Endoplasmic Reticulum Stress and the Hallmarks of Cancer

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Running head: ER stress in cancer

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ABSTRACT

Tumor cells are often exposed to intrinsic and external factors that alter protein homeostasis thus yielding endoplasmic reticulum (ER) stress. To cope with this, cells evoke an adaptive mechanism to restore ER proteostasis known as the unfolded protein response (UPR). The three main UPR signaling branches initiated by IRE1α, PERK and ATF6 are critical for tumor growth and aggressiveness as well as for microenvironment remodeling or resistance to treatment. Here we provide a comprehensive overview of the contribution of the UPR to cancer biology and the acquisition of malignant characteristics, thus highlighting novel aspects including inflammation, invasion and metastasis, genome instability, resistance to chemo/radio therapy and angiogenesis. The therapeutic potential of targeting ER stress signaling in cancer is also discussed.

THE UNFOLDED PROTEIN RESPONSE AS AN EMERGING COMPONENT OF CANCER BIOLOGY

Tumor cells are exposed to several cell-intrinsic and environmental perturbations that generates selection pressure and trigger a variety of adaptive mechanisms to favor cell transformation and to promote the acquisition of several tumor capabilities required for cancer progression [1]. Among this factors, named "hallmarks of cancer" [1], the control of protein homeostasis (referred to as *proteostasis*) is one of the emerging processes involved in tumor progression. Extrinsic factors such as hypoxia, nutrient deprivation and acidosis alter the normal function of the endoplasmic reticulum (ER), one of the major compartments involved in protein synthesis in the cell [2]. On the other hand, intrinsic stresses to which solid tumors are exposed such as oncogenic activation, alteration in chromosome number [3] and exacerbated secretory capacity [4] cause high demand in protein production. Moreover, genomic instability, increased mutation rate and redox imbalance further perturb global proteostasis. All these factors involved in cancer progression promote the accumulation of misfolded proteins at the ER lumen, a cellular condition known as "ER stress". To cope with ER stress, cells activate a series of adaptive mechanisms to enhance the folding and clearance capacity and restore ER proteostasis that as a whole is termed the unfolded protein response (UPR) [5].

Activation of the UPR has been described in different human tumors and multiple cellular and animals models of cancer [6]. In tumors, the upregulation of UPR markers is often observed indicating the occurrence of ER stress. Protein translation is altered in hypoxic tumors [7, 8], however recent findings indicate that the UPR may also contribute to cancer independent of protein misfolding (see next sections). Solid tumors often exhibit elevated levels of ER chaperones including GRP78 and GRP94, which are classical UPR markers [9]. Elevated expression of GRP78 is associated with increased proliferation rate and invasion and is correlated with poor prognosis in different types of cancer [10]. Furthermore, the contribution of individual core components of the UPR to tumor growth is also well defined and supported by many functional studies in preclinical models (reviewed in [11]). Most of the evidence available supports a concept where ER stress signaling is involved in the adaptation and survival of cancer cells to stress conditions [6]; however, new emerging concepts indicate unanticipated roles of the UPR in other central aspects of tumor biology. In fact, individual components of the UPR have been linked to cell transformation, dormancy, angiogenesis, immunogenicity, genomic instability, metastasis and resistance to treatment [12]. The UPR may also impact mitochondrial function and bioenergetics, aspects that will not be discussed herein (reviewed in [13]). Over the past few years, the UPR has

become a central player in tumor development [14], and now represents an attractive therapeutic target in many solid and blood cancers [15].

This review provides a comprehensive overview of UPR signaling in tumors and how this drives different hallmarks of cancer. An emphasis is given to discuss novel functions of the UPR in tumor progression and its potential use as a therapeutic target.

