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Analysis on endoplasmic reticulum stress in the cancer cells

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Abstract. One consequence of being in a low-oxygen environment is endoplasmic reticulum (ER) stress, and the unfolded protein response (UPR) is one mechanism to alleviate this condition. In recent years, numerous researchers have proposed employing the UPR in cancer therapy. Apoptosis of cancer cells can be induced by targeting the UPR in a variety of ways. This can be triggered by a number of drugs, some of which induce ER stress while others suppress the unfolded protein response and hence cause death in cancer cells. Through a literature review and analysis, this paper will discuss ER stress in a hypoxic microenvironment, the role of the unfolded protein response in cancer cells, and the therapeutic targeting of the unfolded protein response's protective pathways in the treatment of cancer.

Keywords: endoplasmic reticulum stress, cancer cells, hypoxic tumor microenvironment.

1. Introduction

Endoplasmic reticulum (ER) stress is the result of a hypoxic microenvironment, and the UPR is a type of defense mechanism against ER stress. Numerous researchers have recently proposed employing the UPR in anti-cancer therapies. Apoptosis of cancer cells can be induced by various approaches that target the UPR pathway. Several drugs have been shown to enhance ER stress, and others have been shown to suppress the unfolded protein response in cancer cells, resulting in death.

This paper will utilize a literature review and analytical methods to discuss ER stress in a hypoxic microenvironment, the unfolded protein response, and their roles in cancer cells, as well as the therapeutic targeting of the unfolded protein response's protective pathways in the treatment of cancer. What is described in this section is a novel approach to cancer treatment that has the potential to become one of the most effective methods available.

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2. The hypoxic tumor microenvironment and roles of ER stress and UPR in the cancer cells

2.1. The hypoxic tumor microenvironment

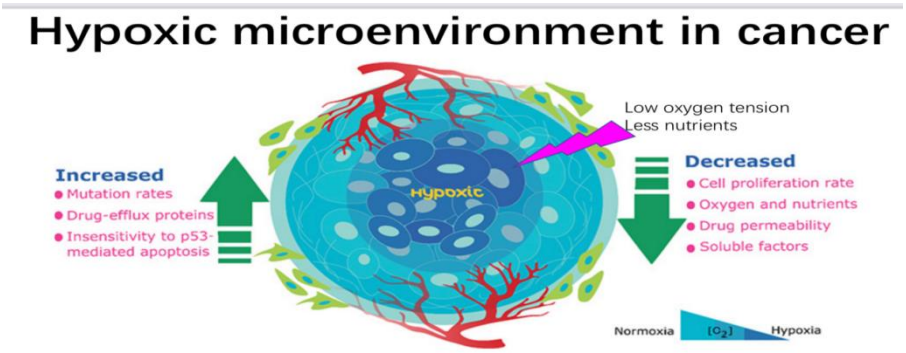

Figure 1. Hypoxic microenvironment in cancer [1].

Figure 1 shows that solid tumors rapidly outgrow their blood supply, resulting in oxygen concentrations in tumor locations that are much lower than those found in healthy tissues [2]. Increased rates of mutation, drug-efflux, and apoptosis evasion are observed in hypoxic cancer cells, whereas overall cell proliferation, drug solubility, and production of soluble cytokines and nutrients are all reduced.

