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Review

Cell intrinsic and extrinsic activators of the unfolded protein response in cancer: Mechanisms and targets for therapy

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ABSTRACT

A variety of cell intrinsic or extrinsic stresses evoke perturbations in the folding environment of the endoplasmic reticulum (ER), collectively known as ER stress. Adaptation to stress and re-establishment of ER homeostasis is achieved by activation of an integrated signal transduction pathway called the unfolded protein response (UPR). Both ER stress and UPR activation have been implicated in a variety of human cancers. Although at early stages or physiological conditions of ER stress, the UPR generally promotes survival, when the stress becomes more stringent or prolonged, its role can switch to a pro-cell death one. Here, we discuss historical and recent evidence supporting an involvement of the UPR in malignancy, describe the main mechanisms by which tumor cells overcome ER stress to promote their survival, tumor progression and metastasis and discuss the current state of efforts to develop therapeutic approaches of targeting the UPR.

1. Introduction

The endoplasmic reticulum (ER) is an extensive membranous network found in all eukaryotic cells. The ER regulates calcium (Ca^{2+}) homeostasis, lipid biogenesis and folding of secretory and membrane bound proteins. The complexity of the ER depends on the predominant functions of the cell type. For example, highly secretory cells such as pancreatic islets, immune B cells and endothelial cells demand a well-developed ER to perform their functions. Proper protein folding and post-translational modifications (glycosylation and lipidation) require both an oxidizing and a Ca^{2+}-rich environment, which is accomplished by the high concentrations of ER chaperone proteins, such as the glucose-regulated protein 78 (GRP78, also known as BiP), calnexin, calreticulin and protein disulfide isomerases (PDI). Many of these chaperones are Ca^{2+} dependent, underscoring the significance of maintaining the ER Ca^{2+} concentrations at high levels [1,2]. Depletion of Ca^{2+} levels, oxidative stress caused by reactive oxygen species (ROS), low oxygen (hypoxia) or glucose deprivation encountered in pathological conditions (malignancy, neurodegenerative diseases, viral infections), affect ER homeostasis, leading to the accumulation of unfolded/misfolded proteins, known as "ER stress" [3]. To overcome these perturbations, a set of signal transduction pathways are activated which are collectively named the unfolded protein response (UPR) [4]. (Fig. 1).

In mammalian cells, there are three major ER stress sensors, pancreatic ER kinase (PKR)-like ER kinase (PERK), inositol-requiring enzyme 1 (IRE1) and activating transcription factor-6 (ATF6), whose main role is to convey the signal from the ER lumen to cytoplasm and nucleus in order to initiate mechanisms to alleviate ER stress [4]. Primarily, cells aim to restore ER homeostasis by increasing the ER capacity, reducing the load of newly synthesized proteins in the ER lumen through inhibition of global protein synthesis and by enhancing ER associated degradation of misfolded proteins (ERAD) [5,6]. However, if the ER stress persists or ER homeostasis cannot be restored, the role of the UPR tilts toward cell death primarily by initiating apoptosis [7,8]. The UPR pathway integrates transcriptional and translational responses that enable cells adapt to both cell autonomous and non-cell autonomous stresses. This pathway is often co-opted by cancer cells to promote growth and survival in unfavorable conditions. In this review, we will highlight the role of the UPR signaling in cancer and discuss new developments in the field with an emphasis on new therapeutic opportunities targeting ER stress pathways.

2. Evidence of UPR involvement in cancer

Activation of all arms of the UPR has been widely reported in a variety of human tumors including glioblastoma, lymphoma, myeloma and carcinoma of the cervix and breast [9–12]. Tumor

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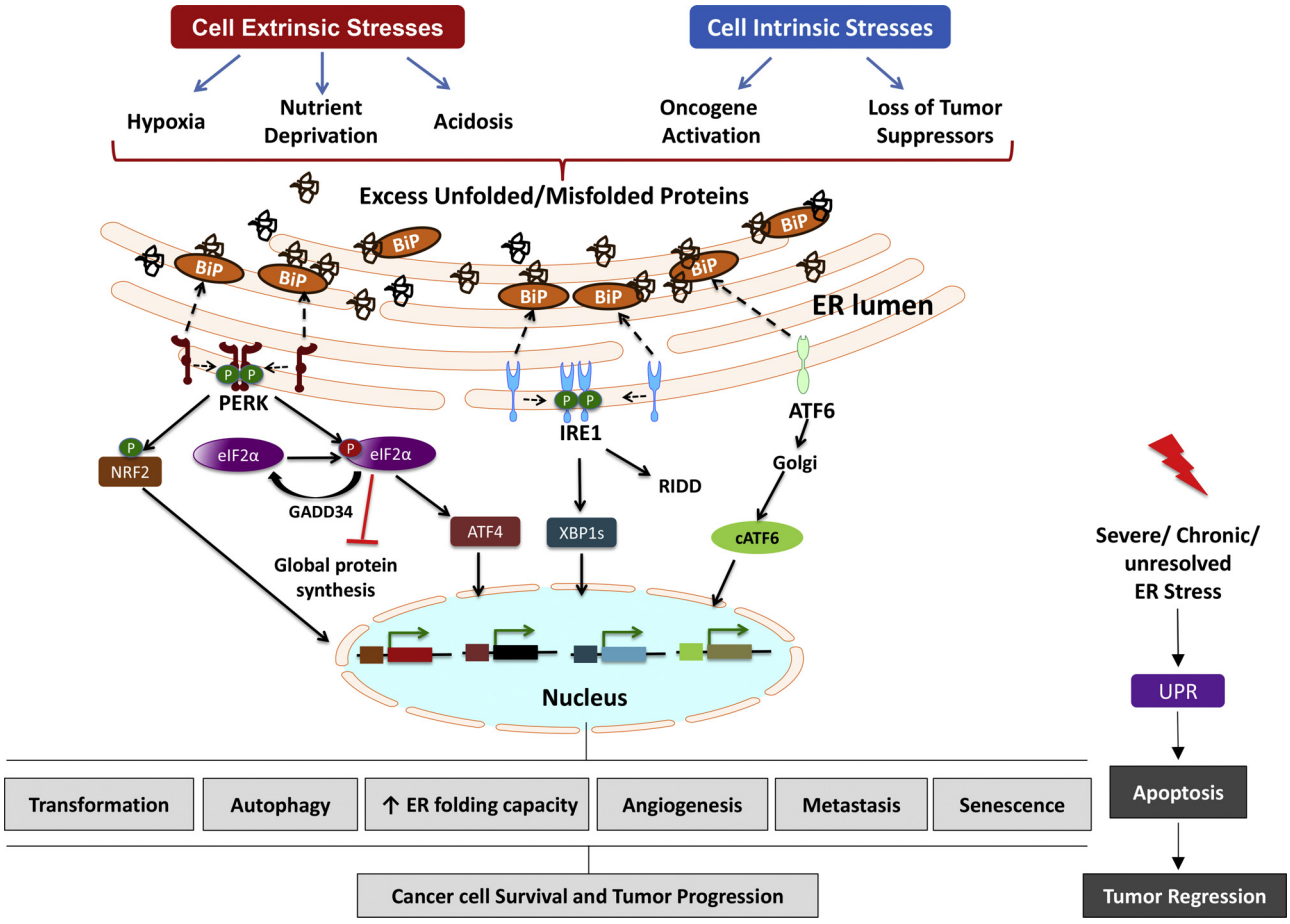

