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Immunogenic cell stress and death in the treatment of cancer

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Abbreviations

APC, antigen presenting cell; DAMP, damage associated molecular pattern; DC, dendritic cells; ICD, immunogenic cell death; ICI, immune checkpoint inhibitor

Abstract

The successful treatment of oncological malignancies which results in long-term disease control or the complete eradication of cancerous cells necessitates the onset of adaptive immune responses targeting tumor-specific antigens. Such desirable anticancer immunity can be triggered via the induction of immunogenic cell death (ICD) of cancer cells, thus converting malignant cells into an *in situ* vaccine that elicits T cell mediated adaptive immune responses and establishes durable immunological memory. The exploration of ICD for cancer treatment has been subject to extensive research. However, functional heterogeneity among ICD activating therapies in many cases requires specific co-medications to achieve full-blown efficacy. Here, we described the hallmarks of ICD and classify ICD activators into three distinct functional categories namely, according to their mode of action: (i) ICD inducers, which increase the immunogenicity of malignant cells, (ii) ICD sensitizers, which prime cellular circuitries for ICD induction by conventional cytotoxic agents, and (iii) ICD enhancers, which improve the perception of ICD signals by antigen presenting dendritic cells. Altogether, ICD induction, sensitization and enhancement offer the possibility to convert well-established conventional anticancer therapies into immunotherapeutic approaches that activate T cell-mediated anticancer immunity.

Main text

Cancer has long been regarded as a cell intrinsic disease, that arises solely due to the occurrence and accumulation of genomic mutations allowing malignant cells to thrive. Nevertheless, it has been a subject of longstanding hypothesis (but only more recently it has been demonstrated) that oncogenesis and malignant progression are in fact multistep processes. Today it is known that such multistep processes also encompass the evasion of malignant cells from immunosurveillance mechanisms, thus avoiding the immune destruction of nascent tumors and allowing cancer growth (1). Adaptive anticancer immunity is orchestrated by the coordinated action of dendritic cells, that capture and present tumor antigen, with a dynamic pool of antigen-specific T effector cells that can expand and mediate cytotoxic effects on malignant cells. Cancers have developed mechanisms to avoid immune destruction such as the attraction of immunosuppressive cells such as regulatory T cells (Treg) and myeloid derived suppressor cells (MDSC) in the tumor microenvironment that can subvert anticancer immunity. As a consequence, the re-establishment of anticancer immunosurveillance via the stimulation of adaptive immune responses has become a hot spot of scientific research in both academia and the pharmaceutical industry. At this moment, clinically available immunotherapeutic approaches for the routine management of cancer mainly focus on the (re)-activation of T cell mediated cancer cell killing by means of monoclonal antibodies. Such antibodies are targeting immune checkpoints including cytotoxic T-lymphocyte associated protein 4 (CTLA4) or they inhibit the interaction between programmed cell death 1 (PDCD1) and its ligand CD274, better known as the PD-1/PD-L1 axis. Immune checkpoint inhibition (ICI) has shown remarkable effects in the adjuvant and neoadjuvant treatment of malignant indications, above all in highly immunogenic melanoma (2-4). Nevertheless, the success of ICI strongly depends on the abundance of immune checkpoint molecules, the general immune tonus of the patient, as well as the mutational burden of the malignancy. Additional therapeutic strategies to overcome such

shortcomings and means to sensitize malignancies to subsequent immune checkpoint blockade are still urgently awaited.

Immunogenic cell stress and cell death signaling.

As opposed to the immunologically silent clearance of apoptotic cells by efferocytosis immunogenic cell death (ICD) can induce desired adaptive anticancer immune responses that can prime tumors for subsequent immunotherapies such as ICI (5-8). The induction of ICD can be triggered by distinct treatments including certain systemic chemotherapies, targeted agents, oncolytic viruses and physicochemical treatments such as photodynamic therapy and radiation oncology (9-14). Irrespective of their origin or their specific mode of action, all *bona fide* ICD inducers are endowed with the ability to induce anticancer vaccinating effects when tested in immunocompetent animal models (15).

In the course of ICD stressed and dying cells release damage-associated molecular pattern (DAMP) molecules, which in their correct sequence and spatial appearance act as adjuvants that facilitate the onset of adaptive anticancer immune responses (16, 17). Mechanistically, ICD-emitted DAMP molecules can be detected by innate pattern recognition receptors (PRRs) expressed by antigen presenting cells (APCs) and in turn induce APC activation and maturation. The array of ICD-specific DAMPs includes adenosine triphosphate (ATP) and annexin A1 (ANXA1), which upon release from cancer cells can ligate purinergic receptors (such as purinergic receptor P2X 7 (P2RX7)) and formyl peptide receptor 1 (FPR1) expressed on professional antigen presenting dendritic cells (DCs) thus facilitating the chemoattraction and tumor homing of DCs, respectively (18-20). ICD-specific DAMPs also encompass surface exposed calreticulin (CALR) and heat shock proteins (HSPs) HSP70 and HSP90, which interact with LDL receptor related protein 1 (LRP1) and serve as a *de novo* uptake signals thus allowing the DC-mediated phagocytosis of (parts of the) cancer cell(s) (21-24). Furthermore, high mobility group box 1 (HMGB1), that is released from dying cancer cells, can interact with Toll-

