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Endoplasmic reticulum stress regulates tumor growth and anti-tumor immunity: A promising opportunity for cancer immunotherapy

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Abstract

The endoplasmic reticulum (ER) stress is a cellular process that occurs as a consequence of several stress circumstances, such as the accumulation of unfolded proteins in the lumen of the ER or distinct insults that disturb the ER normal function. Different conditions in the tumor microenvironment (TME), including hypoxia, nutrient deprivation, and the elevated production of reactive oxygen and nitrogen species destabilize the loading and dispatching of the newly synthesized proteins, triggering ER stress in cancer cells and tumor-infiltrating leukocytes. In order to cope with TME-induced ER stress, tumor and stromal cells initiate an adaptive response process that aims to resolve ER stress and to restore cellular homeostasis, which is referred as the Unfolded Protein Responses (UPR). Paradoxically, the UPR can also induce cell death under severe and/or permanent ER stress. The UPR is started through three mediators, the activation of the inositol-requiring enzyme-1 α (IRE-1 α), the pancreatic ER kinase (PKR)-like ER kinase (PERK), and the activating transcription factor 6 (ATF6). In this minireview, we will discuss the pro and anti-tumorigenic role of the UPR in cancer cells. In addition, we will describe the effects of the TME-induced ER stress in the immunosuppressive activity of tumor-infiltrating myeloid cells. Also, we will review the results of emerging therapeutic interventions that target ER stress and the UPR mediators in cancer. We postulate that the inhibition of ER stress or the UPR-related elements could represent a significant approach to increase the efficacy of various forms of cancer immunotherapy.

Keywords

Tumor microenvironment; Myeloid-derived suppressor cells; Regulatory Myeloid Suppressor Cells; T cells; Endoplasmic reticulum stress; Unfolded protein responses

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Introduction

The endoplasmic reticulum (ER) is the cellular organelle where production, folding, and proper modifications of proteins occur [1]. It also functions as a major quality control step for several protein assembly processes. Properly folded proteins are usually secreted outside the ER via defined pathways. On the other hand, unfolded or improperly folded proteins undergo ER-associated degradation (ERAD) to ensure their elimination [2]. The balance between the entry of nascent peptides and the secretion of correctly folded and modified proteins is maintained by the ER under normal physiological conditions. Due to the harsh environmental cues that are associated with infections, injuries or tumorigenesis, the ER homeostatic balance cannot be maintained, leading to ER stress [3]. Cellular ER stress is sensed through the dissociation of the inactive form of the HSP70-type BiP/GRP78 [4], leading to the activation of three intraluminal ER sensors; the inositol requiring enzyme-1 α (IRE-1 α), the protein kinase RNA-(PKR) like ER kinase (PERK), and the activating transcription factor 6 (ATF6) [3]. When these mediators are activated, several related signaling pathways are initiated and referred as the Unfolded Protein Responses (UPR). The ultimate physiological goal of the UPR is to restore the functions of the ER back to homeostatic conditions, which ensures cellular survival. However, under unresolved ER stress conditions, the same UPR elements may ultimately trigger cell death [5]. In this minireview, we will summarize the physiological and pathological role of the UPR in cancer cells and immune populations such as myeloid cells and T lymphocytes (Fig. 1). Also, we will illustrate some approaches that target ER stress or the specific UPR mediators and that we postulate could serve as novel platforms for therapies against cancer.

UPR mediators

At steady state, the three UPR mediators, IRE-1 α , PERK, and ATF6, are sequestered in an inactive form by binding to the chaperone BiP [4]. However, because BiP exhibits a higher affinity for misfolded proteins, the induction of ER stress causes the dissociation of BiP from the associated-UPR elements, leading to their activation and subsequent initiation of the UPR signaling pathway. Following is a brief description of how those mediators initiate UPR to cope with stress conditions and promote cellular survival or apoptosis.