2.2. Roles of ER stress and UPR in the cancer cells

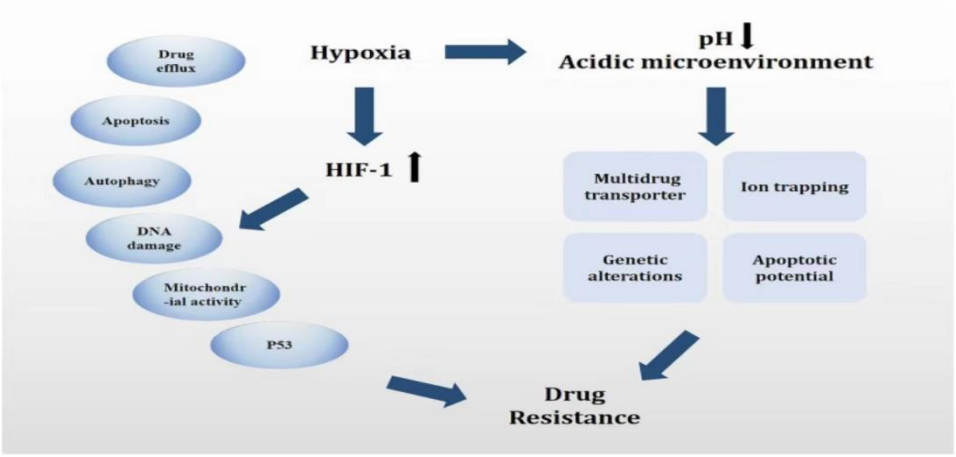

Figure 2. Inducers of ER stress in the tumor microenvironment [3].

Figure 2 depicts how unrestrained cancer cell proliferation in developing tumors creates an unfriendly microenvironment with high metabolic demand, hypoxia, nutritional constraints, and acidosis, disrupting calcium and lipid homeostasis in several cell types. ER stress is caused by the buildup of misfolded or unfolded proteins within the ER as a result of the cumulative effect of these adverse conditions on cancer cells and invading immune cells. As a result of oncogenic processes, cancer cells exhibit increased global transcription and translation rates [3]. In an effort to increase adaptability to various stressors and return the ER to homeostasis, the tumor then activates the UPR. Depending on the level of ER stress, certain therapeutic methods can cause cancer cells to behave abnormally in the tumor microenvironment (TME) [3]. That is the cancer cell microenvironment that this paper is concerning, and it is what causes ER stress.

3. Cancer treatment by targeting UPR protective pathways

This section of the paper summarizes the mechanisms and pathways that lead to ineffective medication therapy in the presence of HIF. Apoptosis, autophagy, DNA damage, mitochondrial activity, p53, and drug efflux are only some of the signaling pathways that HIF-1 activates to impart resistance to

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conventional therapy. In addition, hypoxia lowers pH, making the TME more acidic. Tumor acidic microenvironment contributes to multidrug resistance through several mechanisms, including lower drug concentration due to "ion trapping," diminished apoptotic potential, genetic abnormalities (such as p53 mutations), and increased activity of a multidrug transporter p-glycoprotein (P-gp) [3]. Figure 3 depicts two potential approaches to cancer treatment that focus on the UPR perspective. Both medications that raise the consistent intensity of ER stress and those that block the UPR components can be used to induce apoptosis in cancer cells.

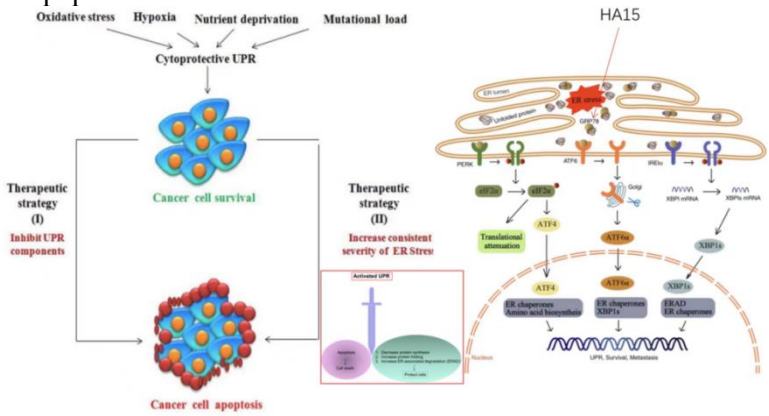

Figure 3. Two main ways to cause the cancer cell apoptosis by using UPR [3].

