal repair and maintenance (**Fig. 2**).[63]

Little research has been performed on the link between telomere maintenance, telomerase activity, senescence, and therapy-induced ER stress. Chemical ER stressors such as thapsigargin, ionomycin, and tunicamycin (**Table 1**) have been shown to cause an early transient increase in telomerase activity and/or expression in cancer cells that eventually subsides; this increased telomerase activity/expression was found to play a prosurvival role.[81,82,83] Interestingly, BiP/GRP78 can have antisenescence effects;[84] this observation has not yet been translated to therapeutics targeting BiP/GRP78 *in vivo* (**Table 1**) but targeting this

molecule may help to induce cancer senescence and could be a promising course of investigation in the near future (**Fig. 3**).

Another interesting strategy for targeting the telomere–telomerase axis is through genetically engineered tumor-specific and replication-selective oncolytic viruses (**Table 1**). Researchers have been successful in constructing oncolytic viruses (e.g., OBP-301, Telomelysin, both based on adenoviruses) whose replication is driven by the telomerase promoter such that the oncolytic virus only replicates in, and causes the demise of, cancer cells overexpressing telomerase.[85,86] This strategy has shown promising results in preclinical studies using mice models relevant for clinical scenarios (**Fig. 3**).[85,86] This option might be more promising than the telomerase inhibitors proposed for targeting this hallmark of cancer, which alone have shown very limited clinical efficacy.[87] Genetically engineered oncolytic viruses can also induce cancer senescence, as demonstrated recently for an adenovirus.[88] Last, but not least, it has been reported that Hypericin, the active photosensitive drug component of the Hyp-PDT–based strategy

of 'focused' or 'on-target' oxidative-ER stress induction (**Table 1**), is by itself able to decrease the expression levels of telomerase at concentrations as low as 500 nM.[89] Whether this telomerase-targeting activity of Hypericin also works during Hyp-PDT treatment is an intriguing question that deserves further attention in the near future (**Fig. 3**).

Interestingly, the DNA repair and maintenance machinery that ends up supporting cancer genomic instability in the long run (one of the reasons why chemotherapeutics targeting DNA repair proteins have shown clinical success; **Table 1**) is also targeted by therapy-induced ER stress. For example, ER stress induced by 2-deoxyglucose causes downregulation of DNA repair genes and DNA damage checkpoint genes, accompanied by concomitant upregulation of apoptosis-related genes.[90] From a mechanistic sense, it has been proposed that ER stress affects DNA repair capacity by altering Rad51 stability to induce apoptosis. In line with this, tunicamycin was shown to cause selective degradation of Rad51 via the 26S proteasome thereby impairing DNA double-strand break repair and causing apoptosis.[91]

Recently, a very interesting angle has emerged with respect to chromosomal or genomic instability, antitumor immunosurveillance, and therapy-induced ER stress. Specifically, it has been shown that increased polyploidy or hyperploidy (i.e., an increased number of chromosomal copies due to defective cell division) in cancer cells causes induction of ER stress.[92] This ER stress causes mobilization of ecto-CRT that facilitates phagocytosis of cancer cells experiencing hyperploidy-mediated ER stress.[92] Interestingly, various microtubule-binding chemotherapeutics (**Table 1**) have been proposed to facilitate hyperploidy-based ER stress, which in turn facilitates ecto-CRT–based anticancer immunosurveillance (**Fig. 3**).[92] Moreover, it has been reported that Hyp-PDT also induces hyperploidy in cancer cells by ROS-based targeting of ER membrane-associated microtubules,[93] suggesting that Hyp-PDT might also be able to exploit this route for anticancer activity.