THE UNFOLDED PROTEIN RESPONSE

The UPR is mediated by at least three major stress transducers localized at the ER membrane including the Activating transcription factor 6 (**ATF6**), the PKR-like ER kinase (**PERK**) and the Inositol-requiring enzyme 1 (**IRE1**) (Figure 1) [5]. **IRE1α** is a kinase and endoribonuclase (RNAse) that dimerizes/oligomerizes and auto-transphosphorylates upon ER stress, leading to RNase activation. Active IRE1α catalyzes the excision of a 26-nucleotide intron within the X-box binding protein-1 (XBP1) mRNA, and the RTCB-mediated ligation of the remaining 5' and 3' fragments [16] shifts the reading frame to translate a stable and active transcription factor known as XBP1s (spliced form). Active XBP1s modulates the expression of several UPR target genes involved in ER folding, glycosylation and ERAD [17]. In addition, the IRE1α RNAse activity can target other mRNAs and microRNAs through a process termed Regulated IRE1-Dependent Decay (RIDD). RIDD has emerged as a novel UPR regulatory component that controls cell fate under ER stress [18]. Under ER stress conditions, **PERK** inhibits global protein translation through the phosphorylation of the eukaryotic translation initiation factor eIF2α at serine 51, thereby decreasing the load of newly synthesized proteins. In addition, this mechanism allows the selective translation of the Activating transcription factor 4 (ATF4) mRNA, which controls the expression of a gene cluster involved in amino acid metabolism, antioxidant response, autophagy and protein folding [17]. ATF4 expression is also crucial in the activation of proapoptotic programs by regulating the expression of CHOP, a transcription factor that upregulates pro-apoptotic members of the BCL-2 protein family [19]. This pathway also induces the expression of GADD34, an adaptor to the eIF2α phosphatase PP1c adaptor, which regulates eIF2α phosphorylation timing for stress recovery or proteotixicity [20, 21]. **ATF6** encodes a type II transmembrane protein bearing transcription factor activity on its cytosolic domain that is located at the ER at basal conditions. Upon ER stress, ATF6 is transported to the Golgi apparatus and processed by specific proteases S1P and S2P, which releases the cytosolic fragment of the protein ATF6f that functions transcription factor. ATF6f regulates the expression of genes related to ER-associated degradation (ERAD) of misfolded proteins [5].

The immediate response of the UPR enforces cell adaptation to protein folding stress by reducing protein influx into the ER through eIF2α phosphorylation, degradation of ER-related mRNAs by RIDD, and by detaching of mRNAs from ribosomes [22]. This is followed by the reprogramming of gene expression through the combinatorial action of several transcription factors that overall promote the recovery of proteostasis and enhance the folding capacity of the cell, the efficiency of protein quality control mechanisms and protein degradation pathways [5]. When the buffering capacity of the UPR is overwhelmed, apoptotic programs are engaged to eliminate damaged cells [19]. The mechanisms defining the threshold that switches UPR signals from adaptive to proapoptotic are just starting to be understood. Fine-tuning this balance in cancer cells therefore represents an interesting target for therapeutic intervention. In the next section we summarize the different outputs of the UPR that are relevant to the evolution of cancer.

THE UPR IN CELL TRANSFORMATION AND CANCER PROGRESSION

Classical role of the UPR in tumorigenesis

The UPR is known to operate as an adaptive mechanism during cancer progression. It acts modulating mechanisms that trigger cell transformation, enhance survival and adjust the metabolic status of the cell (Figure 1); however, UPR activation at different phases of cancer progression is far more complex than anticipated. The involvement of the UPR during the initial phase of cancer development was described in models of Ras-transformed melanoma [23] and Ret-induced fibroblast transformation [24], where it prevented oncogene-induced malignant progression. In both cases, transformed cells, identified as those cells surviving the oncogene-induced apoptotic crisis, exhibited high levels of UPR activation in conditions where ER stress was not triggered by external factors. Historically, PERK signaling has been implicated in the initiation and progression of different classes of tumors. PERK deficient cells give rise to smaller tumors and associate with increased animal survival [7, 8]. This is highly dependent on eIF2α phosphorylation and regulation of protein translation in hypoxic tumors [7]. PERK signaling also modulates other pathways including NRF2 and the regulation of the cellular redox [25, 26]; and metabolism [27] and lipid biosynthesis (reviewed in [28]). Importantly, selective inhibition of PERK using a small molecule shows beneficial effects by reducing tumor growth and increasing survival in human pancreatic tumor xenograft models [29, 30].

The IRE1α/XBP1 signaling pathway is implicated in the progression of tumors. High expression of XBP1s protein correlates with poor prognostic in glioblastoma [31], triple negative breast cancer (TNBC) [32] and pre-B acute lymphoblastic leukemia [33]. Several

reports also indicate an important role of IRE1α/XBP1 in the pathogenesis of multiple myeloma [34, 35], where the use of specific inhibitors of the IRE1α endoribonuclease activity is beneficial [36-38]. Moreover, IRE1α is one of the human kinases more susceptible to be a cancer driver when mutated [39]. Interestingly, although some of these mutations have a functional kinase and endoribonuclease activity, the ability to induce apoptosis in culture cells is lost [40, 41]. The IRE1α/XBP1 signaling axis also has been linked to metastatic progression and resistance to chemotherapy [42]. More recently it was demonstrated that IRE1α is important for growth, angiogenesis and invasion in a glioblastoma model [43, 44]. Due to the pleiotropic role of IRE1α in different aspects of tumor progression (see next sections), this stress sensor represents an attractive candidate for targeted therapy [45].