4. Transmissible ER stress

As seen in figure 4, cancer cells can transfer ER stress to nearby myeloid cells in the TME via soluble substances such TEVs, proteins, or lactic acid. The molecule(s) that increase ER stress in receptive myeloid cells through TLR-4 remain unclear. It has been demonstrated in figure 5 that TERS suppresses T cell activation and proliferation by decreasing DC antigen-presenting ability, disrupting DC lipid metabolism, and increasing TAM/MDSC CHOP expression and arginase 1 production [4]. This weakens the body's ability to fight tumors and speeds up the spread of cancer.

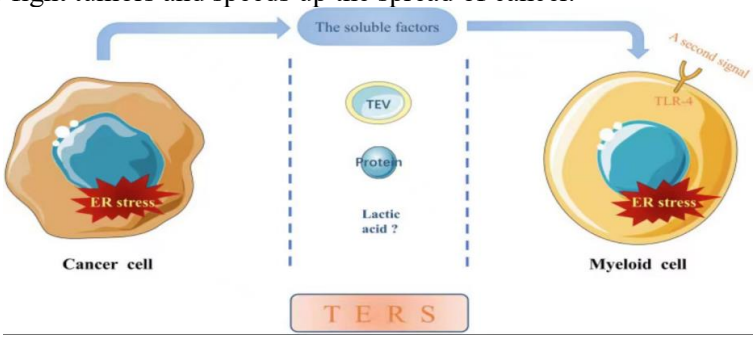

Figure 4. The soluble factors mediating TERS [4].

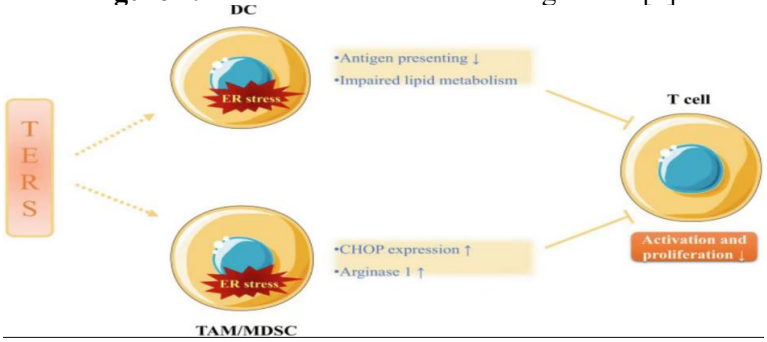

Figure 5. The immunosuppressive effects of TERS [4].

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4.1. Inducers of ER stress in the tumour microenvironment

As tumors grow, malignant cells multiply unrestrained, creating a toxic microenvironment that involves elevated metabolic demand, hypoxia, nutritional restrictions, and acidosis that disrupts cell calcium and lipid homeostasis. These challenges impede the endoplasmic reticulum's (ER) capacity to fold proteins, resulting in ER stress in cancer cells and invading immune cells. Furthermore, cancer cells' global transcription and translation rates are increased due to oncogenic processes. The unfolded protein response (UPR) is then engaged to enable adaptability to multiple tumor insults and reestablish ER homeostasis [1]. The typical behavior of cancer cells in the TME can be altered by treatment techniques that induce ER stress. ER stress can trigger cellular reprogramming, adaptability, autophagy, or death depending on the variety of cells, intensity, and clinical situation. UPR activation occurs strongly and continuously in cancer cells and immune cells that penetrate tumors in vivo due to the combined impact of numerous ER stressors simultaneously amplified within the TME throughout cancer commence, development, and treatment [1].

4.2. The magnitude of ER stress and its differential outcomes in malignant cells

Oncogenic pathways, alterations in metabolism, and the tumor microenvironment cause low-grade but persistent endoplasmic reticulum (ER) stress responses, which stimulate multiple mechanisms that aid cancer cell growth, metastasis, chemoresistance, angiogenesis, and immune evasion (Figure 6). A terminal UPR can also cause dying of cells in response to excessive ER stress caused by misfolded protein accumulating in this organelle that exists. Multiple myeloma cells induce proapoptotic ER stress responses through hyperactivation of the PRKR-like ER kinase (PERK)-eukaryotic translation initiation factor 2 (eIF2)-activating transcription factor 4 (ATF4)-C/EBP homologous protein (CHOP) arm of the UPR [1]. Due to ER stress reactions that increase immunogenic cell death (ICD), some cytotoxic medicines, such as anthracyclines, can induce antitumor immunity (BOX 2). Thus, UPR activation promotes life or death depending on stress kind and duration.