Targeting Tumor-Associated Angiogenesis

During tumorigenesis, 'starved' cancer cells recruit their own vasculature to increase the delivery of oxygen and nutrients (**Fig. 2**). This improves their fitness and allows continuous tumor growth, thus facilitating metastasis. Under physiological conditions angiogenesis is highly regulated; however, in tumors the unbalanced production of pro- and antiangiogenic factors drives abnormal vessel growth thereby supporting tumorigenesis. Tumor angiogenesis is a result of continuous crosstalk between cancer cells and endothelial cells and/or other stromal cells (**Fig. 2**).

Several types of ER stress-inducers have been shown to increase the production of proangiogenic factors in different types of cancer cells *in vitro* (**Fig. 3**); as an example, tunicamycin (**Table 1**) promotes breast cancer cell-based secretion of the proangiogenic cytokines VEGF and interleukin 8 (IL-8).[94] In line with this, upregulation of a large number of proangiogenic factors has been reported after treatment with ER stress-inducers such as thapsigargin and tunicamycin in medulloblastoma,

glioma, and neuroblastoma cells (**Table 1**).[95] Interestingly, increased VEGFA secretion after induction of ER stress may be a result of 2 parallel processes: (1) increased transcription, through the binding of XBP1 and ATF4 (but not ATF6) to the promoter of *VEGFA*, and (2) increased translation, through increased *VEGFA* mRNA stability via activation of the stress-induced AMP kinase.[95] Another study in glioma cell lines showed that treatment with bortezomib (**Table 1**) increased VEGF secretion. Furthermore, conditioned medium derived from these bortezomib-treated cancer cells increased proliferation of endothelial cells in a VEGF-dependent manner.[96]

In endothelial cells, on the other hand, therapy-induced ER stress has been shown to have antiangiogenic effects *in vitro*. For example, thapsigargin reduced endothelial cell proliferation and microvessel formation in an isolated aorta ring assay.[97] Similarly, bortezomib reduced cell proliferation, chemotaxis, fibronectin adhesion, and capillary formation in endothelial cells derived from patients with multiple myeloma. Bortezomib also reduced VEGF and IL-6 secretion by the endothelial cells.[98] More recently, tunicamycin was found to inhibit endothelial cell migration, invasion, and chemotaxis *in vitro* and microvessel density *in vivo*.[99] Additionally, RL66, an analog of curcumin (**Table 1**) that is known to induce ER stress, has been shown to reduce endothelial cell migration and tube formation *in vitro*.[100]

Interestingly, when *in vivo* tumors are treated with certain ER stressors, resulting in simultaneous targeting of the cancer cells and endothelial cells, the antiangiogenic effect on the endothelial cells seems to overrule the proangiogenic effect mediated by the cancer cells (**Fig. 3**). In line with this, tunicamycin has been shown to reduce tumor angiogenesis in ER⁻/PR⁻/EGFR⁺ grade III breast adenocarcinoma and a triple negative ER⁻/PR⁻/EGFR⁻ breast tumor xenograft in mice.[99] Also, RL66 has been reported to reduce vessel density in ER⁻ breast cancer[100] and bortezomib has been observed to reduce vessel density in xenografts of squamous cell carcinoma.[101]

The antiangiogenic properties of bortezomib in tumors grown in mice have been confirmed in a pilot study in patients with multiple myeloma, in which bortezomib treatment reduced microvessel density in 6 out of 9 patients, which was associated with a better prognosis.[102] It is tempting to speculate that this reflects the interplay between the effects of bortezomib on tumor cell-derived proangiogenic factor production *versus* the effect on the endothelial cells. These data suggest that the antiangiogenic action of bortezomib might contribute to its anticancer effects and serve as a prognostic marker for therapeutic efficacy (**Fig. 3**).