Emerging role of the UPR in tumorigenesis

Besides proliferation, during cancer evolution, tumor cells acquire several capabilities that allow them to adapt and survive to stress conditions. New evidence links UPR activation to many hallmarks of cancer, including angiogenesis, genomic instability, invasion, cell dormancy, proliferation, survival and cell death resistance (Figure 2). Although, these characteristics have been observed in different types of cancers, recent evidence demonstrate that the UPR is involved in the acquisition of many hallmarks of cancer, as illustrated in Glioblastoma multiform (GBM) (Box 1) and other forms of cancer. Bellow, we highlight and discuss recent advances supporting novel roles of the UPR in tumor progression.

Tumor angiogenesis regulation

The insufficient perfusion of solid tumors induces hypoxia, nutrient deprivation and the subsequent decrease in ATP production. In turn, neo-angiogenesis or vessel cooption are triggered in the tumor to cope with the lack of oxygen and adjust the metabolism [46]. Several observations indicate that the UPR can promote angiogenesis by regulating the transcription of several pro-angiogenic factors [47] (Figure 2). Vascular endothelial growth factor (VEGF) is upregulated in cells undergoing ER stress, promoting cell survival in rapidly growing tumors [48]. The expression of VEGF is controlled directly by the binding of ATF4 to VEGF promoter [47, 49]. This mechanism not only occurs in tumor cells such as TNBC [32] but also in endothelial cells [50], where XBP1s expression is crucial for angiogenesis, possibly through physical interactions with HIF1α, a central regulator of VEGF [32]. Unexpectedly, VEGF also activates the UPR in endothelial cells through an unconventional mechanism that requires PLCγ and mTORC1 and in the absence of evident signs of ER

stress, thereby promoting endothelial cell survival and angiogenesis [51]. Thus, VEGF and hypoxia in tumors operate as an amplifying loop of angiogenesis using the UPR as transducer in tumor and endothelial cells [52, 53]. Together, these findings suggest that the UPR signaling machinery has a relevant function in the regulation of pro-angiogenic factors in the tumor and endothelial cells beyond ER stress.

Tumor inflammation and immune response

A novel aspect in the field of ER stress is its impact in the modulation of the extracellular inflammatory and immune microenvironment, and how this reaction spreads to the surrounding cells (Figure 2). The observation that an ER stress response can be transmitted in a cell-to-cell manner in myeloid cells, promoting macrophage activation eliciting a pro-inflammatory response in the tumor microenvironment, gave rise to the concept of "transmissible ER stress-inducing factor" [54]. These phenomena reduce antigen processing and presentation and diminish T-cell proliferation [55], suggesting that the immunosuppressive effects of tumor cells undergoing an ER stress response are mediated by myeloid antigen-presenting cells [55]. Of note, it has been suggested that the UPR can be activated in a cell non-autonomous manner in other experimental systems [56], a concept that remains to be determined in cancer. XBP1 is also essential for the development and survival of dendritic cells [57, 58]. A recent study indicates that tumor-infiltrating dendritic cells exhibit high levels of spliced XBP1, thus accelerating the progression of primary and metastatic ovarian carcinoma [59]. Remarkably, UPR activation in tumor dendritic cells results in poor immune function, which is accompanied by impaired lipid metabolism and subsequent reduction of T-cell anti-tumor immunity. Therefore, targeting XBP1 in dendritic cells restores their immuno-stimulatory function and prolongs host survival by inducing a protective anti-tumor immune response [59]. Mechanistically, ER stress in tumor dendritic cells was associated with increased ROS production and the generation of lipid peroxidation byproducts, which may initiate and sustain pro-tumorigenic ER stress. Other studies also indicate that CHOP is upregulated in tumor infiltrating myeloid-derived suppressor cells by tumor-induced ROS and peroxynitrite. Here, CHOP dampens the immune inhibitory activity to induce anti-tumor responses [60]. In summary, this evidences support a new function of the UPR in modulating the inflammatory environment of tumors, thus fine-tuning immune responses in cancer.