IRE-1 α

A type I transmembrane protein that contains both kinase and RNase domains. Once the luminal side senses the unfolded proteins, IRE-1 α undergoes oligomerization, which activates its RNase domain that subsequently cleaves the X-box binding protein-1 (XBP-1) mRNA in the cytosol [6]. The cleaved fragments are then ligated by RNA ligase to yield the active form, XBP-1s [6]. XBP-1s functions as a transcription factor that activates several genes encoding for ER stress chaperones, lipids biosynthesis enzymes, and ERAD mediators [7,8]. IRE-1 α can also attenuate protein synthesis during ER stress by degrading various mRNAs through a mechanism known as IRE-1-dependent decay of mRNA (RIDD). Besides the RNase function, IRE-1 α also autophosphorylates via the activity of its own kinase domain, which creates docking sites for the adaptor protein TNF-receptor associated factor 2 (TRAF2) [9]. The formed IRE-1 α -TRAF2 complex enables the inhibition of various BCL2

family members through ER stress-induced JNK kinases, thereby leading to cellular apoptosis.

PERK

A type I transmembrane kinase that promotes protein translation arrest under ER stress through the phosphorylation of the eukaryotic initiation factor 2 α (eIF2 α) [10]. Phosphorylation of eIF2 α inhibits the initiation of *de novo* protein synthesis, which reduces the protein loading in the ER and therefore alleviates ER stress. Some transcripts such as the activation transcription factor 4 (ATF4) escape the translation block induced by phospho-eIF2 α , thereby controlling the final effects induced by this pathway [10]. As such, ATF4 induces the expression of the pro-apoptotic factor, CAAT/enhancer binding protein (C/EBP) homologous protein (CHOP), which leads to programmed cell death [10]. Paradoxically, PERK-induced ATF4 also promotes survival of ER-stressed cells through the transient expression of the microRNA miR-211, which degrades/downregulates CHOP mRNA [11]. Thus, PERK plays a dual role in deciding the fate of cells depending on the strength and duration of the ER stress signal.

ATF6

A type II transmembrane protein with a bZIP transcription factor in its N terminal end. In response to ER stress, ATF6 is translocated via COPII-coated vesicles to the Golgi apparatus where it undergoes sequential cleavages. That process leads to the release of the ATF6 N-terminal domain, which translocates to the nucleus to initiate the transcription of several UPR downstream genes involved in ER membrane expansion and ERAD [12]. In contrast to IRE-1 α , systemic deletion of ATF6 is not embryonic lethal [9]. However, ATF6 deficiency affects cell survival under chemically induced ER stress, suggesting an interplaying role between ATF6 and the other UPR-related elements [13].

The intrinsic role of the UPR in malignant cell physiology

Several reports have provided evidence of the increased activation of UPR mediators in patients with different cancer types and their overexpression usually correlated with poor prognosis and/or resistance to various therapies. As such, injection of mice with malignant cells lacking IRE-1 α , XBP-1, PERK, or ATF6; or treatment of tumor-bearing mice with specific inhibitors of the UPR mediators resulted in reduced tumor growth, which was attributed to low angiogenesis, increased sensitivity to hypoxia, and elevated production of reactive oxygen species (ROS) [14]. Furthermore, the upregulation of the UPR sensors or their master regulator BiP in cancer cells induced an elevated tumor growth and resistance to chemotherapy [15]. Also, XBP-1 mediated the aggressiveness and chemoresistance of triple negative breast cancer (TNBC) by assembling a transcriptional complex with the hypoxia-inducible factor 1 alpha (HIF-1 α) and promoting the expression of HIF-1 α target genes [16]. Although the severe and/or prolonged activation of the PERK and ATF6 arms of the UPR are known to result in pro-apoptotic effects through CHOP induction, the stimulation of these mediators after tolerable ER stress has also been shown to promote survival of the malignant cells. In fact, transient activation of PERK in tumor cells blocked the expression of CHOP through the induction of miR-211 [11]. In addition, NF-E2-related factor-2 (Nrf2)

phosphorylation and activation through PERK was found to protect stressed cells by maintaining glutathione levels, thereby blocking the accumulation of deleterious ROS [17]. ATF6 promoted the survival of tumors and their adaptation to chemotherapy treatments by activating mTOR signaling [18]. Furthermore, a recent study demonstrated that the activation of Notch1 pathway by ATF6 confers resistance of human glioblastoma cells to gamma radiation [19]. These results suggest the dual effect of the UPR mediators depending on the severity and time of exposure to the ER stress insult.

