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REVIEW

Biological Function of HYOU1 in Tumors and Other Diseases

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Abstract: Various stimuli induce an unfolded protein response to endoplasmic reticulum stress, accompanied by the expression of endoplasmic reticulum molecular chaperones. Hypoxia-upregulated 1 gene (HYOU1) is a chaperone protein located in the endoplasmic reticulum. HYOU1 expression was upregulated in many diseases, including various cancers and endoplasmic reticulum stress-related diseases. HYOU1 does not only play an important protective role in the occurrence and development of tumors, but also is a potential therapeutic target for cancer. HYOU1 may also be used as an immune stimulation adjuvant because of its anti-tumor immune response, and a molecular target for therapy of many endoplasmic reticulum-related diseases. In this article, we summarize the updates in HYOU1 and discuss the potential therapeutic effects of HYOU1.

Keywords: HYOU1, tumor, endoplasmic reticulum, anti-tumor immunity

Introduction

The endoplasmic reticulum (ER) is involved in protein synthesis, post-translational modifications, and correct folding of proteins, and plays a key role in many cellular processes.[1,2] The endoplasmic reticulum is highly sensitive to changes in a range of intracellular environment or extracellular stimuli, especially in malignant cells, including hypoxia, increased protein synthesis, impaired ubiquitination and proteasomal degradation, insufficient energy, nutrition, excessive or restricted substances, and imbalanced calcium levels.[3–5] These stimuli can lead to accumulation of misfolded proteins in the endoplasmic reticulum cavity, and when the accumulation of misfolded proteins in the endoplasmic reticulum exceeds a certain level, the endoplasmic reticulum will initiate a series of unfolded protein reactions (UPR) to ensure a balance between protein folding capacity and demand.[6–10] This process initiated by three ER-localized transmembrane proteins-protein kinase-like ER kinase (PERK), inositol-requiring enzyme 1 (IRE1α), and activating transcription factor 6α (ATF6α).[11–15] The process of endoplasmic reticulum stress is usually accompanied by an increase in endoplasmic reticulum chaperone protein expression, including 78 kDa glucose-regulated protein (GRP78) and Hypoxia-upregulated 1 (HYOU1).[16,17] Heat shock protein 70 (Hsp70), as a molecular chaperone, is used to maintain and restore the homeostasis of cells. Under stress, Hsp70 has a strong cell protection function. Hsp70 has also been shown to cross-present with major histocompatibility complex class-1 (MHC-1) molecules and has immunomodulatory effects.[18–22]

Hypoxia-upregulated 1 gene (Hyou1) which belongs to the Hsp70 family, also known as 150 kDa oxygen-regulated protein (ORP150). HYOU1 is induced by

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a variety of stimuli, including endoplasmic reticulum stress, hypoxia, ischemia, glucose deficiency, and N-glycosylation inhibitor tunicamycin.[23] The up-regulation of HYOU1 expression is related to many diseases related to endoplasmic reticulum stress, such as diabetes, degenerative neurological diseases and cardiovascular diseases.[16,24,25] In this review, we outline the latest advances in HYOU1 in human cancer and other diseases, discuss the regulatory mechanisms of HYOU1 in diseases, and discuss possible therapeutic approaches.

Structure and Function of HYOU1

Hypoxia-upregulated 1 gene (Hyou1), also known as 150 kDa oxygen-regulated protein (ORP150), was first found in rat astrocytes cultured under hypoxic conditions and belongs to the Hsp70 family.[26] It consists of 999 amino acids encoded by the 3301 bp full-length gene located on the q-arm of chromosome 11.[27] The sequence of HYOU1 contains a CCAAT-rich cis-acting element called ER stress response element (ERSE), located in the promoter region between intron 1 and exon 2 of the HYOU1 gene. The ERSE element induces HYOU1 during the UPR process by interacting with transcription factors containing consensus sequences.[28] HYOU1 has a typical HSP70 domain structure, consisting of an N-terminal nucleotide binding domain (NBD), a b-sheet domain, and a C-terminal helix domain.[29–31]

HYOU1 is induced by a variety of stimuli, including endoplasmic reticulum stress, hypoxia, ischemia, glucose deficiency, reducing agent, and tunicamycin.[23] The up-regulation of HYOU1 is related to many diseases related to endoplasmic reticulum stress, such as diabetes, degenerative neurological diseases and cardiovascular diseases.[16,24,25] HYOU1 plays an important role in cross-presentation,[32] generates an anti-tumor immune response, and may be used as an immune stimulation adjuvant.[30,33]

The anti-apoptosis and anti-tumor immune response of HYOU1 plays an important role in the occurrence and progress of cancer.[29,34,35] HYOU1 is involved in the insulin secretion of pancreatic β cells. HYOU1 can reduce insulin resistance and improve glucose tolerance in diabetes.[36] HYOU1 can protect neurons from cell death and plays an important role in neurodegenerative diseases.[25,37–39] HYOU1 can protect cardiomyocytes and vascular cells from apoptosis, and plays an important role in improving atherosclerosis and regulating cardiac ischemia/reperfusion.

The Role and Mechanism of HYOU1 in Tumor Progress

The supply of glucose, oxygen and other nutrients in the microenvironment of most neoplastic tumors is insufficient, resulting in stress in the endoplasmic reticulum and an increased response to unfolded proteins. Survival chaperones protect tumor cells from ER stress-induced cell death. Studies have shown that many endoplasmic reticulum-resident molecular chaperones, including GRP78, calreticulin, can protect cancer cells from endoplasmic reticulum stress-induced apoptosis. Therefore, the molecular partners of endoplasmic reticulum have become a hot topic in cancer treatment.