Tumor dormancy and resistance to treatments

Cancer “cell dormancy” is characterized by a cease of cell division, arrest in the G0/G1 phase of the cell cycle and entry into quiescence [61]. Dormant cells become reactivated when optimal environmental conditions for cell proliferation and metabolic activity resume. In several types of cancer dormant cells are observed in the early stages of tumor growth and in distant micrometastases [62]. The reactivation of dormant cells is a main reason of cancer recurrence after chemo- and radio-therapies [62]. Recent data suggests a functional link between the UPR and tumor dormancy. Recurrent tumors express high levels of ATF6 [63] and ATF6 was shown to correlate with poor prognosis of colon tumors [64]. High ATF6 expression is also found preferentially in metastatic lesions rather than in primary tumor [65]. These findings can be partially explained by the fact that ATF6 is constitutively active, as observed human squamous carcinoma models [66]. In these tumors, ATF6 silencing reduces cell survival and tumor growth due to down-regulation of the adaptive pathways such as mTOR [66]. ATF6 also controls the expression of novel and specific proteins associated with tumor transformation [67] and the increase of chemo-resistance [68]. Interestingly the role of ATF6 in tumor growth and resistance to radiotherapy was recently illustrated in GBM (Box 1), where ATF6 regulates the expression several pro-oncogenic proteins including GRP78 and Notch1. These findings might help explaining in part why recurrent tumors are refractory to second rounds of chemotherapy.

Different components of the UPR may alter quiescence states through different signaling outputs. IRE1α can control cyclin D1 expression in a XBP1- dependent manner in prostate cancer, thereby affecting cell cycle progression and proliferation [69]. PERK also negatively regulates cyclin D1 expression and induces cell cycle arrest in G1, which possibly correlates with tumor dormancy [70]. Moreover, both PERK activation and eIF2α phosphorylation contribute to drug resistance of dormant cells [71]. Although the data available is still mostly correlative, increasing evidence suggests that the UPR may regulate cancer cell dormancy.

Genome instability and epigenetic regulations

Genomic instability is one of the hallmarks of cancer. Polyploidy triggered-immunogenic cell death is possibly mediated by ER stress-related signaling [72]. This observation raises the question of whether there is a connection between protein misfolding and genome integrity during cancer development. Genetic inactivation of PERK has been reported to trigger genomic instability which correlates with the occurrence of oxidative DNA damage in mammary carcinoma [73]. Similarly, Ire1p deficiency in yeast alters genome integrity by increasing chromosome loss. [74]. It has been suggested that ER stress generates oxidative

stress and consequent DNA damage possibly through an imbalance in the cycle that regulates the redox state at the ER mediated by PDI and ERO1α oxidoredutase [75].

Some reports also linked ER stress with the DNA damage response. For example: p53-deficient or ATM-deficient cells develop spontaneous ER stress [76, 77]; XBP1 has been suggested to control a cluster of DNA repair genes [78] and aneuploidy and gene copy-number variations may be translated into global proteostasis alterations and proteotoxicity [79]. Other indirect evidence has also linked ER stress with DNA repair and genome stability (reviewed in [12]). Interestingly, proteostasis is also targeted by Histone DeACetylase (HDAC) inhibitors [80] that synergize with activation of ER stress in cancer cells [81]. This could represent an attractive way to enhance proteotoxicity in such pathological system. HDAC mediated proteostasis control is also linked to an AAA+ ATPase network implicating both p97/VCP and RUVBL2 [82, 83], both proteins being involved in misfolded protein disaggregation and degradation as well as genome integrity. In addition, ER stress can impact chromatin remodeling through the regulation of chromatin posttranslational modifications as methylation and acetylation impacting transcription of ER target genes (reviewed in [84]). A key modification observed under ER stress and DNA damage response in cancer is the acetylation of H3K14, promoting survival of tumor cell lines [85].

Although still correlative these data provide a novel framework that could functionally connect ER proteostasis control to genome surveillance in cancer cells; however, functional and systematic studies in models of cancer *in vivo* are needed to understand the link between ER stress and genomic instability.