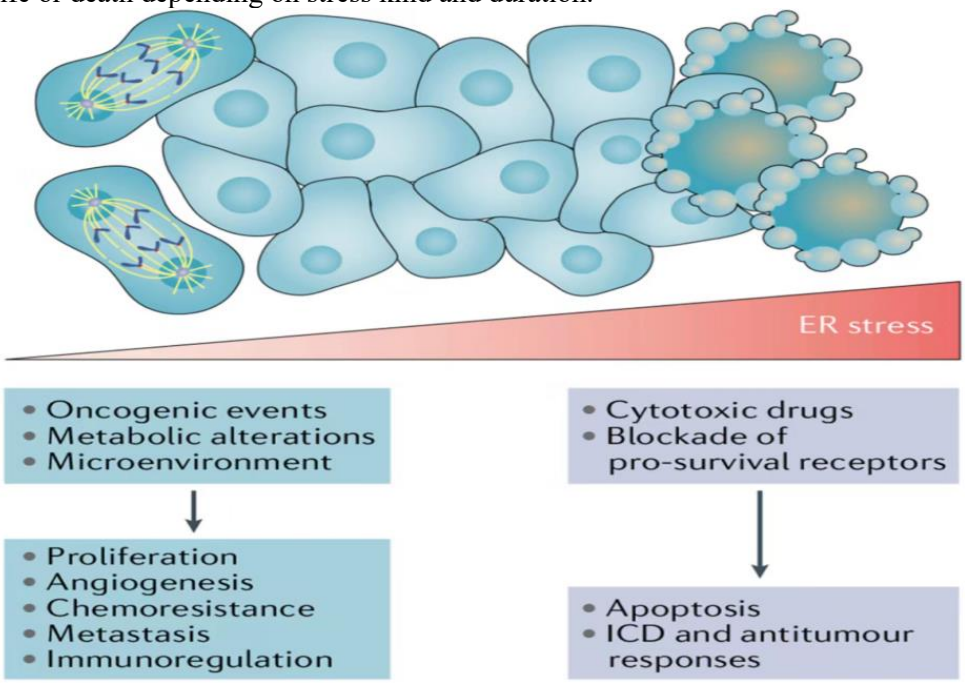

Figure 6. The magnitude of endoplasmic reticulum stress and its differential outcomes in malignant cells [1].

4.3. Integration of oncogenic programmes and ER stress responses in the cancer cell

Multiple pathways stimulate the UPR by oncogenic MYC. All branches of the unfolded protein response are activated by MYC-induced worldwide transcription and translation upregulation, which increases

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ER protein manufacturing and protein load (Figure 7). MYC interacts to promoter and enhancer regions of the 1α (IRE1α) gene, positively regulating transcription and boosting IRE1α protein levels. MYC and XBP1s can form a heterodimer in the nucleus and regulate traditional unfolded protein response (UPR) and lipid metabolism genes. Prostate cancer and NK cell XBP1s enhance MYC transcription. MYC binds PERK and GCN2 to start the integrated stress response and eIF2α phosphorylation [1]. MYC controls amino acid transporters, biosynthesis, antioxidant pathways, and autophagy via ATF4. 4EBP1 is modulated by MYC-ATF4 to minimize translational and proteotoxic stress. When mTORC1 is active, protein synthesis and ER excess generate unfolded protein [1]. IRE1α-TNFR-associated factor 2-JUN N-terminal kinase-IRS1 axis restricts mTORC1 [1]. The UPR integrates mutant RAS contextually. Mutant HRAS stimulates IRE1 in keratinocytes. Unlike BRAF-V600E, HRAS-G12V-PI3K raises ER content and activates all UPR branches in primary human melanocytes. Mutant RAS boosts global protein translation and ER protein load in all cancers to an unknown level.

