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IRE-1alpha Signaling as a Key Target for Suppression of Tumor Growth

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Abstract

Activation of cell proliferation and surviving as well as an increased angiogenesis are important for tumor growth through signaling pathways of the unfolding protein response/endoplasmic reticulum stress, which is a fundamental phenomenon for secure protection of cells by maintaining the functional integrity of the endoplasmic reticulum. The unfolding protein response aims to resolve stress by expanding the protein-folding apparatus, decreasing the load of newly synthesized proteins, and enhancing the degradation and removal of improperly folded proteins from the endoplasmic reticulum by a process termed ERAD (endoplasmic reticulum-associated degradation). Endoplasmic reticulum stress is mediated by three sensor and signaling pathways (PERK, ATF6, and IRE-1α), which are important for tumor cell survival and proliferation, but the IRE-1α signaling is more significant. It is important to note that the aberrant IRE-1α signaling occurs in various cancers and thus can serve as a target for the development of new treatment of these disorders. The inhibition of IRE-1α leads to a decrease of tumor growth through suppression of angiogenesis and cell proliferation and activation of tumor suppressor and some apoptotic genes. Data concerning the molecular mechanisms of the effect an inhibition of IRE-1α signaling enzyme on glioma growth is discussed, including the changes in the expression of genes controlling angiogenesis, cell proliferation, and cell cycle. A better understanding of the biological role of IRE-1α is necessary to develop novel, original IRE-1α modulators and help to define the best therapeutic targets for the design of effective antitumor drug.

Keywords: Tumor growth; Endoplasmic reticulum stress; Inhibition of IRE-1α; Glioma cells; Angiogenesis; Cell cycle; Proliferation; Tumor suppressors

Introduction

The endoplasmic reticulum is a dynamic intracellular structure with exquisite sensitivity to alterations in homeostasis, and provides stringent quality control systems to ensure that only correctly folded proteins transit to the Golgi and improperly folded proteins are retained and ultimately degraded by a process termed ERAD (endoplasmic reticulum-associated degradation) [1]. The unfolding protein response is triggered by the disruption of endoplasmic reticulum homeostasis, also known as endoplasmic reticulum stress, which is a fundamental phenomenon for secure protection of cells by maintaining the functional integrity of the endoplasmic reticulum [2,3]. Malignant tumors use the unfolding protein response as well as hypoxia-induced signaling pathways to metabolic reprogramming of cancer cells and enhance cell proliferation and surviving under stressful environmental conditions [4-6]. Thus, the rapid growth of solid tumors generates micro-environmental changes in association to nutrient deprivation, hypoxia, and acidosis, which strongly induce cell proliferation and new blood vessels formation mainly through the activation of endoplasmic reticulum stress signalling pathways [5,7].

Endoplasmic Reticulum Stress Signaling Pathways

The unfolded protein response is mediated by at least three sensor and signaling pathways: inositol-requiring enzyme- 1α (IRE-1α), activating transcription factor 6 (ATF6), and double stranded RNA activated protein kinase (PKR)-like endoplasmic reticulum kinase (PERK) [3,8]. All three parts of this stress response are integrated and important for tumor growth and cell survival especially under hypoxic and nutrient deprivation conditions. However, endoplasmic reticulum stress signaling is mainly mediated through the IRE-1α pathway, which is the most evolutionary, conversed and represents a key regulator of the life and death processes [4,5,9]. A better understanding of tumor responses to different signaling pathways of the endoplasmic reticulum stress is required to elaborate acceptable therapeutical strategies of cell sensibilization, based on the suppression of key survival mechanisms including the IRE-1α pathway [9,10].

In terms of physiology, the unfolded protein response is important for the control of cell's life and death decisions together with intracellular reduction-oxidation conditions, depending on the duration and severity of the disruption of endoplasmic reticulum homeostasis [11,12]. Thus, reductive and oxidative activation mechanisms of the unfolded protein response include direct interactions of dedicated protein disulfide isomerases with endoplasmic reticulum stress sensors, protein S-nitrosylation and endoplasmic reticulum Ca (2+) efflux that is promoted by reactive oxygen species. Furthermore, cellular oxidant capacities are extensively remodeled downstream of unfolded protein response signals [11].