Cell invasion and metastasis

Malignant cells metastasize to distant organs. ER stress signaling is emerging as a driver of migration, homing, and invasion of cancer cells. During epithelial-to-mesenchymal transition (EMT), cancer cells acquire a highly secretory phenotype that activates several cellular events including UPR signaling [86, 87] and autophagy [88]. In this context, the PERK arm of the UPR promotes invasion, migration and metastasis [86]. ATF4-mediated activation of lysosomal-associated membrane protein 3 (LAMP3) is also instrumental to metastasis of hypoxic breast cancer cells [89, 90]. This pro-metastatic role of LAMP-3 was also validated in normoxic regions of human neck squamous cell carcinoma [91]. ATF4 is also up-regulated in esophageal squamous carcinoma, where it increases cell invasion and metastasis through the regulation of matrix metalloproteinases expression [92]. Furthermore, the serine/cysteine protease inhibitor SCCA1 (SERPINB3), a relevant pro-metastatic factor during EMT, modulates the activation of PERK and ATF6, but not of IRE1α [87]. Finally, IRE1α activity

modulates the adhesion and migration properties of GBM cells (Box 1) [43]. In TNBC, tumors cells expressing XBP1s metastasize more efficiently to the lungs [32]. In contrast, IRE1α signaling negatively regulates cell adhesion/migration through RIDD-mediated degradation of SPARC mRNA and the subsequent attenuation of RhoA and FAK signaling in GBM [43, 44]. The role of the UPR in metastasis remains to be fully elucidated and the outcome of UPR regulation most likely results from a fine balance between different arms of the pathway within specific tumor contexts.

CONCLUDING REMARKS

The UPR signaling network is emerging as a driver of several aspects of cancer development. Most of the evidence available suggests that the UPR operates as a pro-oncogenic mechanism that increases cancer cell adaptation and survival to cope with major intrinsic changes and adverse environmental challenges. Hypoxia, nutrient deprivation, acidosis and the high demand of production of proteins induced by the activation of oncogenes generate a global ER stress reaction that engages all the three branches of the UPR [93]. Although, in this review we focused mostly in the linear UPR signaling pathways, analyzing the contribution of proximal signaling events (i.e. stress sensors and transcription actors), available data also shows that UPR downstream target genes are related to cancer progression. In addition to the canonical role of the UPR in tumors, new emerging concepts indicate new contribution of ER stress to several hallmarks of cancer (Figure 3). In two examples discussed here, the UPR is involved in the communication and interaction of tumor and stromal cells and modulates angiogenesis and inflammatory/immune response. This concept of tumor cell non-autonomous UPR should be further explored in the context of the complex interaction between cancer and surrounding host cells. In addition, other novel aspects of cancer biology, such as DNA repair pathways and the control of cell migration and remodeling of the extracellular matrix should be investigated further as well. Overall, ER stress-related programs are emerging as relevant player contributing to most hallmarks of cancer (Figure 3). The recent discovery of small molecules that specifically target specific components of the UPR signaling network [15] show promise for novel therapeutic interventions.

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BOX 1 – UPR signaling in GBM and hallmarks of cancer

High-grade glioma (also known as glioblastoma multiform (GBM)) is the most frequent and aggressive brain cancer, for which there is no efficient therapy. GBM tumors are resistant to standard treatments and frequently recur which leads to poor clinical outcome. BiP/GRP78 is frequently overexpressed in cancer including GBMs [94-96]. Moreover, the three branches of the UPR have also been involved in the control of several hallmarks of Cancer. IRE1α contributes to the development of GBM in several experimental models [31, 43, 44, 97, 98]. IRE1α impacts GBM angiogenesis through the regulation of proangiogenic and proinflammatory chemokines [31, 43]. Also, IRE1α RIDD activity controls GBM infiltration through the degradation of SPARC mRNA [44]. A recent study also showed that while the RNAse activity of IRE1α is dispensable for neovascularization, the inhibition of RNAse resulted in increased glioma motility [98]. Finally, in human GBM samples high levels XBP1s splicing correlated with poor prognosis [31]. These data collectively point toward a functional role of IRE1α in the development and progression of GBM tumors. The PERK and ATF6 arms of the UPR are also involved in the control of GBM development. PERK signaling is involved in the control of GBM metabolism [99] and response to treatment [100, 101], whereas the ATF6 pathway contributes to resistance to radiotherapy [102]. High-resolution CRISPR screens also indicate the contribution of the ATF6 arm of the UPR to GBM development [103]. Altogether these results demonstrate an important role of UPR signaling pathways in GBM biology and indicate a potential therapeutic opportunity in a cancer that lacks effective treatments.