It is well known that growing cancer cells produce pro-angiogenic factors as a response to nutrients and oxygen deprivation to initiate the formation of new blood vessels. The IRE-1 α -XBP-1 pathway promoted the transcription of the angiogenic factor, vascular endothelial growth factor A (VEGF-A), through binding of XBP-1 to VEGF-A promoter [20]. Congruently, knockdown of XBP-1 in fibrosarcoma cells turned them to form avascular tumors compared to the wild type counterparts [21]. Moreover, K-Ras oncogene-transformed mouse embryonic fibroblasts lacking PERK showed a decreased angiogenic potential and smaller tumors after injection into mice [22]. Thus, the activation of the UPR mediators in tumor cells promotes their angiogenic potential, and resistance to chemotherapy, supporting the rationale for the combination of regular chemotherapy or radiotherapy approaches with UPR inhibitors as treatments for cancer.

The UPR regulates homeostatic functions of subsets of antigen-presenting cells

The role of UPR in the immune system was first documented in the differentiation of B cells to plasma cells. XBP-1-deficient B lymphocytes displayed a severe defect in their differentiation into immunoglobulin-secreting plasma cells [23]. Additionally, the IRE-1 α -XBP-1 pathway was found to regulate the phenotype and function of CD8 α conventional dendritic cells (cDCs) [24]. XBP-1-deficient CD8 α cDCs failed to cross prime CD8⁺ T cells, suggesting the activating role of XBP-1 in the antigen presentation capacity of CD8 α cDCs. Interestingly, the UPR mediators have been shown to synergize with some pathogen recognition receptors (PRR) like Toll-like receptors (TLRs). Lymphoid deficient XBP-1 mice showed decreased expansion and survival of conventional and plasmacytoid DCs after TLR stimulation [25]. Moreover, TLR2 and TLR4 activation stimulates IRE-1 α -XBP-1 and regulates the optimal production of pro-inflammatory cytokines in macrophages [26]. The canonical ER stress inducer, thapsigargin, was found to synergize with TLR4 agonist to induce the production of IL-23 in DCs [27]. That effect was mediated by CHOP, a major transcription factor downstream of PERK. These observations suggest that under physiological conditions, the UPR is necessary for the maturation, function and activation of various specific populations of antigen-presenting cells (Fig. 1).

The UPR mediators reprogram tumor-associated myeloid cells

Myeloid cells represent the major compartment of immune cells in the TME. The aggressive and hostile conditions, soluble factors, and cytokines within the TME trigger ER stress and the UPR in myeloid cells, thereby promoting their immunosuppressive phenotype (Fig. 2). The specific effect of the UPR mediators in regulating the function of tumor-infiltrating

myeloid cells has been recently studied by different groups. Seminal work by Cubillos-Ruiz et al. showed that over-activation of the IRE-1 α -XBP-1 drives the tolerogenic activity of DCs infiltrating ovarian carcinoma tumors [28]. Mechanistically, the ROS within the TME induced lipid peroxidation in tumor-infiltrating DCs (t-DC) resulting in ER stress and activation of IRE-1 α -XBP-1. Deletion or silencing of XBP-1 or treatment with the antioxidant vitamin E transformed immunosuppressive t-DC into myeloid cells that triggered immunogenic anti-tumor responses. That study introduced a new molecular mechanism that can be a potential target for resolving the dominant immune tolerance mediated by t-DC in the TME [29].