The IRE-1α enzyme is localized in the endoplasmic reticulum membrane and its N-terminus as sensor is localized in the lumen of endoplasmic reticulum. It interacts with chaperons, preferentially with BiP/GRP78/HSPA5 [13,14]. This chaperon functions as negative regulator of all sensing and signaling systems of endoplasmic reticulum stress, because it is associated with all three sensors in normal condition. The IRE-1α enzyme is a bifunctional enzyme which also has cytoplasmic domain for two enzymatic activities: serine/threonine kinase and endoribonuclease [6]. The IRE-1α protein kinase is activated upon

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induction of the endoplasmic reticulum stress and autophosphorylates IRE-1α as well as controls the expression of some stress-responsible genes [10,15]. Thus, IRE-1α-mediated production of epiregulin (EREG) did not depend on IRE-1α endoribonuclease domain, as neither the selective dominant-negative invalidation of the RNase activity (IRE-1α kinase active) nor the siRNA-mediated knockdown of XBP1 had significant effect on EREG expression [10]. This results in the activation and dimerization of IRE-1α in the endoplasmic reticulum membrane as well as in the activation of endoribonuclease. The main function of IRE-1α endoribonuclease is alternative splicing of XBP1 pre-mRNA by excision of 26 bp fragment from the coding part. Resulting alternative splice variant of XBP1 encodes a larger transcription factor with modified C-terminus, which is responsible for regulation of the expression of numerous genes encoded proteins for protein folding and degradation of improperly folded proteins and affects broad aspects of cell fate and the metabolism of proteins, amino acids and lipids [16-18].

The activity of XBP1 splice variant is regulated by kinases and by interaction with other transcription factors [19]. The IRE-1α endoribonuclease is also responsible for selective degradation of some mRNA upon endoplasmic reticulum stress conditions by a process termed RIDD (regulated IRE-1α-dependent decay of mRNA) [20-22]. It is possible that this function of IRE-1α endoribonuclease is very important in selective suppression of some signaling pathways in cancer cells. Moreover, this endoribonuclease also causes endonucleolytic decay of chaperones, but the high level of chaperone expression in malignant tumor cells is considerably responsible for these cells surviving through suppression of apoptosis [23,24].

At the same time, there is data that kinase of IRE-1α enzyme is not obligatory necessary for endoribonuclease activity, because inhibition of kinase by specific inhibitor activates endoribonuclease to confer cytoprotection against endoplasmic reticulum stress [25]. This data is important for clarification of functional integrity of IRE-1α enzyme and a significance of its different enzymatic activities in unfolded protein response. Furthermore, the IRE-1α enzyme has also an important additional function, because peptides derived from this enzyme can modulate activity of IRE-1α and protect cells from endoplasmic reticulum stress [26]. Therefore, the endoplasmic reticulum stress is a regulatory mechanism that allows cells to adapt to a series of metabolic, redox, and other environmental changes as well as directly influences life/death decisions at a cellular level.

Inhibition of IRE-1α Enzyme Suppresses Glioma Growth

The inhibition of IRE-1α in U87 glioma cells by dominant-negative construct of IRE-1α (dn-IRE1) has been shown to result in a significant anti-proliferative effect in glioma growth through suppression of angiogenesis and cell proliferation [10,27,28]. This is due to down-regulation of prevalent pro-angiogenic factors and up-regulation of anti-angiogenic genes both *in vitro* and in the chorio-allantoic membrane (CAM) model, as well as in mice engrafted intracerebrally with U87 glioma cell clones. It was shown that A549/8 and U87 cancer cells expressing a dominant-negative IRE-1α transgene as well as IRE-1α-knockout mouse embryonic fibroblasts were unable to trigger vascular endothelial growth factor-A (VEGF-A) up-regulation upon either oxygen or glucose deprivation [27,28]. This data suggests an essential role of IRE-1α-dependent signaling pathways in response to ischemia identifying this protein as a potential therapeutic target for control of both the angiogenic switch and tumor development. Thus, IRE-1α is a common determinant linking hypoxia and unfolded protein responses to the up-regulation of VEGF-A and other pro-angiogenic as well as pro-proliferative factors [10,28-30].