like receptor 4 (TLR4) and activate MYD88 innate immune signal transduction adaptor (MYD88)-mediated antigen processing and DC maturation (25, 26). Moreover, the TLR3-mediated stimulation of autocrine (or paracrine) type-1 interferon (IFN) response circuitries in DCs results in the release of C-X-C motif chemokine ligand 10 (CXCL10) which in turn stimulates the recruitment of T lymphocytes via C-X-C motif chemokine receptor 3 (CXCR3) (27-30). Besides, tumor cell-derived double-stranded genomic DNA as well as mitochondrial DNA can elicit the cyclic GMP-AMP synthase (CGAS)/stimulator of interferon response CGAMP interactor 1 (STING1) pathway in both cancer cells and DCs, thus further stimulating antigen cross-priming (31). Along similar lines, the release of transcription factor A, mitochondrial (TFAM) from apoptotic mitochondria and its binding to advanced glycosylation end-product specific receptor (AGER) expressed on DC contributes to some instances of immunogenic cell death (32).

Mechanistically the emission of immunostimulatory (as opposed to inhibitory) DAMPs strongly depends on several underlying stress responses including, but probably not entirely limited to, the induction of autophagy which facilitates the availability and lysosomal secretion of ATP, the onset of ER stress, that drives the exposure of HSPs and CALR, as well the final execution of cell death which altogether allow the active emission preceding a passive exodus of DAMP molecules during the course of ICD (16, 33-39). Moreover, ICD associated cellular stress can lead to the generation of non-mutational tumor neoantigens resulting from epigenetic shifts in gene expression, alternative splicing, the translation of unconventional coding sequences as well as the post-translational modification of nascent proteins (40). In sum, ICD associated cellular stress and death increases both the adjuvanticity and antigenicity of malignant cells, thus facilitating antigen-specific local immune responses along with systemic effects that can target the primary tumor as well as distant metastases, respectively. Of note, in recent years the concept of ICD, initially reported in cells undergoing apoptotic cell death, has

been extended to additional cell death modalities including necroptosis, pyroptosis, and ferroptosis, as well as to cellular senescence (41-51).

On a molecular level ICD associated cellular stress is integrated and orchestrated by the master regulator eukaryotic translation initiation factor 2 subunit 1 (EIF2S1, better known as eIF2 α) that acts as an early responder to disturbances in cellular homeostasis including nutrient deficiency, viral infection, the accumulation of unfolded proteins as well as heme deprivation, which can be detected by the upstream signaling kinases EIF2A kinase 1 (EIF2AK1 better known as GCN2), EIF2AK2 (better known as PKR), EIF2AK3 (better known as PERK) and EIF2AK4 (better known as HRK), respectively (52). Of note the stress kinase PERK exhibits an overlapping functional embedment in the conserved signaling networks of both the integrated stress response (ISR) and the unfolded protein response (UPR), placing it into a central position for the control of cellular stress responses as they have been described ICD induced by cytotoxic agents (39, 53).

Thus, phosphorylation of eIF2 α at serine residue 51 ignites a multitude of adaptational cellular measures, including a halt in general Cap-dependent translation, while concomitantly initiating the preferential translation of ISR-specific mRNAs characterized by a 5' untranslated region (5' UTR) open reading frame (uORF), which shifts the global transcriptional program resulting in changes in the (surface) proteome, thus impacting the antigenic makeup of cancer cells (54). Of note, the onset of the UPR also leads to an increased expression of endoplasmic reticulum (ER) chaperones including HSP70, HSP90, and CALR, all serving as uptake signals when exposed on the cell surface during ICD (55). In line with this notion, cancer cells expressing the non-phosphorylatable eIF2 α mutant (eIF2 α ^{S51A}) that are treated with the prototypic ICD inducer mitoxantrone fail to expose CALR on their surface and consequently cease to trigger anticancer immunity *in vivo* (39, 53, 56, 57). Furthermore, in conditions where adaptive mechanisms for cellular recovery from transient stress fail and stress is enduring or remains unresolved, the expression of pro-apoptotic proteins ultimately triggers cell death (58, 59).

Moreover, eIF2 α phosphorylation initiates autophagy in conditions of starvation and virus infection, as well as in response to a variety of distinct pharmacological agents (60, 61). Besides its function as the central signaling hub for ICD, eIF2 α might be functionally coupled to additional intracellular stress responses such as the inhibition of RNA synthesis, which has recently been described for certain immunogenic chemotherapies (62, 63). In malignant cells from lung cancer patients as well as from patients suffering from acute myeloid leukemia (AML), the level of eIF2 α phosphorylation correlates with CALR surface exposure and translates into prognostically favorable immune response (64). Altogether, this underlines the central function of eIF2 α in most (but not all) courses of ICD acting at crossroads of autophagy, ER stress, and cell death, thus impacting both the adjuvanticity and the antigenicity of the treatment (**Fig. 1**)(65, 66).