TREND BOX

High proliferative tumors are exposed to several intrinsic and extrinsic factors that induce adaptation to stress conditions. Endoplasmic reticulum (ER) stress is a common feature in different types of blood a solid cancer. Adaptation to ER stress is achieved by the activation of the unfolded protein response (UPR).

The UPR is involved in acquisition of several malignant characteristics that allows tumor growth. ER stress signaling also occurs in stromal cells such as endothelial, macrophages and dendritic cells suggesting a novel concept of “transmissible ER stress”.

Although the acquisition of tumor characteristics is drive by UPR signaling events, some of these features are independent of ER stress as observed in angiogenesis and tumor-promoting inflammation.

Several specific small molecules that inhibit UPR stress sensors (IRE1α and PERK) provide beneficial effects in multiple myeloma and pancreatic cancer.

OUTSTANDING QUESTIONS

How intrinsic and extrinsic challenges to ER proteostasis integrate to drive tumor progression?

In terms of intrinsic stress, while oncogene-induced ER stress has been established, what is the contribution of accumulating mutations to the protein misfolding burden in cancer cells?

What is the impact of somatic mutations of UPR components in cancer cells properties and tumor characteristics?

Is it possible to predict the evolution of a cancer by measuring ER stress signature? Is it possible to stratify cancer patients according to UPR markers?

GLOSSARY BOX

Endoplasmic reticulum (ER): Arranged and dynamic tubular network involved in metabolic processes, such as gluconeogenesis, lipid synthesis and biogenesis of autophagosomes and peroxisomes. It is also the major intracellular calcium reservoir in the cell.

Proteostasis: a portmanteau of the words protein and homeostasis. Refers to the concept of integrated biological pathways within cells that control the biogenesis, folding, trafficking and degradation of proteins present within and outside the cell.

Endoplasmic Reticulum (ER) stress: a cellular condition generated when misfolded proteins accumulate inside the endoplasmic reticulum.

Unfolded protein response (UPR): A series of adaptive mechanisms triggered by ER stress to cope with protein-folding alterations through the transcriptional regulation of proteins involved in folding and clearance capacity in order to restore ER proteostasis.

ER-associated degradation (ERAD): A pathway to eliminate misfolded proteins along which proteins are transported from the ER to the cytosol for further degradation by the proteasome.

Proteotoxicity: Pernicious condition generated by an exacerbated increase of proteins or the presence of misfolded proteins.

Regulated IRE1-dependent decay (RIDD): The degradation of a subset of mRNAs encoding for proteins located in the endoplasmic reticulum and microRNAs through the activation of the RNase domain of IRE1.