Therefore, in a human glioma model, inhibition of IRE-1α by stable overexpression of dn-IRE1 correlates with down-regulation of different pro-angiogenic factors including interleukins IL-1beta, IL-6, and IL-8 and significant up-regulation of anti-angiogenic factors such as SPARC, CTGF, HSPG2, decorin, thrombospondin-1, and several other extracellular matrix proteins functionally linked to mesenchymal differentiation and glioma invasiveness [28]. These changes were correlated with *in vivo* reduction of angiogenesis and blood perfusion, a decreased growth rate, and blood vessel cooption both in the chick chorio-allantoic membrane assay and in the mouse orthotropic brain model [28]. Interestingly enough, this phenotypic change is consistently associated with increased overall survival in glioma-implanted recipient mice and ectopic expression of IL-6 in IRE-1α-deficient tumors restored angiogenesis but did not reverse the mesenchymal/infiltrative cell phenotype [28]. At the same time, an angiogenesis is a complex network and is regulated by hundreds of pro-angiogenic and anti-angiogenic factors. Thus, CD138-purified myeloma cells from 300 untreated patients do not show a significantly higher median number of expressed pro-angiogenic or anti-angiogenic genes, but almost all of these myeloma cell samples aberrantly express at least one of the angiogenic factors: HGF (hepatocyte growth factor), IL-15 (interleukin 15), ANG (angiogenin), FNFSF13/APRIL (tumor necrosis factor (ligand) superfamily member 13/a proliferation-inducing ligand), CTGF (connective tissue growth factor) or TGFA (transforming growth factor alpha) [31].

It was recently shown that epidermal growth factor (EGF) receptor ligand epiregulin contribute to the development of malignant glioma in relation to the activity of the unfolded protein sensor IRE-1α through EGF receptor ErbB1/HER1 [10]. Thus, the high-expression rate of EREG in U87 cells was therefore linked to IRE-1α, because its inhibition by dn-IRE-1α dramatically reduced EREG expression in both cell culture and in human xenograft tumor models as well as suppressed glioma cell proliferation. Moreover, a stimulatory autocrine loop mediated by EREG was evidenced by the decrease in cell proliferation using specific blocking antibodies directed against either ErbB1 (cetuximab) or EREG itself [10].

In addition, IRE-1α-mediated production of EREG did not depend on IRE-1α endoribonuclease domain, as neither the selective dominant-negative invalidation of the RNase activity by dnr-IRE-1α (kinase of IRE-1α is active) nor the siRNA-mediated knockdown of XBP1 had significant effect on EREG expression [10]. Finally, chemical inhibition of c-Jun N-terminal kinases (JNK) by the SP600125 compound reduced the ability of U87 cells to express EREG, demonstrating a link between the growth factor production and JNK activation under the dependence of signaling enzyme IRE-1α. Noting that EGF receptor also suppresses the maturation of specific tumor-suppressor-like miRNAs in response to hypoxic stress through phosphorylation of AGO2 [32].