Discovery of immunogenic anticancer agents

In view of the therapeutic significance of ICD, large efforts have been undertaken in recent years for the discovery (or repurposing) of pharmacological agents that are capable of inducing anticancer immunity. In a seminal work published in 2005 Casares and coworkers showed that the anticancer efficacy of doxorubicin is blunted in immunodeficient as compared to immunocompetent mouse models (67). Indeed, among a panel of cytotoxic agents, the anthracyclines mitoxantrone, doxorubicin, and idarubicin stand out for their capacity to act as ICD inducers *in vivo*, correlating with their capacity to elicit the surface exposure of CALR on cancer cells. Knockdown of CALR blunted the immunogenicity of anthracycline-treated cells in a model of prophylactic immunization against malignant rechallenge in mice (22). Since then, additional classes of anticancer agent have been described to induce ICD, as exemplified by taxanes and some platinum-based compounds including oxaliplatin and more recently the platinum-pyrophosphate conjugate PT-112 (68-70). The proteasome inhibitor bortezomib was shown to induce the exposure of HSP90 on cancer cells, thus enhancing DC-mediate anticancer immunity in models of multiple myeloma, lymphoma, and breast

cancer (24), but later studies explained that bortezomib induces ICD by CALR exposure as well (71, 72). Furthermore, *in vitro* high-throughput screening (HTS) campaigns employing transgene-encoded fluorescent biosensors as surrogate markers for systematic ICD fingerprinting or for monitoring cell stress parameters have been used for the phenotypic detection of ICD hallmarks (73, 74). These approaches, together with hypothesis-driven research, yielded several novel ICD inducers including (but not limited to) the cardiac glycosides digoxin and digitoxin that induced the hallmarks of ICD *in vitro* and rendered cancer cells immunogenic in murine models of prophylactic anticancer vaccination (73). More recently oleandrin, yet another cardiac glycoside, was found, to induce ICD via the PERK-eIF2 α axis in breast cancer (75). Unbiased screening of the National Cancer Institute (NCI) mechanistic diversity led to the discovery of the experimental anticancer agent septacidine as *bona fide* ICD inducer that conferred prophylactic anticancer vaccination efficacy and reduced tumor growth in immunocompetent animals yet failed to do so in nude mice (76). Moreover, immunization with a whole-cell vaccine based on the chemotherapeutic agent arsenic trioxide (ATO) restrained the growth of syngeneic tumors. Underlying death routines included traits of autophagy, apoptosis, ferroptosis, necroptosis, and pyroptosis (42). Oncolysis through either the infection with oncolytic viruses or the local application of oncolytic compounds LTX-315, LTX-401, DTT-205, DTT-304, and MPM-1 have been shown to trigger the hallmarks of ICD, to induce abscopal effects (that is anticancer effects distant from the treated lesion) in rodent models and to generate immunological memory in cured animals (77-93).

Furthermore, the antibody-drug conjugate (ADC) belantamab mafodotin that targets the B-cell maturation antigen (BCMA) with its conjugated cytotoxic payload maleimidocaproyl monomethyl auristatin F (mcMMAF) triggered the hallmarks of ICD and induced antitumor immune responses *in vivo* (94, 95). Of note, belantamab mafodotin was approved for the treatment of refractory multiple myeloma. Similarly, the type II anti-CD20 antibody GA101 (obinutuzumab) that was glycoengineered to increase antibody-dependent cellular cytotoxicity (ADCC) was shown to induce

non-apoptotic cell death in malignant B cells characterized by the release of ICD-associated DAMPs, enhanced dendritic cell maturation and ultimately T-cell activation (96).

The synthetic TLR7 ligand imiquimod was shown to induce ICD in prophylactic and therapeutic settings of melanoma in murine models (97). Furthermore, a synthetically engineered polypeptide-based K⁺ ionophore was reported to trigger the release of ICD-associated DAMPs and suppress tumor proliferation *in vitro* and *in vivo* (98). ICD was also shown to be induced by certain physical interventions including radioimmunotherapy with ionizing gamma or UV-C irradiation as well as photodynamic therapies (PDT) based on redaporfin, hypericin, porphyrazine, indocyanine green loaded liposomes with pardaxin peptide (Par-ICG-Lipo) and aluminum-phthalocyanine nanoemulsion that are activated with conventional or near-infrared (NIR) irradiation (13, 56, 99-110). Additional physical therapies that have been described to elicit hallmarks of ICD are pulse waveform electroporation-based therapies and magnetic hyperthermia (111, 112). The local application of gaseous nitric oxide (NO) induced ICD in distinct tumor models in mice and potentiated subsequent ICI (113). Spautin-1, an inhibitor of ubiquitin-specific peptidases, was shown to induce ICD *in vitro* and *in vivo* depending on the release of TFAM by cancer cells and the interaction of TFAM with AGER expressed on DC (32). Recently, it has been shown that certain local anesthetics that are used for oncological surgery can elicit immune-dependent anticancer effects, thus impacting metastasis-free survival (114).

Rather unconventional agents that have been shown to induce ICD include ethanolic extracts of the fungus *cordyceps militaris* that have been shown to cause ICD-like cell death in breast cancer cells (115), as well as capsaicin, the pungent alkaloid of red pepper, that may induce ICD in primary effusion lymphoma (PEL) cells (116). Moreover, a multitude of novel nanomedicine procedures have been employed to generate a large number of novel galenic formulations for ICD induction. In many cases, such formulation consists of a carrier molecule loaded with cytotoxic and immunostimulatory compounds that are released into the tumor microenvironment (78-81, 117). Such approaches include

the hydrogel-mediated localized delivery of docetaxel (DTX) and carboplatin (CPT) (DTX-CPT-Gel therapy), as well as the use of pegylated arginine deiminase (ADI-PEG 20) that induces traits of ICD *in vitro* and increases phagocytosis by bone marrow-derived dendritic cells (BMDCs) (118, 119). Moreover, ultrasound-directed nanosystems that can be used for the targeted release of payloads have been developed to trigger anticancer immunity by ICD (78, 80, 81, 120-123). In sum, an ever-increasing number of anticancer regimens are developed based on their capacity to induce ICD (**Tab.1**).