FIGURE LEGENDS

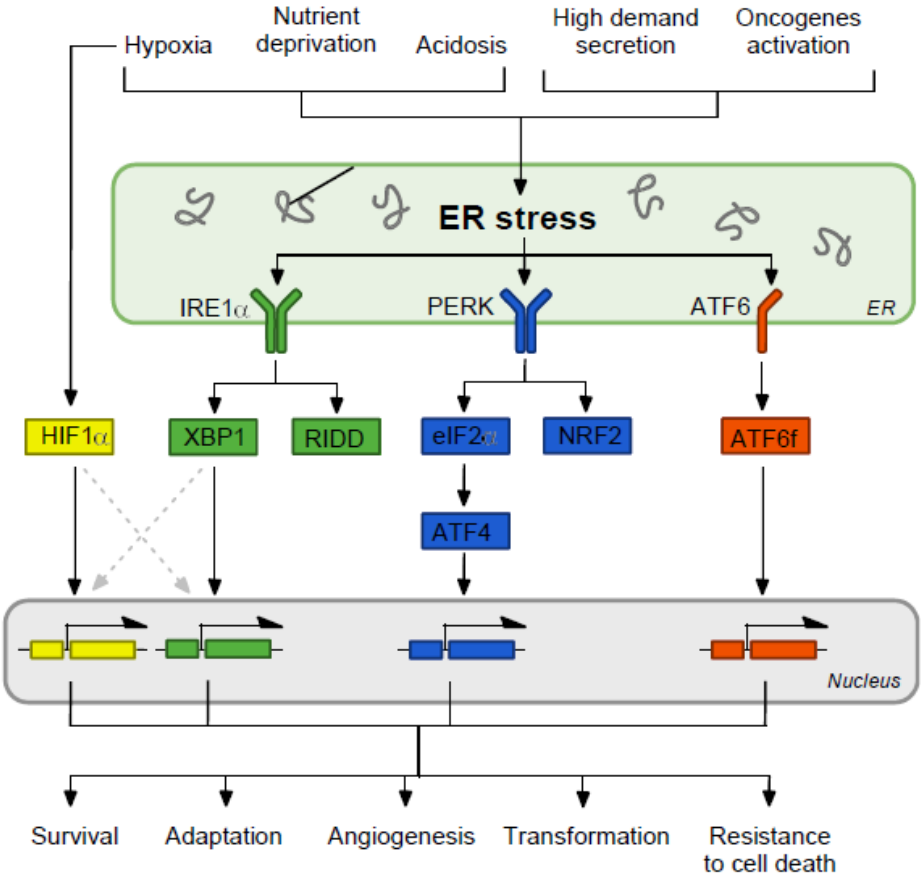

Figure 1. Classical role of the Unfolded Protein Response in tumorigenesis.

Different extrinsic (hypoxia, acidosis and nutrient deprivation) and intrinsic (high demand of secretion and activation of oncogenes) factors causes Endoplasmic reticulum (ER) stress and triggers the Unfolded protein response (UPR). Upon ER stress, the Inositol-requiring enzyme 1 (IRE1α) endoribonuclease activity regulates the expression of the transcription factor X-box binding protein-1s (XBP1s), in addition to induce degradation of several mRNAs by Regulated IRE1-dependent decay (RIDD). PKR-like ER kinase (PERK) signaling blocks general translation through eukaryotic translation initiation factor 2α (eIF2α) phosphorylation and regulates de expression of Activating transcription factor 4 (ATF4). Activating transcription factor 6 (ATF6) is cleaved at the Golgi and generates de active transcription factor ATF6f. Together, XBP1s, ATF6f and ATF4 regulate the expression of several genes that ultimately induces adaptation, survival, transformation, angiogenesis and cell death resistance in tumor cells. In addition, some of these features are mediated through a crosstalk with Hypoxia-inducible factor 1α (HIF1α).