Recently it was shown that the expression of pro-proliferative transcription factors such as E2F8, EPAS1, ATF3, FOXF1, and HOXC6 is down-regulated in U87 glioma cells after inhibition of IRE-1α; however, transcription repressor TBX3 is increased in these cells [33]. Moreover, kinase and endonuclease deficient IRE-1α in glioma cells had a less profound effect on the expression of E2F8, HOXC6, and TBX3 genes than the blockade of the endoribonuclease activity of IRE-1α alone. This data also has shown the complex interaction between two enzymatic activities of IRE-1α. At the same time, inhibition of only endoribonuclease of IRE-1α leads to the up-regulation of ATF3 and FOXF1 gene expressions, while kinase and endonuclease deficient IRE-1α suppresses these gene transcripts. Thus, inhibition

of IRE-1α, especially only its endoribonuclease activity, correlates with deregulation of proliferation related genes and thus slower cell proliferation and tumor growth [28,33]. Moreover, the blockade of both enzymatic activities of IRE-1α (kinase and endoribonuclease) in glioma cells led to a significant down-regulation of insulin-like growth factor binding proteins (IGFBP1, IGFBP2, and IGF2BP3) gene expressions and strong up-regulation of HTRA1 gene [34]. At the same time, the inhibition of IRE-1α endoribonuclease significantly increased the expression of IGFBP1, IGFBP2, and HTRA1/PRSS11 genes and did not affect the IGF2BP3 gene expression. It is interesting to note that the HtrA protein family combines chaperone and protease activities and is essential for protein quality control in many organisms [35]. Protease HTRA1 has IGF binding domain and possibly controls the level and functional activity of IGFs and IGF binding proteins as well as several other proteins, which control cell proliferation through the modulation of extracellular matrix protein [36,37]. These results demonstrate the dependence of insulin-like growth binding proteins and HTRA1 gene expressions in U87 glioma cells on IRE-1α signaling enzyme function, indicating its participation in the regulation of metabolic and proliferative processes via IGF/INS receptors.

Inhibition of IRE-1α and Cell Cycle Regulation

Furthermore, the IRE-1α arm of unfolded protein response controls cell cycle gene expressions and inhibition of IRE-1α by dn-IRE1 also significantly affects the expression of numerous genes, which participate in cell cycle regulation and cell proliferation [38-43]. Thus, an inhibition of the IRE-1α down-regulates the expression of cyclin D1, which forms a complex with, and functions as a regulatory subunit of cyclin-dependent kinases 4 or 6, whose activity is required for cell cycle G1/S transition and may contribute to tumorigenesis, and up-regulates the expression of cyclin G2, which appears to be a negative cell-cycle regulator in some cancers [39,40,44]. The expression of growth arrest-specific genes GAS1 and GAS6 is strongly up-regulated in glioma cells without IRE-1α activity and down-regulated upon hypoxia [39]. Thus, the suppressive effect of IRE-1α blockade on cell proliferation and tumor growth [10,28] possibly mediated by down-regulation of pro-proliferative cyclin D1 and up-regulation of a negative cell-cycle regulator cyclin G2 as well as growth arrest-specific genes GAS1 and GAS6.

There is also data that inhibition of the IRE-1α enzyme down-regulates PLK1 (POLO-like kinase 1) and up-regulates PLK2 and PLK4 gene expressions in glioma cells [38]. Moreover, these changes in PLK gene expressions are possibly mediated by IRE-1α kinase, because inhibition of IRE-1α endoribonuclease does not change significantly the expression of these genes in U87 glioma cells [38]. It was shown that POLO-like kinases play an important role in cell cycle regulation and participate in tumorigenesis, because PLK1 is highly expressed in a broad spectrum of human tumors, strongly promotes progression of the cell cycle and is responsible for aggressive proliferation of tumor cells [45]. Thus, down-regulation of PLK1 gene expression in glioma cells without IRE-1α enzyme function possibly contributes to suppression of glioma cell proliferation [10,28]. This data correlates to results Harris et al. [46] that polo-like kinase 1 inhibition suppresses medulloblastoma cell growth.

In conclusion, the inhibition of IRE-1α coordinately regulates genes involved in tumor growth, lowering expression levels of pro-proliferative and pro-angiogenic and up-regulating the expression of anti-proliferative genes. This data should help to define the best therapeutic targets for the design of specific inhibitors that could act as potent antitumor drugs by applying selected changes in IRE-1α signaling pathway.

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