Immunogenic cell death sensitizers and enhancers

The transcription inhibitors lurbinectedin and dactinomycin fail to induce full-blown ICD when used as monotherapies, but may sensitize cells to ICD induction and subsequent immune checkpoint blockade (63, 124). Similarly, autophagy induced by short-term fasting or treatment with caloric restriction mimetics (such as aspirin, 3,4-dimethoxychalcone, hydroxycitrate and spermidine) have been shown to sensitize cells to ICD induction by chemoimmunotherapy (97, 125-128). Other autophagy-inducing ICD sensitizers include isobacachalcone, which was found in an unbiased screen for chemoimmunotherapy co-medications (129) and dietary piceatannol that enhances the efficacy of oxaliplatin-based chemotherapy (130). Similarly, thiostrepton, a natural cyclic oligopeptide antibiotic derived from *streptomyces* spp, sensitized cells to oxaliplatin-mediated immunogenic chemotherapy by promoting autophagy (131, 132).

Furthermore, the phytochemical shikonin was shown to induce the emission of DAMPs including CALR and HSP70 by cancer cells, thus enhancing the immunogenicity of tumor vaccines (133). Certain targeted agents such as the ALK receptor tyrosine kinase-specific inhibitors ceritinib and crizotinib, both failed to induce full-blown ICD, but potently rendered the non-ICD cytotoxic agent cisplatin immunogenic and maximized the response to subsequent immune checkpoint blockade (11, 134). Moreover, certain engineered nano-medicines such as manganese zinc sulfide nanoparticles augmented the efficacy of immunotherapy against metastatic melanoma (135). Altogether, these

findings underline the potential of ICD sensitizers to potentiate the efficacy of clinically established non-immunogenic regimens as well as to further boost the response to anticancer immunotherapies.

More recently, we identified yet another class of agents that contrary to ICD inducers and ICD sensitizers, which act on malignant cells to stimulate anticancer immunity, target antigen presenting DCs. Such “ICD enhancers” specifically target DC-relevant immune checkpoints, thus increasing antigen cross presentation (136). In an unbiased screening campaign employing immortalized DC precursors that can be differentiated into immature DCs, we found ikarugamycin, an antibiotic isolated from *streptomyces* spp to be particularly potent in stimulating the presentation of ovalbumin (OVA) antigen to B3Z T cell hybridoma (137-139). Mechanistically, ikarugamycin inhibits hexokinase and upregulates DC activation markers including CD40, CD80, and CD86, resulting in the enhanced capacity of DCs to present antigen to T cells *in vitro*. *In vivo*, ikarugamycin synergized with oxaliplatin-based chemotherapy due to augmented T cell-mediated anticancer immune responses. (138). The same screen unveiled the capacity of astemizole to act as an unspecific T cell stimulator, which can also enhance ICD-mediated immunity. Moreover, CRISPR-mediated gene editing enabled us to screen the entire genome for gain-of-function phenotypes that increase DC-mediated cross presentation. In this campaign, we identified BCL2, the knockout of which increased DC maturation and their cross-presentation capacity. It can be speculated that BCL2 constitutes a mitochondrial immune checkpoint that also operates in immune cells (140). Accordingly, the BCL2 inhibitors navitoclax and venetoclax stimulated the perception of ICD by DC and optimized the response to ICI (141)

Concluding remarks

Here we summarized recent discoveries in the field of ICD and outlined strategies for the identification of ICD inducers, sensitizers, and enhancers. ICD sensitizers and inducers act on cancer cells to stimulate adaptive anticancer immunity, induce cellular stress and thus prime malignant cells

for subsequent (chemo)immunotherapy. While ICD sensitizers have little or no anticancer activity on their own, they can be combined with ICD inducers (which show single-agent activity) to obtain improved anticancer effects. ICD enhancers improve anticancer immunosurveillance by stimulating the molecular crosstalk between cancer cells and DCs (**Fig. 2**).

ICD inducers have the capacity to increase both the immunogenicity and adjuvanticity of cancer cells, thus converting them into an *in situ* vaccine that elicits adaptive anticancer immunity, culminating with cognate T cell responses. Chemotherapeutic and radiotherapeutic induction of ICD is often afflicted with severe side effects. For example, the prototypic ICD inducers mitoxantrone and doxorubicin cause severe cardiotoxicity, whereas physical interventions such as ionizing irradiation or PDT damage adjacent healthy tissues, thus limiting the therapeutic window (142-144). Moreover, the efficacy of ICD inducers can be limited by drug resistance caused by the heterogeneity of tumors and the genetic plasticity of malignant cells (136).

ICD sensitizers are agents that stimulate cellular stress responses that facilitate the emission of ICD-associated DAMPs and that impact the antigenic makeup of malignant cells, essentially preparing them for full-blown ICD induction by co-treatment with low-dose ICD inducers. The use of ICD sensitizers as monotherapy against cancer has little to no effect. However, ICD sensitizers potentiate the effects of ICD inducers, potentially reducing the dose required for achieving therapeutic effects and hence diminishing side effects.