Targeting Resistance to Cell Death

Unlimited proliferative behavior requires "cellular fitness" capable of evading natural barriers to excessive cell division at the expense of the tissue, organ, or organism. In addition to senescence and telomere instability, such natural barriers include cell death, a major tumor suppressor mechanism (**Fig. 2**).[63] Thus, not surprisingly, tumor cells have evolved capabilities to evade or resist cell death induced by increasing metabolic and oxidative

stress, or by anticancer treatments. Most common mechanisms of cell death resistance include loss of tumor suppressor genes (e.g., *TP53* or *PTEN*),[63] increased levels of antiapoptotic proteins (e.g., various Bcl-2 proteins) or prosurvival factors (e.g., Igf1/2), decreased levels of proapoptotic proteins (e.g., Bax, Bim, Puma), deregulated proapoptotic caspase signaling (e.g., caspase 8 mutations, Apaf-1 silencing, IAP overexpression), and/or deregulation of the extrinsic death receptor-based cell death pathways (e.g., decoy receptors, FADD, and caspase-8/10 mutations).[63] Last, but not least, tumor cells may also suppress cell death through autophagy, which has frequently been shown to be cytoprotective due to its ability to recycle damaged proteins or organelles thereby blunting possible pro-death signals that might be emanating from or through them (**Fig. 2**).[64]

The main aim of the ER stress-induced UPR is to promote cell survival.[40] Activation of the UPR has been proposed to trigger 4 "waves" of cellular responses:[27] (1) an initial response that decreases the amount of ER-associated unfolded protein; (2) upregulation of UPR-associated proteins to facilitate protein homeostasis; (3) a transition phase; and (4) the terminal stage that culminates in apoptotic cell death.[27] As far as therapy-induced ER stress is concerned, the decision between cell survival and cell death hinges on different parameters, such as the amplitude and duration of ER stress,[27] and the mechanisms shaping and modulating UPR signaling. In general, therapeutic agents that are capable of exerting strong and persistent ER stress have a better chance of inducing cancer cell death than those that induce transient or mild ER stress.[27,40] Various lines of research[27,40] including our studies[35] have indeed shown that either primary (and strong) ER stress inducers (e.g., Hyp-PDT or mTHPC-PDT, oncolytic viruses, thapsigargin, tunicamycin, and BiP/GRP78 inhibitors; **Table 1**) or secondary (but strong) ER stress inducers (e.g., proteasomal inhibitors such as bortezomib, brefeldin A, celecoxib, edelfosine, HSP90 inhibitors; **Table 1**) cause UPR-based apoptosis in cancer cells (**Fig. 3**). Therapies that induce secondary ER stress of a mild nature may not be able to facilitate ER stress-based apoptosis since in such cases the ER stress-based prosurvival pathway may tend to prevail (e.g., anthracyclines, bleomycin; **Table 1**).[40,103]

Therapy-induced ER stress that leads to cell death has several advantages with respect to certain cancer cell death resistance mechanisms (**Fig. 3**). For example, many lethal ER stressors tend to induce apoptosis independent of TP53 activity[104,105]—a major advantage since the majority of cancers or tumors show loss-of-function of this "guardian of the genome." In fact, in certain contexts lethal ER stressors can also upregulate the downstream proapoptotic targets of TP53 like Puma or Noxa, independent of TP53 activity.[28,40] Moreover, therapy-induced lethal ER stress frequently tends to progress through the intrinsic apoptosis pathway thereby making caspase-8 and extrinsic death receptor-based signaling dispensable for cancer cell death in this context,[26-28,40,106] a major advantage considering the widespread deregulation of these signaling modules in human cancers. Certain lethal ER stressors also gain advantage by targeting proteostasis systems that cancer cells use to gain a prosurvival edge. For example, proteasomal degradation, BiP/GRP78 upregulation,

and increased HSP90 chaperone function help to reduce proteotoxicity and facilitate ER homeostasis.[26,28,40] Thus, therapies that inhibit these functions tend to induce strong ER stress-based cell death (**Table 1**). However, the ability of therapy-induced lethal ER stress to preferentially induce intrinsic apoptosis through increased proteotoxicity is also its "Achilles' heel" because cancer-associated defects that deregulate intrinsic apoptosis (e.g., loss-of-function of Bax and increased expression of antiapoptotic Bcl-2 proteins) also deregulate lethal ER stress-induced apoptosis.[27,28,40,103] Thus, therapy-induced ER stress could be a good candidate for combinatorial therapy with proapoptotic BH3 mimetics and/or inhibitors of proapoptotic Bcl-2 (**Fig. 3**).