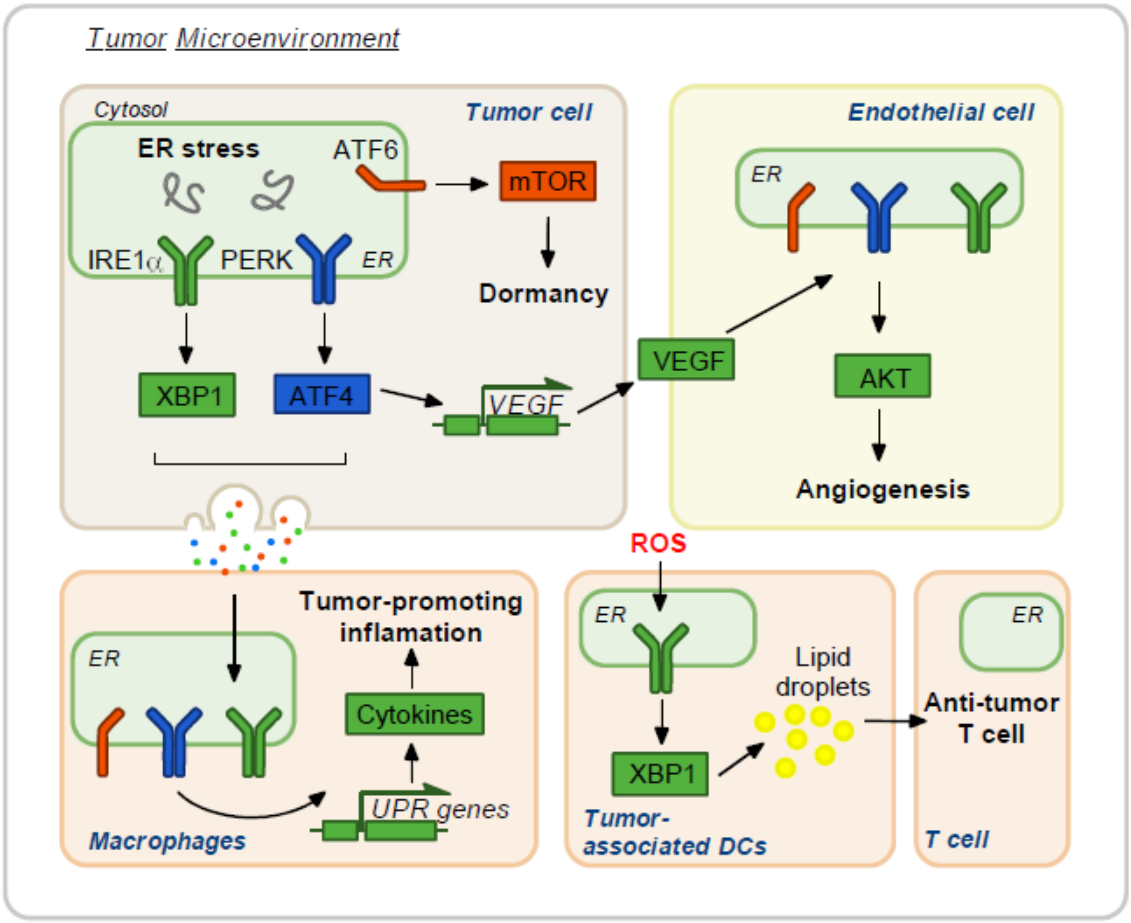

Figure 2. Novel outputs of the UPR in tumor microenvironment.

Endoplasmic reticulum (ER) stress in tumor cells leads to the activation of Activating transcription factor 6 (ATF6) that contributes to tumor dormancy through Rheb and mTOR. Activation of Inositol-requiring enzyme 1 (IRE1α) and PKR-like ER kinase (PERK) in tumor cells induces the expression of vascular endothelial growth factor (VEGF). VEGF induces the activation of the three branches of the Unfolded protein response (UPR) on an ER stress independent-manner in the endothelial cells. These pathways in endothelial cells are involved in survival and angiogenesis. Tumor cells secrete different unknown factor that induce the activation of the UPR in macrophages. This event upregulates UPR target genes and pro-inflammatory cytokines leading to tumor-promoting inflammation. The production of Reactive oxygen species (ROS) in tumor-associated dendritic cells induces IRE1α activation and X-box binding protein-1s (XBP1s) expression leading to abnormal lipid accumulation, formation of lipids droplets and the inhibition of dendritic cells function.

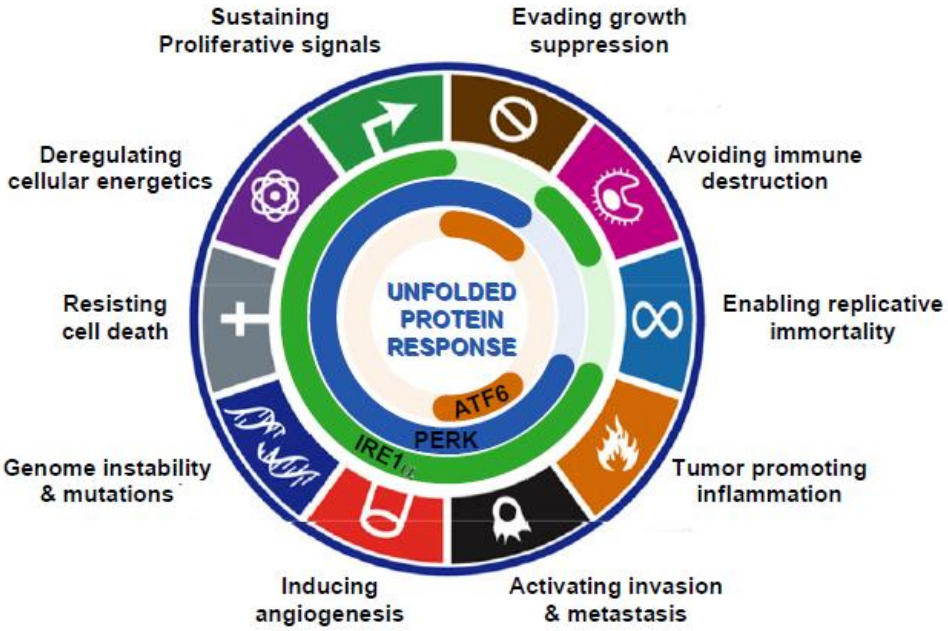

Figure 3. ER stress and the hallmarks of cancer.

Cancer cells acquire several features that allow disease progression. The Unfolded protein response (UPR) is involved in most hallmarks of cancer [1]. Activating transcription factor 6 (ATF6) is mostly linked to metastasis and dormancy; however, Inositol-requiring enzyme 1 (IRE1α) signaling has been linked to most hallmarks except tumor dormancy. Data available suggests that the PKR-like ER kinase (PERK) pathway has a more diverse functions in processes related to tumor growth and cancer progression.

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