Myeloid-derived suppressive cells (MDSC) are a heterogeneous population of immature cells that accumulate in individuals with tumors and block protective anti-tumor T cell responses. In mice, MDSC can be divided into monocytic MDSC (M-MDSC, CD11b⁺ Ly6G⁻ Ly6C^{high}) and granulocytic MDSC (PMN-MDSC, CD11b⁺ Ly6G⁺ Ly6C^{low}). A recent work from Condamine et al. showed the role of ER stress in MDSC survival. Results showed that ER stress occurred primarily in tumor-infiltrating MDSC and promoted MDSC apoptosis through the TNF-related apoptosis induced ligand receptor 2 (DR5) and caspase 8 activation [30]. Latest results from the same investigators showed that pharmacological targeting of IRE-1 α -XBP-1 reprogrammed the low density immunosuppressive G-MDSC into high density anti-tumor neutrophils [31]. The upregulation of the lectin-type oxidized LDL receptor-1 (LOX-1) upon ER stress also enabled the discrimination between suppressive PMN-MDSC and non-tolerogenic neutrophils. We also studied the role of the ER stress-downstream target CHOP in tumor MDSC. When MDSC were isolated from tumors of CHOP-deficient mice, they showed lower ability to impair T cell responses compared to their wild type counterparts [32]. This correlated with a heightened expression of MHC-II and co-stimulatory molecules, and a higher ability to increase T cell responses after DC vaccination. This effect appears to be mediated through a decreased C/EBP β and IL-6/p-STAT-3 signaling, which are known to regulate the function and expansion of MDSC [33]. Accordingly, CHOP levels controlled the development of “alternatively activated” myeloid cells that produced cytokines known to impair T cell responses [27,11], suggesting a potential master role of ER stress mediators and CHOP in the immunosuppressive function of tumor myeloid cells.

A recent report has pointed on the role of the UPR mediator IRE-1 α on the secretory function of tumor-associated macrophages (TAM) [34]. Type 2 T helper cells (Th2) cytokines like IL-4, IL-6 and IL-10 synergize to instigate ER stress and activate IRE-1 α in TAM, which enhanced the production of Cathepsin protease, thereby facilitating invasion of tumor cells. Importantly, deletion of the Th2 signaling or inhibition of IRE-1 α in TAM was sufficient to reduce tumor growth and invasion. This suggests the importance of the UPR in TAM in the regulation of cancer cell invasion.

Collectively, all those studies outlined the effect of the ER stress on triggering myeloid cell dysfunction within the TME (Fig. 2). Also, they emphasized that the UPR mediators can be promising targets to either inhibit the suppressive capacity of myeloid cells in tumors or to induce their reprogramming into highly immunogenic antigen-presenting cells. Because the accumulation of myeloid cells in tumors is a major obstacle to current forms of

immunotherapy, the development of strategies to reprogram tumor-associated myeloid cells into immunogenic populations is expected to significantly increase the efficacy of these forms of cancer treatments.

A cross talk between UPR-undergoing tumor cells and myeloid cells

The UPR mediators induce multiple intracellular changes, but also lead to specific extrinsic effects. Several reports showed that tumor cells experiencing ER stress promote tolerogenic signals in the myeloid cells [35]. Macrophages and MDSC cultured in a conditioned medium of ER-stressed tumor cells upregulated the ER stress response genes *BiP*, *Chop* and *Xbp-1s*, increased the production of pro-inflammatory cytokines IL-6, TNF- α , and IL-23, and elevated the expression of the immunosuppressive enzyme arginase I and the pro-angiogenic molecule VEGF, all of which are known to promote tumor growth and metastasis [36]. TLR4 in macrophages was crucial to mediate that response. These results suggest that ER stress in tumor cells can potentially alter the behavior of myeloid cells within the TME. However, it remains unknown the factors and molecular mechanisms by which the ER-stressed tumor cells triggered this immunotolerogenic effect in myeloid cells.