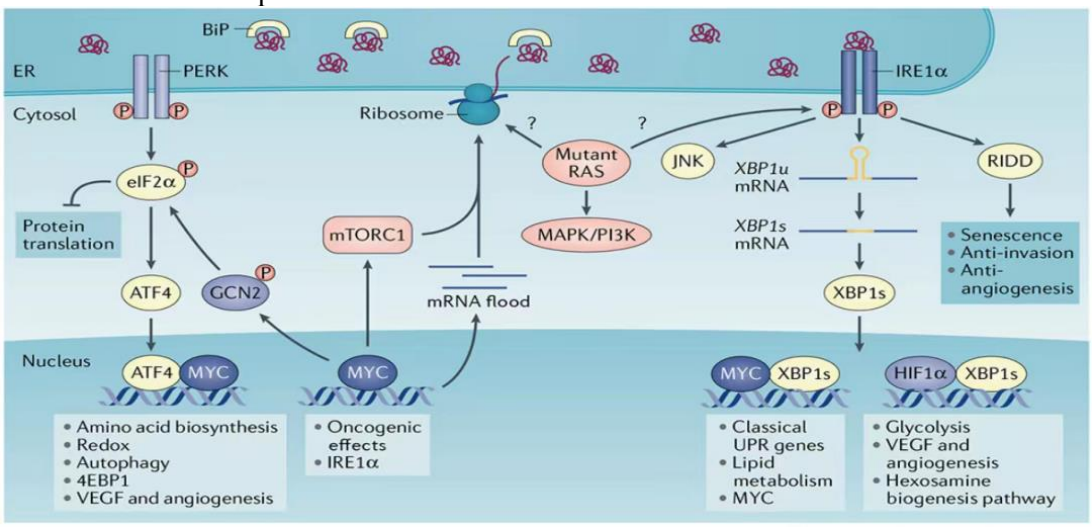

Figure 7. Integration of oncogenic programmes and endoplasmic reticulum stress responses in the cancer cell.

4.4. Immunomodulatory effects of ER stress signals in the tumour microenvironment

IRE1α or PERK cancer cells release mediators that boost angiogenesis and myeloid cell migration to tumor sites, altering NK cell tumor detection (Figure 8). IRE1α and PERK control angiogenesis. XBP1s and ATF4 bind the promoter to control VEGF [1]. Nutrient deprivation, ROS accumulation, or soluble chemicals that limit glucose uptake cause ER stress and prolonged activation of the unfolded protein response (UPR) arms IRE1α-XBP1 and PERK-C/EBP homologous protein (CHOP) in intratumoral T-cells [1]. High TME cholesterol enhances intratumoural T cell IRE1α-XBP1 signaling and PD1 production. MDSCs suppress type I interferon via NRF2-driven PERK responses [1]. CHOP regulates T-cell suppressors. TME turnover and TRAIL-R expression stress MDSC ER. Cancer PMN-MDSCs and normal neutrophils express LOX1 and other ER stress-related genes differentially. IRE1α overexpresses LOX1 and immunosuppresses ER-stressed neutrophils. ROS-induced ER stress, prolonged IRE1α-XBP1 activation, and uncontrolled lipid droplet formation prevent tumor-associated DCs from delivering local antigens to intratumoral T cells. IRE1α/XBP1-activated ER-stressed DCs generate immunosuppressive PGE2. Cancer may circumvent immune system. TME cancer cell invasion and immunosuppression are promoted by macrophage IRE1α-XBP1 branch production of cathepsins, PDL1, and Arginase 1.

