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MINI-REVIEW

ER stress mediated inflammation in cancer pathogenesis

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ABSTRACT

Inflammation is a complex process which is associated with the initiation and progression of cancer. Prolonged Endoplasmic Reticulum (ER) stress triggers inflammation which is a key factor associated with cancer pathogenesis. ER stress also contributes to immune suppression in inflammatory and tumor microenvironment. It stimulates the production of pro-inflammatory cytokines by regulating the activation of various transcription factors and inflammatory signalling pathways. Targeting ER stress is an exciting possibility that can be used as a therapeutic strategy for cancer treatment. This mini review focuses on the emerging link between ER stress-induced inflammatory responses in cancer development.

Keywords: ER stress; inflammation; cancer; UPR response

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1. Introduction

The endoplasmic reticulum (ER) is a large membrane enclosed cellular organelle seen in all eukaryotic organisms. ER has several essential cellular functions including the synthesis and folding of secreted and transmembrane proteins, calcium storage, and lipid synthesis for membrane biogenesis or energy storage. ER also helps in maintenance of calcium homeostasis and regulation of intracellular signalling pathways[1]. Disruption of any of the ER functions can lead to ER stress. ER stress can occur due to physiologic stresses, such as increased secretory load, or pathological stresses, such as the presence of mutated proteins that cannot properly fold in the ER, ultimately leading to an imbalance between the demand for protein folding and the capacity of the ER for protein folding. To sense and respond to ER stress, eukaryotic cells have developed an elaborate network of adaptive responses that are collectively known as the unfolded protein response (UPR). The UPR re-establishes homeostasis *in vivo* through transcriptional and translational control with the help of three mechanistically distinct signaling events that are initiated by the ER-resident protein folding sensor inositol-requiring enzyme 1 (IRE1), protein kinase RNA-like endoplasmic reticulum kinase (PERK), and activating transcription factor 6 (ATF6)[2]. These proteins bear domains protruding into the ER lumen, which sense ER stress, coupled to cytosolic effector domains. Protein folding is an error prone process tightly regulated by

several molecular chaperons and enzymes. One of the best-characterized ER chaperones is the 78-kDa glucose-regulated protein (GRP78), also known as BiP or HSPA5. Normally, the three trans-ER membrane proteins bind specifically to GRP78 in the ER lumen and when ER stress occurs, GRP78 dissociates, binds to unfolded or misfolded proteins in the lumen to aid in correct folding and triggers downstream pathways and effector mechanisms that remodel the ER to restore homeostasis *in vivo*[3]. However, the UPR may not always play the protective role in regulating homeostasis. In response to chronic or severe ER insults that cannot be alleviated through protective remodelling, prolonged UPR activation leads to pro-apoptotic signalling leading to ER dysfunction and disease[4].

Numerous studies have shown that ER stress is closely related to multiple pro-inflammatory signalling pathways such as PI3K/AKT and NF-κB. These signalling pathways are involved in the transformation of inflammation to cancer. In cancer cells, UPR maintains various stresses (including oxidative stress), and studies have shown that UPR signalling pathways are closely related to autophagy, apoptosis, inflammatory response and oxidative stress in tumor cells. Therefore, UPR is currently considered to play a key role in tumor progression, metastasis, tumorigenesis and survival[5]. In this mini review we will focus on the relationship between ER stress and UPR on the various inflammatory responses in cancer.