The role of UPR in T cells under physiological and pathological conditions

Seminal studies have provided evidence on the role of the UPR signaling in T cell differentiation and activation. Through applying a XBP-1-GFP reporter system, researchers revealed that the IRE-1 α -XBP-1 branch is active in CD4⁺CD8⁺ T cells from the thymus, indicating a role of the UPR in T cell development [37]. Another study reported that ablation of Rpl22 (RP ribosomal protein L22), which restrains ER stress, blocked the development of $\alpha\beta$, but not $\gamma\delta$ T cell progenitors [38]. On the other hand, T cells containing a point mutation in the *Kdelr1* gene (encoding ER chaperone KDEL receptor 1) have higher levels of phospho-eIF2 α and impaired T cell survival [39]. Similar to this finding, *Skfn2* null T cells undergo chronic ER stress, which leads to proliferation inhibition and low viability. Interestingly, this developmental abnormality was reversed after deleting CHOP or XBP-1 [40]. Those studies suggest that evoking UPR is necessary for T cell development, but elevated stress will lead to impaired T cell function and survival.

T cells are activated by TCR-peptide-MHC recognition plus a secondary stimulatory interaction with APCs, which can be mimicked by anti-CD3/CD28 antibodies or the combination of the PKC activator PMA and the Ca²⁺ ionophore ionomycin. Elevated ER chaperones components were found after T cell priming with anti-CD3/CD28 [41,42]. In the process of CD4⁺ T cell polarization into Th2 cells, high levels of BiP, ATF4, and CHOP were detected [43]. Furthermore, spliced XBP-1 mRNA is increased during CD8⁺ T cell activation and the overexpression of XBP-1 spliced isoform enhances CD8⁺ T cell cytotoxic function [44]. Those discoveries indicate that elevated UPR is necessary during T cell activation. Besides this, UPR also regulates T cell apoptosis. In *Gimap5* null hosts, which have spontaneous apoptosis in T cells, knocking down of CHOP inhibited T cell apoptosis [45]. In addition, a recent study revealed that deletion of Hrd1, an E3 ligase involved in UPR-induced ERAD, led to reduced T cell numbers and attenuated T cell polarization into

Th1, Th2 and Th17 [46]. Therefore, moderate UPR promoted T cell function, whereas overwhelming UPR signaling will lead to impaired T cell responses and cell death.

Abnormal UPR amplitudes or dysregulated expression of core UPR components are related to pathological disorders, giving a possibility that UPR mediators can be a therapeutic target in such diseases. XBP-1-mediated UPR is critical for CD8⁺ T cell differentiation during acute bacterial or viral infection [44]. Increased XBP-1 splicing, but not PERK or ATF6 activation, along with high expression of BiP and CHOP were found in acute necrotizing enterocolitis (A-NEC) patients who also had lower Th17 and Treg numbers [47]. In the experimental autoimmune encephalomyelitis (EAE) model, downregulating UPR via weakening ERAD leads to low disease progress, indicating that targeting UPR pathways may be a promising therapeutic option for multiple sclerosis [46]. Currently, whether UPR regulates T cell viability and function in the TME remains mostly elusive.

Therapeutic approaches targeting the UPR mediators

Severe ER stress incites immunogenic cell death in tumor cells

Malignant cells killed by intrinsic or extrinsic stress factors within the TME generate danger associated molecular patterns (DAMPs), including HMGB-1, ROS, IL-1 α , ATP and plasma membrane exposure of the ER resident protein calreticulin (CRT) that evoke inflammation and immunogenic responses [48]. This phenomenon is known as immunogenic cell death (ICD). Based on this, ICD inducers have evolved as potential anti-cancer agents and were classified into two categories based on the mechanisms through which they target the ER and induce apoptosis of tumor cells [49]. Type I ICD inducers, as Cyclophosphamide and gamma radiation, stimulate immunogenic apoptosis via secondary ER stress effects, while type II ICD triggers, as Hypericin-based photodynamic therapy, activate immunogenicity by directly disrupting ER homeostasis leading to UPR. The relationship between ER stress and ICD is more likely to be bidirectional and regulated throughout highly complexed mechanisms. The release of HMGB1 upon ICD and its binding to RAGE receptor was found to activate UPR mediators in bystander cells [50]. On the other hand, cytotoxin-induced ICD was found to be mediated through PERK activation and calcium flux [51]. Accordingly, the PERK-eIF2 α pathway was shown to be involved in CRT exposure following anthracyclines and oxaliplatin treatment [52] and the phosphorylation of eIF2 α was documented to be a key parameter correlated with ICD [53]. The combination of cisplatin with ER stress inducers like, tunicamycin or thapsigargin, was found to be therapeutically effective in some tumors rather than using cisplatin alone [54]. Those findings indicate that the activation of the UPR arms mediates the production of ICD-associated factors and represents a mechanistic prerequisite for the clinical outcome of various ICD-inducing agents in cancer.