Targeting the Autophagy–ER Stress Interplay

Autophagy, literally translated as "self-eating", is a cellular process during which superfluous or damaged cellular components are targeted for lysosomal degradation. During autophagy a double membrane encapsulates the cargo to form an autophagosome, which subsequently fuses with a lysosome where degradation of the cargo occurs and the building blocks are recycled.[107] A wide array of compounds have been shown to induce autophagy concomitant with ER stress; however, knowledge about the regulation of the autophagy machinery in response to ER stress is limited.[108,109] In general, autophagy is thought to play a cytoprotective role by removing damaged proteins and organelles and thereby suppressing cell death. Indeed, most studies support a protective role for autophagy induced by ER stress; for example, our laboratory observed increased cell death after autophagy inhibition in cells exposed to ER stress induced by Hyp-PDT (**Table 1**).[76] Similarly, autophagy was found to be cytoprotective after treatment with several other types of ER stressors (**Table 1**), including co-treatment with vorinostat and sorafenic,[110] the flavanoids ampelopsin[111] and baicalein,[112] imatinib mesylate,[113] BRAF inhibitors,[80] the non-flavanoid resveratrol,[114] ionizing radiation,[115] 2-deoxy-D-glucose,[115] tunicamycin,[115] bortezomib[116] and curcumin analogs.[117]

In specific cases, however, autophagy has been reported to promote cell death after ER stress-inducing therapies. A well-known example of this is Δ^9-tetrahydrocannabinol (THC), the main active component of marijuana, which induces cell death in human glioma through stimulation of autophagy both *in vitro* and *in vivo*.[118] Similarly, autophagy induced by the ER stressors nelfinavir[119] and yessotoxin[120] (**Table 1**) has been shown to promote cell death. Classification of the role of autophagy in the modulation of ER stress-induced cell death is further complicated by the differences in outcome depending on the cellular context. For example, in apoptosis-competent cells autophagy can play a cytoprotective role after Hyp-PDT induced ER stress, whereas apoptosis-deficient Bax/Bak double knock-out cells in the same setting die via an autophagic cell death pathway. Interestingly, autophagy induced by the ER stress inducers tunicamycin, thapsigargin, and brefeldin A alleviates ER stress and supports cell survival in cancer cells, but contributes to cell death in non-transformed cells.[121] Under these conditions the role of

autophagy provoked by ER stress is independent of the Bax/Bak status of the cells.[121] In line with this, autophagy inhibition was found to increase cell death after treatment with the ER-stress inducers fenretidine and bortezomib in BRAF[Wild-Type] cells but not in BRAF[V600E] mutant cancer cells.[122]

Interestingly, autophagy not only influences cell death, but also the "immunogenic character" of the dying cells. Autophagy induced through Hyp-PDT–based ER stress was found to reduce ecto-CRT expression on the dying cells, culminating in a reduction in dendritic cell (DC) maturation and proliferation of IFN-γ–producing CD4+/CD8+ T cells.[123] In conclusion, depending on the cellular context and the therapeutic ER stress inducer under consideration, autophagy can either help the cells cope with ER stress or participate in the mechanism of ER stress-induced cell death. Therefore, it is essential to understand the complex regulation of autophagy in response to ER stress-inducing agents in order to correctly target this cellular process to overcome resistance and improve therapeutic outcome.