In contrast to ICD inducers and sensitizers, ICD enhancers directly act on antigen presenting DCs, hence allowing to mediate broad immunotherapeutic effects against an array of malignancies independent of the characteristic limitation of each cancer type. Thus, ICD enhancers may be added to the arsenal of therapeutic options that stimulate anticancer immune responses. Nevertheless, on theoretical grounds, overstimulation of DCs, especially in combination with ICIs, bears the risk of fatal autoimmunity (145, 146), calling for prudent combination strategies.

Clinical validation of the utility of ICD inducers has been obtained in retrospective studies, as well as in prospective clinical trials (64, 73, 147-152). On a hypothetical basis, low-dose combinations of ICD inducers with ICD sensitizers might reduce adverse side effects, while stimulating optimal and specific anticancer immunity. Immune checkpoint blockade could further boost such regimens, especially in the neoadjuvant setting. At this point, results from ongoing clinical trials combining ICD inducers with immune checkpoint blockade and future clinical studies developing the concept of ICD enhancers are urgently awaited.

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Conflicts of interest

O.K is a scientific co-founder of Samsara Therapeutics. Outside of this work, GK has been holding research contracts with Daiichi Sankyo, Eleor, Kaleido, Lytix Pharma, PharmaMar, Osasuna Therapeutics, Samsara Therapeutics, Sanofi, and Vascage. GK is on the Board of Directors of the Bristol Myers Squibb Foundation France. GK is a scientific co-founder of everImmune, Osasuna Therapeutics, Samsara Therapeutics and Therafast Bio. GK is in the scientific advisory boards of Hevolution, Institut Servier and Longevity Vision Funds. GK is the inventor of patents covering therapeutic targeting of aging, cancer, cystic fibrosis and metabolic disorders. GK's wife, Laurence Zitvogel, has held research contracts with Glaxo Smyth Kline, Incyte, Lytix, Kaleido, Innovate Pharma, Daiichi Sankyo, Pilege, Merus, Transgene, 9 m, Tusk and Roche, was on the on the Board of Directors of Transgene, is a cofounder of everImmune, and holds patents covering the treatment of cancer and the therapeutic manipulation of the microbiota. GK's brother, Romano Kroemer, was an employee of Sanofi and now consults for Boehringer-Ingelheim.

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Figure legend

Figure 1. Crosstalk between the integrated stress response (ISR) and immunogenic cell death (ICD). The phosphorylation of eukaryotic translation initiation factor 2 subunit 1 (EIF2S1, better known as eIF2 α) acts as a key regulatory event integrating cellular stress signals stemming from EIF2A kinases that detect disturbances of cellular homeostasis. In response to the treatment with ICD inducers EIF2AK3 (better known as PERK) that act at the overlap between the ISR and the unfolded protein response (UPR) drives the phosphorylation of eIF2 α and thus orchestrates the downstream expression of the endoplasmic reticulum (ER) chaperones CALR. Moreover, eIF2 α phosphorylation plays a pivotal role in the initiation of autophagy and is functionally coupled to additional intracellular stress responses such as the inhibition of RNA synthesis and translation, all linked to the onset of ICD.

Figure 2 Induction of immunogenic cell stress and death induction and its integration by dendritic cells. Immunogenic cell stress encompasses autophagic and ER stress circuitries that facilitate the emission of damage-associated molecular pattern (DAMP) molecules and are orchestrated by the phosphorylation of (EIF2S1, better known as eIF2 α). The therapeutically beneficial induction of immunogenic cell stress in tumor cells can be achieved by a number of immunogenic cell death (ICD) sensitizing agents, which are endowed with the ability to boost the immunogenicity of the malignant cells. Despite a partial functional overlap ICD sensitizer can be advantageously combined with ICD inducers, that also act on cancer cells, to potentiating the therapeutic efficacy of the latter. ICD enhancers target antigen presenting dendritic cells and augment their ability to present antigens and to stimulate adaptive anticancer immune responses and the establishment of T cell memory.