The increased production and accumulation of ROS in cells have been related with ICD after chemotherapy. The inflammatory responses associated with ICD were reduced in the presence of anti-oxidants [55]. As such, ER stress synergizes with ROS production to promote ICD by increasing the levels of DAMPs. However, it is still unknown if ICD can also occur in immune cells infiltrating tumors and whether that can have any impact on cancer therapy. In addition, a clear understanding of the mechanisms regulating the

immunogenic vs. immunosuppressive effects induced by the UPR mediators in the context of ICD remains to be determined.

Blocking UPR mediators as cancer therapy

It is an interesting fact that ER stress is crucial for the survival of malignant cells, but also could drive cancer cells towards ICD and recognition by the immune system. That can be explained in terms of the severity of the ER stress. In other words, cancer cells undergoing moderate ER stress activate the UPR mediators as a response to adapt to the aggressive tumor milieu, while cancer cells exposed to severe or permanent ER stress activate UPR to mediate cell death and potentially ICD. In agreement with the therapeutic potential of blocking moderate ER stress in cancer cells, pharmacological inhibition of the UPR arms in malignant cells resulted in tumoricidal effects *in vivo*. A class of compounds that includes toyocamycin, STF-083010, MKC-3946 and B-I09 can interfere with the endoribonuclease domain of IRE-1 α and showed therapeutic benefits in multiple myeloma and chronic lymphocytic leukemia models [56,57]. Also, oral administration of the PERK inhibitor, GSK2656157, delayed tumor growth of xenografts in immunocompromised mice [58]. Similar results were obtained after treatment of tumor-bearing mice with the ER stress scavengers, Tauroursodeoxycholic acid or 4-phenylbutyrate. Furthermore, induction of severe ER stress using tunicamycin or thapsigargin have shown to impair tumor growth and increase the effects of ICD-inducers [54].

Although the systemic inhibition of UPR mediators showed to induce anti-tumor effects [56], it can also trigger side effects such as the pancreatic toxicity associated with the inhibition of PERK [59]. Therefore, specific targeting of UPR mediators in myeloid cells will remain a big challenge to the field. Based on their unique phagocytic properties, t-DC, MDSC and TAM can be considered as candidates for nanoparticle therapies. Targeting t-DC with siRNA-loaded nanoparticles against XBP-1 transformed them into immunogenic cells that primed anti-tumor T cell responses [28]. Knocking down IRE-1 α by siRNA in bone marrow derived macrophages blocked their ability to express cathepsin in response to Th2 cytokines, thereby, preventing macrophage-mediated cancer cells invasion [34]. Specific blocking of UPR mediators in tumor-associated myeloid cells can be a potential approach to either reprogram them into effectors or deprive them from producing pro-tumorigenic factors. Also, they might improve the therapeutic effect when combined with checkpoint blockades, adoptive cell therapy or tumor vaccines.