Targeting Cancer Invasion and Metastasis

The ability of cancer cells to invade, disseminate, and grow at distant sites during the metastatic process is an important hallmark of malignancy (**Fig. 2**). Various mechanisms contribute to increased invasion and metastasis of cancer cells.[63] Most prominent among such mechanisms is the plasticity exhibited by cancer cells in switching between 2 differentiation-related programs of epithelial-to-mesenchymal transition (EMT) and mesenchymal-to-epithelial transition (MET).[63] Initially, at the stage of invasion and metastatic dissemination, cancer cells can undergo EMT-based dedifferentiation (characterized by loss of typical epithelial differentiation markers such as E-cadherin) thereby altering their shape, producing extracellular matrix (ECM) degrading enzymes (e.g., matrix metalloproteinases or cysteine cathepsin), and losing their attachment to neighboring cells and the ECM.[63] When these cells reach their site of metastatic seeding they undergo a reverse MET-based redifferentiation to allow formation of new cancer colonies.[63] Moreover, cancer invasion and metastasis can also be supported by stromal cells or immune cells, which secrete certain chemokines or cytokines (e.g., CCL5) that stimulate invasion or produce ECM-degrading enzymes that enable dissemination.[63]

Recent research suggests that therapy-induced ER stress might be the most promising and selective way of targeting the EMT phenotype in cancer cells compared to any other available therapeutic strategy (**Fig. 3**). Specifically, in a recent breakthrough, after scanning a chemical library of 315,000 compounds 3 chemicals were characterized as exhibiting selective toxicity toward cancer cells exhibiting a strong EMT phenotype.[124] Further analysis showed that these compounds caused cell death in EMT-cancer cells through selective induction of ER stress.[124] Moreover, in this particular situation, other prominent ER stress inducers such as thapsigargin, BiP/GRP78 inhibition, and tunicamycin (**Table 1**) also selectively killed EMT-cancer cells.[124] The investigators found that the basis for this selectivity

of therapy-induced ER stress for EMT-cancer cells was the highly secretory nature of EMT-cancer cells, which use an expanded secretory apparatus to increase ECM secretion.[124] Therapy-induced ER stress interfered with the increased secretory capacity, thereby primarily targeting the EMT-cancer cells. These observations clearly suggest that strong therapy-induced ER stress can selectively kill EMT-cancer cells (**Fig. 3**), especially ER stressors that interfere with or slow down the secretory trafficking of cancer cells such as brefeldin A (**Table 1**). In fact, we recently observed that Hyp-PDT (**Table 1**) can substantially decrease (but not inhibit) the total extracellular secretory protein content while allowing secretion of very selective proteins/biomolecules[56] (e.g., as a part of selective danger signaling as discussed later). In line with this observation, brefeldin A and Hyp-PDT have also been shown to strongly inhibit or downregulate the secretion of invasion-supporting matrix metalloproteinase 9 (MMP-9)[125,126] Last but not least, EMT-cancer cells have also been reported to be susceptible to oncolytic virotherapy with herpes simplex virus (**Table 1**).[127]

Although these results are very promising, it is necessary to extend these observations to more preclinical and experimental systems, especially for certain specific ER stress inducers like thapsigargin and tunicamycin that have context-dependent activity because such agents may support EMT-based dedifferentiation in non-cancerous/normal cells through the induction of autophagy together with activation of c-Src kinase.[128-130] This caution is substantiated by the observation that tunicamycin induces increased expression of MMPs such as MMP-13, MMP-9, and ADAM10 in renal carcinoma cells.[131] Similarly, bleomycin (**Table 1**) has recently been reported to cause ER stress-based EMT induction.[132] On the other hand, oncolytic viruses exhibit an interesting paradox when it comes to MMPs. Studies suggest that MMPs can in fact increase the effectiveness of oncolytic virotherapy since their ECM-degrading activity can assist in better viral distribution within the tumors.[133,134] In this regard, genetically-engineered oncolytic viruses can be created that selectively kill tumor cells expressing MMPs; for example, oncolytic herpes simplex virus "armed" with MMP-antagonizing transgenes.[135]