Table 1 Immunogenic cell stress and cell death inducers

| Agent | Stress | DAMPs | Cytokines | Immune infiltrate | ICI combination | Clinical use | Ref. |
|--|-----------|--------------------------------|---|---|--------------------------------------|---|--------------------|
| ALK TKIs (including crizotinib and ceritinib) | ER stress | CALR, ATP, HMGB1 | ↑Type I IFNs, IL-17 | ↑DCs, CD8+ CTLs, NKT cells; ↓Treg cells | Anti-PD-1, anti-PD-L1 | Treatment of non-small cell lung carcinoma | (10, 12) |
| Amphotericin B | NA | CALR, HMGB1, ATP | ↑IL-12p70, IFN-γ, | ↑DCs (CD80, CD86, HLA-DR) | Anti-PD-1 | Treatment of mycotic infections | (153) |
| Anthracyclines (including doxorubicin, daunorubicin, epirubicin and idarubicin.) | ROS | CALR, ATP, HSP70, HMGB1, ANXA1 | ↑IL-1β, IL-6, IL-12, IL-17, CXCL10, type I IFNs, IFNγ | ↑DCs, CD8+ CTLs, γδ TH17 cells; ↓Treg cells, MDSCs | Anti-PD-1, anti-CTLA4 | Treatment of leukemias and Hodgkin's lymphoma. Treatment of Cancers of the bladder, breast, stomach, lung, ovaries, thyroid, soft tissue sarcoma, multiple myeloma, and others. | (67, 154) |
| Arginine deiminase | NA | CALR, ATP, HMGB1 | NA | NA | NA | NA | (118) |
| Arsenic trioxide (ATO) based whole-cell vaccine | ROS | CALR, ATP, HMGB1 | IFNβ1 | NA | Anti-PD-1 | Treatment of acute promyelocytic leukemia | (42, 155) |
| Astemizole (plus oxaliplatin) | NA | ↑IFN-γ, IL-2 | ↑CD4+ and CD8+ T cells, DCs | ↑CD8+/Foxp3+, CTL/Treg, F4/80+CD-11c+MHC-II+ | Anti-PD-1 | second-generation antihistamine drug | (138) |
| ASTX660 | NA | CALR, HSP70, HMGB1 | NA | ↑T cell, NK cell and DCs | NA | NA | (156) |
| Auranofin (thioredoxin reductase 1 (TrxR) inhibitor) | ROS | CALR, ATP, HMGB1 | NA | ↑CD86+/MHC-II+ DC | NA | Treatment of rheumatoid arthritis | (157, 158) |
| AXL kinase inhibition (bemcentinib or siRNA) | NA | CALR, ATP, HMGB1 | NA | ↑MHC-I+ cells | NA | Undergoing six Phase II trials in various solid and hematological tumors | (159) |
| Belantamab mafodotin ADC (GSK2857916) | ER stress | CALR, ATP, HMGB1, HSP70, HSP90 | IL8 | ↑DCs, CD8+ CTLs, CD4+ T cells; NK cells, ↓Treg cells | Agonistic OX86 (mouse OX40) antibody | Treatment of relapsed/refractory multiple myeloma | (95, 160) |
| Bortezomib | | CALR, HSP70, HSP90 | ↑IFN-γ; type-I interferons | ↑DCs, CD8+ CTLs | Anti-PD-1 | Treatment of multiple myeloma and mantle cell lymphoma; treatment of Relapsed or Refractory Multiple Myeloma (AMBUSH Trial, phase 2, NCT05514990) | (24, 71, 72) |
| Brucine | NA | CALR, HMGB1 | NA | NA | NA | Treatment of arthritis and traumatic pain | (161) |
| Caloric restriction mimetics | NA | ATP | NA | ↑CD8+ CTLs; ↓Tregs | NA | NA | (125, 128, 129) |
| Capsaicin | NA | CALR, HSP70, HSP90, ATP | ↑IFN-γ | ↑CD86, CD80 and CD83 DCs | NA | NA | (116, 162, 163) |
| Cardiac glycosides (including digitoxin, digoxin and oleandrin) | ER stress | CALR, ATP, HMGB1, HSP70 /90 | ↑IL-2, IFNγ; ↓IL-10 (co-cultured with DCs) | ↑CD80, CD86 DCs, CD8+ CTLs, | NA | Treatment of various diseases including congestive heart failure, abscesses, asthma and so on. | (73, 75, 164, 165) |
| CDK4/6 inhibition | NA | CALR | GzmB, IFN-γ | ↑CD3+ and CD8+ T cells, CD86 and MHCII CD11c+ DCs; ↓CD25+/FoxP3+ Treg | Anti-PD-1 | Treatment of breast cancer (including Ibrance, Kisqali, Verzenio) | (166) |