Fig. 1. Cell extrinsic stresses such as hypoxia, nutrient deprivation and acidosis as well as cell intrinsic stresses that result from oncogene activation and loss of tumor suppressors lead to accumulation of unfolded/misfolded proteins in the ER creating an imbalance between nascent polypeptides and chaperones. Upon ER stress, GRP78 (BiP) is titrated away from ER resident transmembrane proteins to help fold nascent polypeptides and misfolded proteins. Activation of PERK, IRE1 and ATF6 is often seen in tumors and found to be important in regulating processes such as transformation, autophagy, ER folding capacity, angiogenesis, metastasis and senescence, thus promoting tumor initiation and progression. However during chronic or severe ER stress that cannot be mitigated, the UPR can also elicit apoptosis which promotes tumor regression. Thus, the UPR can be a double-edged sword during tumorigenesis.

cells are often characterized by increased rates of protein synthesis and also face conditions of glucose and oxygen deprivation in the tumor microenvironment [13,14]. Adaptation to such adverse conditions requires an ER with enhanced folding capacity achieved by increased presence of chaperones and folding enzymes. Indeed, elevated levels of ER chaperones such as GRP78 and GRP94 have been widely reported in tumors and associate with poor outcome and recurrence [15]. Historically, the glucose-regulated proteins were found to be induced during glucose starvation and subsequently their expression was shown to also be increased during ER stress [16,17]. Specifically, GRP78 was shown to promote tumorigenesis through the regulation of proliferation, invasion and metastasis, angiogenesis as well as therapy resistance through extensive studies in cell culture and transgenic mouse models of cancer [18–21].

GRP78 has been firmly established as a major regulator of the ER stress sensors PERK, IRE1 and ATF6 [22]. According to the current models, in non-stressed conditions, GRP78 associates with PERK, IRE1 and ATF6 keeping them in an inactive state. During ER stress, GRP78 dissociates from the ER stress sensors to aid in the folding of nascent polypeptides, resulting in activation of the UPR transducers [23]. Upon GRP78 dissociation, PERK is activated through oligomerization and transautophosphorylation [24]. Active PERK regulates translation through phosphorylation of the alpha subunit of eukaryotic initiation factor (eIF2α) at serine 51 [25]. This phosphorylation prevents the exchange of guanidine diphosphate (GDP) to guanidine triphosphate (GTP) on eIF2α [26]. Thus, by decreasing the pools of GTP-bound eIF2α, PERK transiently inhibits global translation, reducing the influx of nascent polypeptides to the ER and allowing time for recovery. Concomitant with suppression of translation, phosphorylation of eIF2α enhances the preferential translation of select mRNAs such as the transcription factor ATF4. ATF4 induces the transcription of chaperones, antioxidants and autophagy promoting genes [27,28]. Moreover, ATF4 relieves translation inhibition by indirectly upregulating growth arrest and DNA damage gene 34 (GADD34), a protein phosphatase 1 (PP1) cofactor, responsible for eIF2α dephosphorylation, completing a negative feedback loop [29]. In addition to eIF2α, PERK phosphorylates the transcription factor NF-E2-related factor-2 (NRF2), which promotes redox homeostasis [30].

The PERK arm of the UPR has been implicated in tumor initiation and progression in both solid and hematological cancers [9,10,31]. PERK was shown to play a major role in tumor growth *in vivo* in a xenograft model of RAS^{V12}-transformed mouse embryonic fibroblasts (MEFs). PERK deficiency resulted in significantly reduced tumor size compared to WT tumors. Similar results were observed with colon carcinoma cells expressing a dominant-negative PERK construct [9]. Furthermore, PERK deficiency significantly reduced tumor proliferation, growth and vascularity in a transgenic mouse model of insulinoma (pancreatic beta cell tumor), demonstrating the role of PERK in tumor growth *in vivo* through promoting cell cycle progression and angiogenesis [32]. In a mouse breast cancer model of tumorigenesis, loss of PERK also led to a reduction