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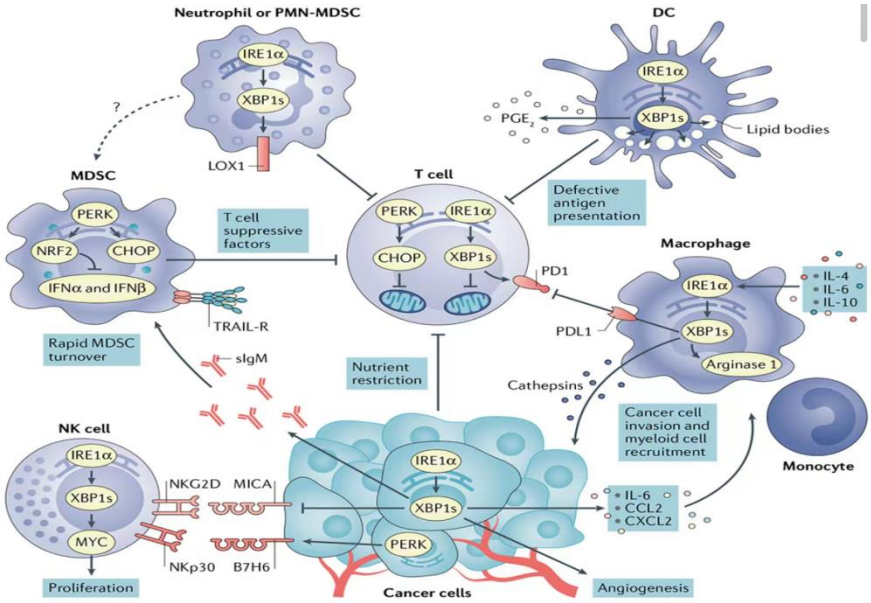

Figure 8. Immunomodulatory effects of ER stress signals in the tumour microenvironment [4].

In addition, in terms of malignant transformation mediated by oncogene, protein perone malfunction increases biosynthetic and bioenergetic demand, leading early ER stress. As tumors grow, they face oxygen and food restriction, lactic acidosis, and therapeutic interventions [2]. Reducing crucia reaction intermediates such 2, N-acetylglucosamine or directly interfering with chaperone activity through reactive oxygen species-mediated lipid may impede ER protein folding.

4.5. Consequences of ER stress in cancer cells

Multicellular 58(IPK), BiP autophagy, and FTa.IRE1α, PERK, and ATF6a sublethal UPR signaling maintains N F2, Nf-KB pathways. ER stress-mediated activation of HIF1α, STAT3, NRF2, and NFkB helps cells survive challenging microenvironments and maintain tumor initiating cell activity [2]. Cytokine-driven angiogenesis feeds tumors, while IRE1α-deficient cells exploit vascular co-option. Cancer cells exploit ER stress to grow with apoptotic resistance.

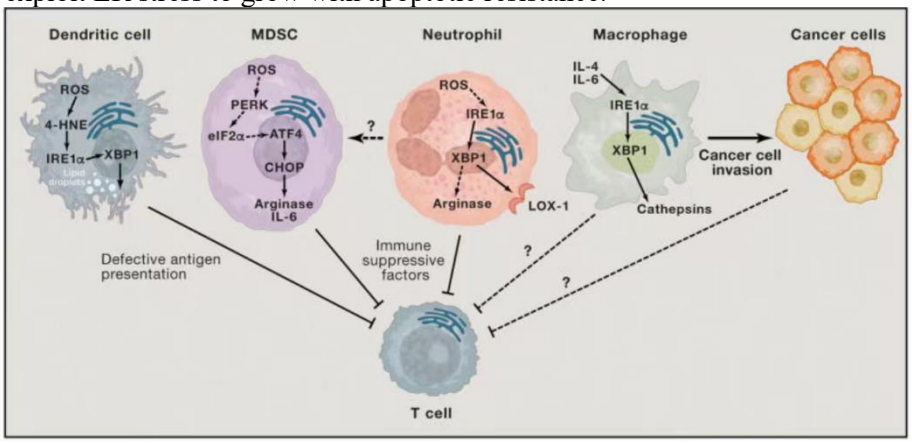

Figure 9. Effects of ER stress in cancer- associated myeloid cells [2].