In the future it will be necessary to characterize all the different therapeutic ER stressors capable of selectively targeting EMT-cancer cells. The threshold of ER stress intensity that must be achieved for this EMT-cell targeting activity should also be determined considering that many chemotherapeutics induce ER stress as a secondary (and thus possibly mild) effect (**Table 1**).[103]

Targeting Cancer Cell Energetics

The high proliferation rate of cancer cells and the necessity to survive fluctuations in nutrient supply within the overwhelmingly hostile tumor microenvironment are very demanding tasks that require "rewiring" of energy metabolism (**Fig. 2**).[136] As first observed by Otto Warburg in the 1920s, cancer cells, even in well-oxygenated conditions, reprogram their glucose metabolism to preferentially use glycolysis ('aerobic glycolysis') over oxidative

phosphorylation for the glucose-dependent production of ATP, a phenomenon termed the "Warburg effect" (**Fig. 2**).[63] Despite being an energetically less efficient process, glycolysis is favored as it generates metabolic intermediates required for tumor growth through the oxidative and non-oxidative arm of the pentose phosphate pathway. This process is supported by the tendency of cancer cells to upregulate glucose transporters like GLUT1 that help increase cytoplasmic glucose levels.[63] Moreover, some cancer cells have also been reported to accumulate mutations in enzymes related to the TCA cycle such as fumarase and succinate dehydrogenase, thereby causing a cytoplasmic increase in levels of their respective substrates.[136] In addition to increased glycolysis, metabolic reprogramming involves increased fatty acid synthesis (*de novo* lipogenesis)[137] to enlarge the lipids pool for enhanced membrane biogenesis, and increased dependence on glutamine metabolism to increase the pool of amino acid precursors and feed the TCA cycle.[138] The metabolic reprogramming in cancer cells is mostly driven by oncogenic mutations altering key signaling pathways supporting proliferation and anabolism, such as those reliant on the PI3K–Akt–mTOR signal, c-Myc, and H-Ras, and by pathways driven by nutrient and oxygen deprivation (mainly coordinated by AMPK, HIF1, p53, and autophagy).[139] Given that translational control by the PERK–eIF2α-P/ATF4 pathway of the UPR (the integrated stress response or ISR) is required to support tumor growth under hypoxia[44] and that the same pathway can also promote anabolism through the upregulation of selected amino acid transporters and aminoacyl-tRNA synthetases through ATF4-mediated transcription,[140] the link between cancer cell metabolic reprogramming and chronic ER stress appears increasingly tight.[141]

Unfortunately, little research has been performed on the direct connection between therapy-induced ER stress and cancer cell energetics, making it hard to theorize how ER stressors might target this hallmark of cancer.

Some of the available evidence suggests that tunicamycin (**Table 1**) can reduce cell surface GLUT1 levels, thereby affecting glucose uptake and lactate production in embryonic fibroblasts.[136] Moreover, administration of tunicamycin to pregnant mice causes a decrease in the mRNA levels of *GLUT1* in the placenta.[142] Although these observations are promising, unfortunately they have not been confirmed in the context of cancerous or neoplastic cells thereby limiting their implications. In this context, some recent studies have opened the door for future investigations and therapeutic opportunities (**Fig. 3**).

O-linked b-N-acetylglucosamine (O-GlcNAc) protein modification, a signal that is elevated in cancer cells, has recently been shown to drive glycolysis in cancer cells through HIF-1/GLUT-1–mediated mechanisms. Interestingly, O-GlcNAc inhibition induced cancer cell death by activation of ER stress and CHOP-mediated apoptosis, which was rescued by overexpression of HIF-1.[143] This suggests that potentiating the induction of ER stress in conjunction with inhibitors of O-GlcNAcylation may be a valuable therapeutic strategy in glycolytic cancer cells.