2. ER stress in cancer cells

Hypoxia, nutrient deprivation and oxidative stress are some of the factors which cause ER stress in cancer cells. Eukaryotic cells have evolved the UPR machinery to guarantee the authenticity and integrity of protein folding and to prevent the misfolded proteins from accumulating in the ER. UPR response is through alteration of cellular transcription and translation programs. The stress state changes protein folding defects. When ER stress occurs, the UPR signalling pathways PERK, ATF6 and IRE1α attenuate protein translation processes and increase ER chaperones and protein degradation[6]. PERK, which is a type I ER transmembrane protein with the N-terminus located in the ER cavity, is known to have a dual role in cancer, tumor suppression and carcinogenic functions[7]. When proteins accumulate in the ER lumen, PERK undergoes homodimerization and autophosphorylation after GRP78 activation. In addition to this, protein accumulation causes the dissociation of PERK from kelch-like ECH-associated protein 1 (KEAP1) by nuclear translocation and activates phosphorylation of nuclear factor (erythroid-derived 2)-like 2 (NRF2). NRF2 and activating transcription factor 4 (ATF4) act synergistically as two different transcription factors and NRF2 recognizes ATF4 after activation during ER stress. It is also reported that PERK-dependent phosphorylation of eukaryotic initiation factor 2 (eIF2α) is regulated to attenuate translation of its mRNA. These attenuated mRNA-encoded proteins are often associated with cell survival and proliferation[8].

Though ATF4 is necessary for UPR to promote cell survival, it also plays an important role in the non-programmed death of cells through transcriptional upregulation of CHOP. The CHOP gene, in contrast to ATF4, inhibits cell growth and promotes DNA damage. Synergistic action of ATF4 and CHOP induces autophagy in a variety of cancer cells. PERK is also responsible for activation of nuclear factor-κB (NF-κB) in cancer cells. IRE1α is another signalling pathway that activates the NF-κB pathway under ER stress. When ER stress occurs, IRE1α is rapidly activated, and when ER stress is changed to chronic, the signal of IRE1α is weakened. This acts as a signal to block survival during chronic ER stress. Though the UPR response triggered by ER stress was originally thought to be a self-regulating way to protect cells from irreversible damage, when the damage exceeds the body's own tolerance, the UPR will signal a self-destruction to prevent further damage.

Cancer cells have a highly hypoxic and low glucose microenvironment. Under hypoxic conditions, the demand for protein synthesis in cancer cells is significantly lower than that of normoxic cells, accompanied by a decrease in protein translation rate, which is unfavorable for cancer cells. In an anoxic environment, the UPR reaction is activated and the UPR response is directly proportional to the stress conditions and the

severity of the unfavorable factors. UPR response is accompanied by apoptosis. The two cell types that support tumor growth in the tumor microenvironment when cancer cells proliferate and differentiate are immune cells and endothelial cells. The UPR reaction stimulates tumor cells to secrete metalloproteinases that regulate various angiogenic factors. In addition to this, the highly proliferative cancer cells activate the UPR response by disrupting the folding of ER proteins, allowing cancer cells to continue to grow in nutrient-deficient environments. Numerous studies have shown that malignant tumor growth, invasion and angiogenesis are associated with activation of the UPR signaling pathway leading to eIF2α phosphorylation.

3. ER stress mediated inflammation in cancer

ER stress is closely associated with the development of inflammation and chronic inflammation is a key process that leads to the development of cancer. Chronic inflammation enhances the tumor growth, survival and metastasis through inflammatory pathways and cytokines. Inflammatory cytokines regulate the tumor development by infiltrating into inflammatory cells in tumor tissue or tumor cells directly. ER stress induced UPR signalling pathway cross talk with NF- κB mediated inflammatory signalling pathway. ER stress sensor proteins, PERK, IRE1α and ATF6 activate inflammatory transcription factor, NF-κB[9] and thereby induce inflammatory response. ER stress induced UPR also activates AP-1 transcription factor which induces the transcription of inflammatory genes like cytokines, interleukins and TNF-α[10]. JNK/AP1 inflammatory signalling pathway cross talks with IRE1, ER stress signalling pathway[11]. ER stress response is reported to stimulate the expression of oncogene, Lipocalin 2 in NF- κB dependent manner[12] (see **Figure 1**).