4u8c, MKC-3946, along with B-109 block the IRE1α RNAse domain, blocking Xbp1 mRNA splicing [2]. IRE1α inhibitors may reduce cancer cell hypoxia, angiogenesis, treatment resistance, and metastasis. These substances reprogramme cancer-linked myeloid cells such macrophages, dendritic cells, and neutrophils. SiRNA-loaded nanoparticles may reduce ERN1 or XBP1 in ovarian cancer-associated DCs [2]. DC cancer therapeutic vaccines could block the IRE1α-XBP1 signaling pathway

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using novel genome-editing technologies. Recent PERK and elF2α inhibitors may reduce MDSC CHOP overexpression and tumor microenvironment immunosuppression. Non-CHOP MDSCs have not been explored for PERK/elF2α [2]. Malignancies may influence immune cell function via the UPR component ATF6α [5].

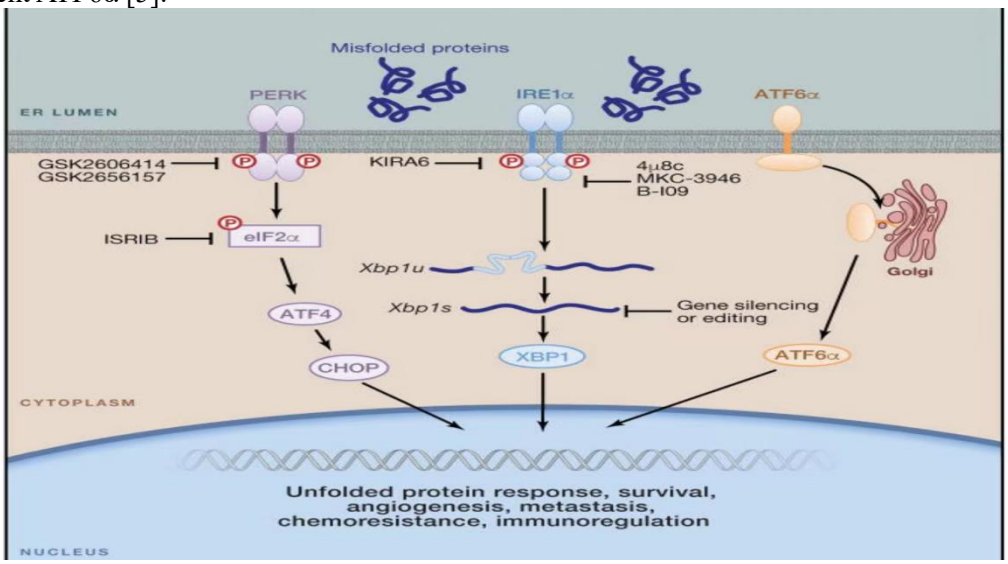

Figure 10. Therapeutic strategies to control ER stress responses in cancer [2].

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5. Conclusion

The research outlined hypoxic microenvironment and ER stress and explained how ER stress is counteracted by the unfolded protein response. In addition, the report highlights the two primary approaches to treating cancer by focusing on the UPR perspective. How soluble factors convey ER stress from cancer cells to myeloid cells is also discussed, as is the formation of ER stress and the Unfolded protein response. However, there are still a number of issues with those research. For instance, researchers have not conducted sufficient samples to draw firm conclusions about the efficacy of certain treatments. In addition, the scope of some studies prevents us from drawing firm conclusions on applications and procedures. There are now two main approaches to cancer treatment, both of which aim to inhibit the unfolded protein response. Although the treatment of cancer by targeting the unfolded protein response is still being worked out on paper, it remains a very optimistic answer to the human cancer problem. Those methods on paper may become reality in a few years.

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