Furthermore, activation of the UPR by thapsigargin or tunicamycin combined with glutamine deficiency (conditions triggering the PERK-eIF2α-ATF4 and GCN2-eIF2α-ATF4 signaling

pathways respectively) in cancer cells has been shown to cooperate in increasing the levels of mitochondrial phosphoenolpyruvate carboxykinase (PEPCK-M), an enzyme that regulates TCA cycle dynamics by catalyzing the conversion of oxaloacetate to phosphoenolpyruvate and whose expression is frequently found to be elevated in different tumors.[144] Reducing PEPCK-M levels blunted MCF7 mammary carcinoma cell growth *in vitro* and increased cell death, especially under ER stress conditions.

These reports suggest that the sensitivity of cancer cells to therapeutic ER stressors may be increased by concomitant inhibition of key targets of the metabolic stress pathways that are altered in cancer cells (**Fig. 3**).

Targeting Protumorigenic Inflammation and Resistance to Antitumor Immunity

A protumorigenic inflammatory microenvironment sustained by various tumor-associated immune cells has rapidly emerged as an important hallmark of cancer and tumors (**Fig. 2**).[63] Chronic inflammation has been shown to assist tumor progression through various mechanisms; for example, the production of tumor-promoting cytokines such as IL-11, IL-1β, IL-6, IL-23, and TNF (under the transcriptional control of factors like NF-kB and AP-1) by cancer cells themselves or by tumor-associated immune cells can support tumor progression because tumor cells express the respective cognate receptors for these cytokines and can utilize these cytokines as growth factors, thereby sustaining proliferative signaling.[29,145,146] Moreover tumor-associated inflammation can also inhibit cancer cell death and facilitate angiogenesis (**Fig. 2**).[145,146]

Tumor-associated ER stress under basal conditions has been shown to support tumorigenic inflammation.[29] This was recently substantiated for hepatocellular carcinoma, in which ER stress-based TNF secretion was found to play a protumorigenic role.[147] For a model schematically explaining this scenario, please refer to various recent reviews.[25,29,40,103,136] In line with this notion, certain ER stress-inducing therapeutics (e.g., tunicamycin and thapsigargin) either support or have the ability to facilitate protumorigenic inflammation.[148] Moreover, oxaliplatin, UV irradiation, and radiotherapy can assist in increasing the activity of NF-kB and AP-1 in cancer cells or tumors, thus driving protumorigenic inflammation (**Fig. 3**).[103] On the other hand, certain ER stress-inducing therapies have the ability to impede or reduce tumor-promoting inflammation; for example bortezomib can inhibit cancer cell-associated protumorigenic NF-kB–based inflammation (**Fig. 3**).[40,103] Similarly, Hyp-PDT and shikonin can inhibit or suppress both NF-kB and AP-1 activity in cancer cells[40,103] and Hyp-PDT can also reduce the pre-existing production of IL-6, an important tumor-promoting cytokine (**Fig. 3**).[54]

Tumor-associated inflammation also suppresses or evades antitumor immunity and antitumor immunosurveillance (extensively reviewed in[145,149,150]). This eventually translates into evasion from, or suppression of, antimetastasis immunosurveillance and antimetastasis immunity, a crucial step responsible for the

majority of cases of clinical relapse. However, it has recently emerged that certain assorted therapeutics are capable of inducing a form of cell death that is immunogenic in nature; i.e., a cancer cell death modality that helps "communicate" the antigenic make up of cancer cells to the adaptive immune system thereby priming antitumor and antimetastasis immune responses and immune memory. This cell death modality has been termed immunogenic cell death (ICD) (**Fig. 2**).