| | | | | | | | |
|--|-----------------------------|---------------------------------|---|---|-----------------------|---|------------|
| Chromomycin A5 | ER stress | CALR, ATP, HMGB1, ERp57 | ↑TNF-α | ↑DCs, CD4+ and CD8+ T lymphocytes | NA | NA | (167) |
| Dactinomycin | | CALR, ATP, HMGB1 | ↑Type I IFNs, IFN γ , IL-17 | ↑DCs, CD8+ CTLs, NK cells; ↓Treg cells | Anti-PD-1 | Treat a number of types of cancer; melanoma (NCT01323517) | (63) |
| Etoposide | NA | CALR, ATP, HMGB1, HSP70, HSP90, | NA | ↑DCs | NA | Treatment of testicular, prostate, bladder, stomach, and lung cancer | (168) |
| Gaseous nitric oxide (NO) | ER stress, ROS | CALR, ATP, HMGB1 | NA | ↑DCs, CD8+ T cells, memory T cells (TCM cells, CD3+ CD8+ CD62L+ CD44+) effector memory T cells (TEM cells, CD3+ CD8+ CD62L- CD44-), CD4+ T cells, TILs; ↓Treg cells | Anti-PD-1 | NA | (113) |
| Imiquimod | ER stress, oxidative stress | CALR, ATP, HMGB1 | NA | ↑CD8+ CTLs, TILs, (CD4+/IFN γ + and CD8+/IFN γ + effector T cells, CD4+/CD44+ and CD8+/CD44+ memory T cells) | NA | Treatment of genital warts, Bowens disease, squamous cell carcinoma, basal cell carcinoma, actinic keratosis | (97) |
| IR-780 | NA | CALR, ATP, HMGB1, HSP90 | ↑IFN- γ , Granzyme B, KLRG1, EOMES, Perforin, BLIMP-1, FOXO3, and CXCL10 | ↑CD80+, CD86+, MHCII+ DCs, CD8+ T cells, CD4+ T cells, CD69+ T cells, CD11c+ DCs, CD8+ CD44+ CD62L- T cells | NA | NA | (169) |
| R848-IVM (resiquimod (R848) plus ivermectin) | NA | HMGB1 | NA | NA | NA | Ivermectin treat of COVID-19 and parasitic diseases; R-848 is used to treat herpes simplex virus and cutaneous T cell lymphoma. | (170, 171) |
| Lactaptin (plus IDO inhibitor) | NA | CALR, ATP, HMGB1, HSP70 | NA | NA | NA | Indoximod is used for treatment of stage IIb to stage IV melanoma. | (172) |
| Liver X receptor (LXR) agonists | NA | CALR, ATP, HMGB1 | NA | NA | NA | NA | (173) |
| Certain local anesthetics | ER stress | CALR, ATP, HMGB1 | NA | ↑CD4+ T cells, CD8+ T cells, | Anti-PD-1 | Wide range of clinical applications | (114) |
| Lurbinectedin | NA | CALR, ATP, HMGB1 | ↑Type I interferon | NA | Anti-PD-1, anti-CTLA4 | Treatment of small cell lung cancer | (124) |
| Mifepristone | NA | CALR, HMGB1 | ↑IFN- γ , TNF, IL- | F4/80+ macrophages, CD3+CD49+ NK cells, CD8+ T cells; ↓Foxp3+ regulatory T (Treg) cell | Anti-PD-1 | Treatment of termination of intrauterine pregnancy, Cushing's syndrome, and uterine leiomyomas | (174) |
| Mecheliolide | Yes | CALR, ATP, HMGB1 | ↑IFN γ , TNF α | ↑DCs, CD4+, CD8+ T cells | NA | NA | (175) |
| MHO7 | ER stress, oxidative stress | CALR, HSP70, HMGB1 | ↑IL-6, IL-1 β , IFN- γ , TNF α | ↑CD86+ and MHC-II DCs, CD8+ T cells, CD4+ T cells; ↓Treg cells | NA | NA | (176) |

| | | | | | | | |
|---|--------------|-------------------------------------|---|---|-----------------------------------|--|----------------------------------|
| Norcantharidin | NA | CALR | NA | ↑DCs, tumor-infiltrating T lymphocytes | NA | Phase I clinical study for solid tumor (NCT04673396) | (177) |
| Certain NSAIDs | Yes | CALR | NA | ↑CD3+ and CD8+TILs, | NA | Pain treatment, anti-inflammatory application | (178) |
| Obinutuzumab (type II anti-CD20 antibody GA101) | ROS | ATP, HMGB1, HSP90 | NA | ↑CD86, CD83 DCs | NA | Treatment of chronic lymphocytic leukemia. | (96) |
| Oncolytics (virus and compounds) | ER stress | CALR, ATP, HMGB1, HSP70 /90 | ↑IFN γ | ↑IFN γ ⁺ CD4 ⁺ , CD8 ⁺ T cells, NK cells; ↓CD45 ⁺ CD11b ⁺ Ly6G ⁺ granulocytic and monocytic MDSC | Anti-CTLA4 | treatment of metastatic cancer NCT00348842 | (77, 79-82, 84, 86-89, 179, 180) |
| Oxaliplatin | ROS | CALR, ATP, HMGB1, HSP70 | ↑IL-1 β , type I IFNs, IFN γ | ↑CD8 ⁺ CTLs, $\gamma\delta$ TH17 cells, CD80 ⁺ CD86 ⁺ DCs, | Anti-PD-1, Anti-PD-L1, anti-CTLA4 | Treatment of colorectal cancer | (181-184) |
| P2Et | NA | CALR, ATP, HMGB1 | IFN- γ | ↑DCs, CD8+ T cells, | NA | Phase 1 study (CS001-SA) | (185, 186) |
| Paclitaxel | ER stress | CALR, ATP, HMGB1 | IFN- γ | ↑DCs, CD8+ T cells, CD4+ T cells | Anti-PD-1, anti-PD-L1 | Treatment of ovarian cancer, esophageal cancer, breast cancer, lung cancer, Kaposi's sarcoma, cervical cancer, and pancreatic cancer | (68, 187) |
| Pingyangmycin | ROS | ATP, HMGB1 | NA | ↑DCs, CD8 ⁺ TILs, CD3 ⁺ T cells, NK cells and NKT cells; ↓Tregs, CD4 ⁺ TILs, | anti-PD-1 | Treatment of breast cancer and liver cancer | (188) |
| PKHB1 (CD47-agonist peptide) | NA | CALR, HSP90, HSP70, HMGB1 | NA | CD8 ⁺ T cells, CD4 ⁺ T cells, lymphocytes and PMN | NA | NA | (189) |
| Pgp inhibitor (plus doxorubicin) | NA | CALR, ATP, HMGB1 | IFN- γ | ↑DCs, CD8 ⁺ T cells | NA | Tariquidar is under Phase I trial for treating solid tumors (NCT00011414) | (190) |
| PT-112 | NA | CALR, ATP, HMGB1 | ND | ↑DCs, CD8 ⁺ CTLs; ↓macrophage, Tregs | Anti-PD-1, anti-PD-L1, anti-CTLA4 | Phase I study (NCT03409458) in advanced solid tumours | (70, 151, 191) |
| Plecstatin-1 | P-eif2a, ROS | CALR, HSP90, HSP70, HMGB1, ATP | NA | NA | NA | NA | (192) |
| Polypeptide-based K ⁺ ionophore | ER stress | CALR | NA | NA | NA | NA | (98) |
| Rafoxanide | Yes | CALR, ATP, HMGB1 | NA | NA | NA | treatment of adult liver flukes' disease | (193) |
| Septacidin | ER stress | CALR, ATP, HMGB1 | NA | NA | NA | NA | (76) |
| Spautin-1 | NA | ATP, HMGB1, TFAM | Ifn β , Il12b/Il-12p40, Ifn γ , Il6/Il-6, Il5/Il-5 | ↑CD69, CD80, CD86, and MHC-II DCs | NA | NA | (32) |
| Shikonin | NA | GRP78, HSP70, HSP90, CRT, and HMGB1 | ↑IFN γ , IL-17A | ↑DCs, Th1/Th17; ↓CD4 ⁺ CD25 ⁺ FoxP3 ⁺ T cells | NA | NA | (194) |
| SHIP1-inhibitor (3AC/shSHIP1) | ROS | ATP, HMGB1 | NA | NA | NA | NA | (195) |
| SR-4835 | p-eif2a | CALR, ATP, HMGB1 | IL-1 β , TNF- α , IL-6 and IL-12p70 | ↑DCs (MHCII ⁺ , CD86 ⁺ , CD80 ⁺ and CD83 ⁺), TILs | Anti-PD-1 | NA | (196) |