Closing Remarks and Future Directions

The role of myeloid cells in the inhibition of anti-tumor immune surveillance and as a major obstacle for the successful development of effective therapies against cancer are subjects of intense interest in the field. To date, however, the approaches to inhibit the accumulation and function of myeloid cells in tumors are limited to myelosuppressive agents or multi-tyrosine kinase inhibitors that are only partially effective and secondarily enhance populations such as MDSC as the bone marrow recovers. We propose that the fundamental problem is that the limited understanding of the central signaling pathways governing the accumulation and function of myeloid cells in tumors have prevented the development of successful therapies.

The results discussed here support the central role of the UPR mediators in the overall behavior of myeloid cells in tumors. We postulate that therapeutic inhibition of ER stress or the UPR elements in tumors could reprogram immunosuppressive myeloid subsets into immunogenic cells being capable to induce protective immunity (Fig. 2), thereby enhancing the effect of chemotherapy, radiotherapy, and immunotherapy. This hypothesis remains to be explored in animal models and clinical studies.

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Abbreviations

A-NEC	Acute necrotizing enterocolitis
ATF4	Activation transcription factor 4
ATF6	Activating transcription factor 6
C/EBP	CAAT/enhancer binding protein
cDCs	Conventional dendritic cells
CHOP	CAAT/enhancer binding protein (C/EBP) homologous protein
CRT	Calreticulin
DAMPs	Danger associated molecular patterns
DR5	TNF-related apoptosis induced ligand receptor 2
EAE	Autoimmune encephalomyelitis
eIF2α	Eukaryotic initiation factor 2 α
ER stress	Endoplasmic reticulum stress
ERAD	ER-associated degradation
HIF-1α	Hypoxia-inducible factor 1 alpha
ICD	Immunogenic cell death
IRE-1α	Inositol-requiring enzyme-1 α
Kdelr1	KDEL receptor 1
LOX-1	Lectin-type oxidized LDL receptor-1
M-MDSC	Monocytic MDSC
MDSC	Myeloid-derived suppressor cells
Nrf2	NF-E2-related factor-2

PERK	Pancreatic ER kinase (PKR)-like ER kinase
PKR	Protein kinase RNA
PMN-MDSC	Granulocytic MDSC
PRR	Pathogen recognition receptors
RIDD	IRE-1-dependent decay of mRNA
ROS	Reactive oxygen species
Rpl22	RP ribosomal protein L22
t-DC	Tumor-infiltrating dendritic cells
TAM	Tumor associated macrophages
Th2	Type 2 T helper cells
TLRs	Toll-like receptors
TME	Tumor microenvironment
TNBC	Triple negative breast cancer
TRAF2	TNF-receptor associated factor 2
VEGF-A	Vascular endothelial growth factor A
UPR	Unfolded protein responses
XBP-1	X-box binding protein-1

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Figure 1.

The UPR mediators have versatile roles in different cell types either in the presence of balanced or unresolved ER stress. Under physiological conditions, the balanced UPR is crucial for the development of cells with secretory functions as pancreatic β islets, hepatocytes and B lymphocytes. Also, the maturation and the antigen presenting capability of CD8 α DCs require moderated activation of UPR that is mediated through IRE1 α -XBP-1 pathway. Furthermore, the effect of the balanced UPR in the T cell development and function is emerging. An exaggerated form of UPR can be triggered by different stress factors associated with pathological conditions as infections, autoimmunity and cancer. Tumors cells either survive or undergo ICD depending on the degree of UPR severity. Tumor infiltrating myeloid cells (t-DC, TAM, and MDSC) are characterized by sustained and amplified UPR activity which converts them into immunosuppressive cells that promote tumor growth and invasion.

Figure 2.

Myeloid cells originate from precursors in the bone marrow and transfer through blood stream until they reach tumor sites. Stress conditions in the tumor microenvironment activate UPR pathways which either retain tumor infiltrating myeloid cells in an immature stage or switch them to tolerogenic populations that can blunt T cells. Therapeutic approaches to block UPR mediators can reprogram immature tumor infiltrating myeloid cells into professional antigen presenting cells rather than immunosuppressive phenotypes. As such, the inhibition of the UPR mediators could serve as a major opportunity for cancer treatments.