ICD is induced by only those anticancer therapies that are capable of inducing both ROS production and ER stress, either sequentially or in parallel, such that oxidative ER stress is mandatory (**Fig. 3**). This is because oxidative ER stress has been shown to be necessary for the emission of immunogenic danger signals that assist in immune cell attraction (e.g., secreted ATP, HMGB1, HSP90, HSP70, or uric acid), antigen uptake (e.g., ecto-CRT, ecto-HSP90, or ecto-HSP70), antigen processing (e.g., released HMGB1 or HSP70), and immune cell polarization favoring anticancer immunity (e.g., secreted ATP, ecto-CRT, or ecto-HSP90).[51,55,56,123,151] In general, a complex interplay between ER stress, oxidative stress, and autophagy has been found to shape ICD and danger signaling.[56,57,123,152,153] ICD inducers stimulate immunogenic fully mature DCs that "prime" anticancer CD4^{+} T cells that secrete IFN-γ and/or IL17A and cancer killing CD8^{+} T cells that secrete IFN-γ. Of note, T cell-based IFN-γ and TNF production has been found to induce senescence in cancer cells.[154] Interestingly, several primary and secondary ER stressors have been found to induce ICD,[103] including various oncolytic viruses such as CVB3 and Newcastle disease virus (Koks et al. unpublished results), Hyp-PDT, 7A7, anthracyclines, mitoxantrone, bleomycin, bortezomib, cardiac glycosides, cyclophosphamide, HDAC inhibitors, HHP, oxaliplatin, radiotherapy, UV irradiation, and shikonin (**Table 1**).[53,103,155] Last, but not least, a number of studies have shown that brefeldin A (**Table 1**) might actually end up hampering ICD by inhibiting danger signaling whereas thapsigargin, MG132, and tunicamycin may encourage tolerogenic immunoevasive cell death (**Fig. 3**).[51,56,57]

Thus, a large number of assorted ER stress-inducing therapeutics have been found to induce ICD, a cell death routine that hampers cancer's resistance to antitumor immunity; however, it is crucial to give precedence to the ICD-inducers that also target and suppress tumor-associated inflammation.

Conclusion

Therapy-induced ER stress does not seem to play a straightforward role in targeting the different hallmarks of cancer. Although certain therapeutics inhibit these hallmarks, others might support them; therefore, when strategizing to target cancer hallmarks it is very important to select the proper therapeutics for ER stress induction taking into account these context-dependent effects. Considering the ability of cancer cells to show microevolutionary capabilities to resist therapeutic intervention, the design of "smart" combinatorial therapies that have a chance of simultaneously targeting almost all the hallmarks of cancer seems to be the most practicable and successful therapeutic approach. From the above discussion and analysis it seems that the development of lethal ER stress-inducing agents that display an intrinsic ability to target multiple hallmarks of cancer is not only an auspicable, but also an attainable, prospect. However, to overcome certain omnipresent hallmarks of cancers (e.g., self-sustained growth, deregulation of intrinsic apoptosis machinery, metabolic reprogramming; see also **Table 1** and **Fig. 3**), ER stressors that target multiple cancer hallmarks with good *in vivo/in situ* anticancer activity might strongly benefit from concurrent or sequential combination with inhibitors of specific cancer cell-intrinsic defects and/or immunotherapy strategies capable of overcoming cancer cell extrinsic barriers to tumor eradication or potentiate induction of cancer cell immunogenicity. Last, but not least, as far as therapeutics inducing ER stress as a secondary effect (**Table 1**) are concerned, few data exist on how secondary ER stress targets the typical cancer hallmarks and for which therapeutics. Although significant information has started to emerge for the immunogenicity-augmenting effects of various therapeutics (e.g., anthracyclines, high hydrostatic pressure, and radiotherapy), this needs to be extended to other hallmarks of cancer. The future challenge in cancer therapy will be to understand when and how modulation of the UPR or ER stress is required (e.g., inhibition of the tumor-promoting UPR during carcinogenesis or potentiation of ER stress-induced immunogenic cell death in advanced cancers). Moreover, the clinical application of therapeutic ER stress-inducers and characterizing the signatures of ER stress that have prognostic impact in clinical settings would be 2 very important areas of future research.

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