| | | | | | | | |
|------------------------------------|-----------|-------------------------|--------------------------------|--|-----------------------|--|-------|
| SS1P (anti-mesothelin immunotoxin) | NA | CALR, ATP, | NA | NA | Anti-CTLA4 | Phase I clinical trial for advanced malignant pleural mesothelioma (NCT01445392) | (197) |
| Thiostrepton | ER stress | CALR, ATP, HMGB1 | NA | ↑CD8 ⁺ CTLs; ↓CD4 ⁺ CD25 ⁺ Foxp3 Treg cells | Anti-PD-1, anti-PD-L1 | FDA- approved antimicrobial drug | (132) |
| TPH104 | NA | CALR, ATP | TNF- α , IL-6 and IL-12 | ↑DCs | NA | NA | (198) |
| TMQ0153 | ROS | CALR, ATP, HMGB1, ERp57 | NA | NA | NA | NA | (199) |

ADC, antibody-drug conjugate; DC, dendritic cells; ER, endoplasmic reticulum; FDA, U.S. Food and Drug Administration, NA, not assessed; NSAID, nonsteroidal anti-inflammatory drug; PMN, polymorphonuclear cells; ROS, reactive oxygen species; TIL, tumor infiltrating lymphocytes; TKI, tyrosine kinase inhibitor

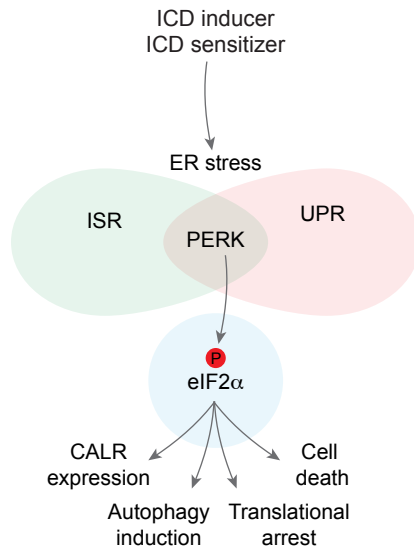


Figure 1

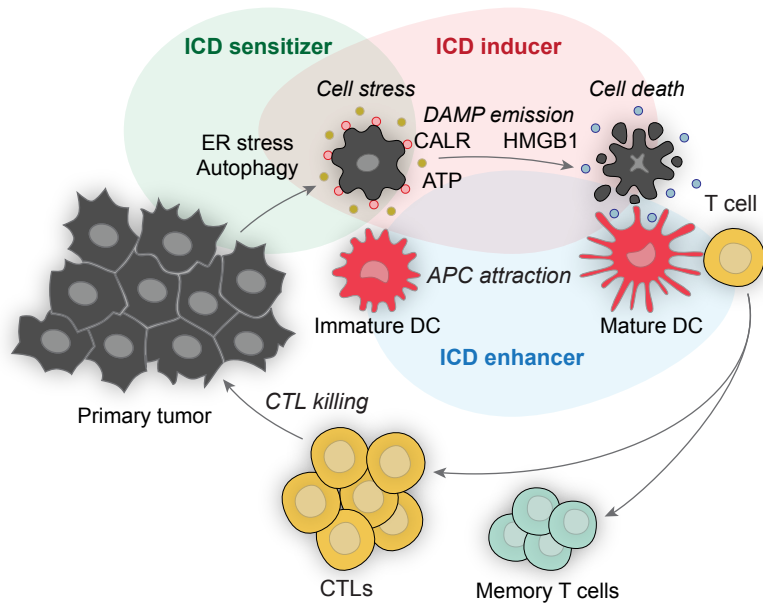


Figure 2