ER stress driven inflammation is a key factor regulating tumorigenesis however recent reports show that ER stress driven inflammation can inhibit tumor development. Pro-inflammatory cytokine, NLRP3 is reported to inhibit colon cancer tumorigenesis[13]. Also Reactive oxygen species (ROS) production linked with ER stress can enhance apoptosis of cancer cells.

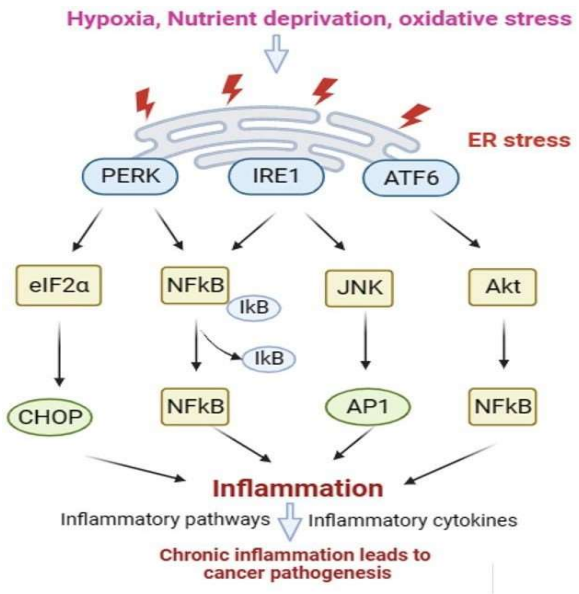

Figure 1. Schematic representation of ER-stress mediated inflammation in cancer development. Pathway has been created with BioRender.com

Modulating ER stress mediated inflammation in cancer as therapeutic strategy

ER stress mediated inflammation is a complex process which possesses both pro-tumorigenic and anti-tumorigenic effects. Inhibiting pro-tumorigenic effects and favouring anti-tumorigenic effects of ER stress induced inflammation is beneficial for therapeutic strategies. Pro-tumorigenic effects of ER stress induced

inflammation can be prevented by neutralising tumor growth promoting cytokines such as TNF-α, IL-6, IL-1, IL-23 and IL-17[14]. Pro-tumorigenic cytokines can be neutralised by treating with anti-cytokines and also antibodies to cytokine receptors[15]. Inhibiting ER stress activated transcription factor, NF-κB which is involved in the production of tumor-promoting cytokines is another treatment strategy. It has been reported that inhibition of NF-κB prevent the progression of inflammation induced tumor growth[16,17].

Another therapeutic strategy is the modulation of UPR response in cancer either by inhibiting UPR that causes pro-tumorigenic effect or by stimulating UPR associated with anti-tumorigenic action particularly by promoting ER stress in cancer cells thereby triggering apoptosis[18,19]. Axten et al.[20] and Atkins et al.[21] reported the anti-tumor activity of a novel PERK kinase inhibitor, GSK2656157. At the same time, another molecule HA15 exhibits anti-tumor activity through activation of UPR by inducing phosphorylation of PERK, eIF2α and ATF4 and CHOP. Conventional anti-cancer treatments can be coupled with these therapeutic strategies for an effective long term treatment effect.

4. Conclusion

ER stress occurs due to the accumulation of misfolded or unfolded proteins in the endoplasmic reticulum. ER stress leads to a cellular unfolded protein response, which helps to restore ER homeostasis by enhancing protein folding capacity and degrading misfolded proteins. However, during prolonged ER stress, the UPR response can induce inflammation. ER stress-mediated inflammation has been implicated in cancer and it can have both pro-tumorigenic and anti-tumorigenic effects. ER stress can promote cancer cell survival, proliferation and metastasis by activating and pro-inflammatory pathways of the UPR whereas it can also cause cancer cell apoptosis, which can elicit anti-tumor immune responses and improve the efficacy of immunotherapy. Therefore, understanding the molecular mechanisms involved in ER stress-mediated inflammation in cancer is essential for developing novel therapeutic strategies for modulating anti-tumor effects.

Conflict of interest

The authors declare no conflict of interest.

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