HYOU1 is highly expressed in many tumors (Table 1). Many studies have shown that HYOU1 is highly expressed in epithelial ovarian cancer, nasopharyngeal carcinoma, and Kaposi's sarcoma.[34,40,41] In addition, other studies have

Table 1 Specific Cancers and Their Association with HYOU1

Cancer Type	Expression	Function	Reference
Epithelial ovarian cancer	Upregulated	Promoting proliferation, invasion and migration	[34]
Breast cancer	Upregulated	Reducing apoptosis	[43]
Thyroid cancer	Upregulated	Reducing apoptosis	[45,52]
Gastric cancer	Upregulated	Reducing apoptosis	[46]
Bladder cancer	Upregulated	Promoting invasion	[42]
Kaposi's sarcoma	Upregulated	Promoting migration and survival	[40]
Prostate cancer	Upregulated	Promoting angiogenesis and tumorigenicity	[44]
Nasopharyngeal carcinoma	Upregulated	Associating with shorter progression-free survival and overall survival	[41]
Non-small cell lung cancer	Upregulated	Promoting invasion, reducing apoptosis, chemoresistance	[49]

shown that HYOU1 expression levels are elevated in breast cancer, bladder cancer, and prostate cancer.[42–44] HYOU1 is also highly expressed in gastric cancer, thyroid cancer, non-small cell lung cancer, and colorectal cancer.[45–48]

Promoting Tumor Progress and the Mechanism

Studies have shown that the cultured C6 glioma cells showed the common expression of HYOU1 and vascular endothelial growth factor (VEGF). Down-regulation of HYOU1 expression reduced the release of VEGF into the culture supernatant, while overexpression of HYOU1 showed an increase in the level of VEGF antigen, which is tumor growth related. The results show that HYOU1 plays an important role in promoting VEGF secretion and promoting tumor growth. The expression of HYOU1 and VEGF in prostate cancer patients was higher than that of normal people. Inhibiting HYOU1 expression can inhibit VEGF secretion, thereby reducing the angiogenesis and tumorigenicity of prostate cancer DU145 cells.[44]

In human nasopharyngeal carcinoma tissues, the expression of HYOU1 was significantly up-regulated at the mRNA level and protein level, and the expression of HYOU1 protein was positively correlated with the clinical stage and metastasis of NPC. NPC patients with high expression of HYOU1 have shorter progression-free survival (PFS) and overall survival (OS). High expression of HYOU1 was one of the poor prognostic factors in NPC patients.[41] Proteomic analysis showed elevated HYOU1 expression in non-small cell adenocarcinoma.[47] Genomic analysis showed that HYOU1 mRNA levels were differentially expressed in colorectal cancer tissues and normal control tissues, and was warranted to further investigate whether it is used as a biomarker for colorectal cancer.[48]

Promoting Tumor Invasion and Migration and the Mechanism

The level of HYOU1 has also been shown to be associated with cancer invasion. It has been documented that the factors secreted by the crosstalk between endothelial cells (EC) and lung cancer cells lead to the increase of HYOU1 expression in lung cancer spheroids, and the direct interaction between them also leads to the increase of HYOU1 expression in multicellular tumor spheroids (MCTS). Downregulation of HYOU1 can promote cell apoptosis and chemosensitivity in lung cancer MCTS, and inhibit the stemness of lung cancer cells and the expression of EMT-related proteins. HYOU1 also controls tumor growth by regulating IFN signaling in lung cancer cells. In addition, the invasion of lung cancer cells induced by HYOU1 is related to the activation of the PI3K/AKT/mTOR pathway. Therefore, the selective inhibitor of HYOU1 expression may be used as a promising therapeutic target to overcome the chemoresistance and tumorigenesis of lung cancer.[49]

The expression level of HYOU1 was significantly up-regulated in epithelial ovarian cancer tissues and cell lines. Down-regulation of HYOU1 expression can inhibit tumor proliferation and colony formation, as well as ability to migrate and invade. Silencing HYOU1 can down-regulate phosphorylated phosphoinositide 3-kinase (p-PI3K), phosphorylated protein kinase B (p-Akt), and cell cycle and epithelial-mesenchymal transition (EMT) related gene expression levels. High expression of HYOU1 was a poor prognostic factor for overall survival, so that HYOU1 can be used as a target to treat epithelial ovarian cancer.[34]

The expression of HYOU1 is very common in bladder cancer and has a higher expression trend at higher stages. There is a significant correlation between the expression of HYOU1 and metalloproteinase-2 (MMP-2), and HYOU1 acts as a molecular chaperone for MMP-2 secretion to promote tumor invasion.[42]

Kaposi's sarcoma-associated herpes virus (KSHV) vIL-6 can be detected in all malignant tumors related to KSHV, and vIL-6 can promote inflammation and tumorigenesis. vIL-6 mainly exists in the endoplasmic reticulum, and HYOU1 interacts with vIL-6. HYOU1 is highly expressed in Kaposi's sarcoma tissue. HYOU1 increases vIL-6 protein expression and promotes vIL-6-induced janus kinase (JAK)/signal transducer and activator of transcription (STAT) signaling, migration, and endothelial cell survival.[40]

Studies have evaluated the expression of HYOU1 at various stages of breast cancer, from non-malignant, premalignant and aggressive lesions. They observed differential expression of HYOU1 in breast tissue adjacent to neoplastic lesions and benign tumors, and found a significant correlation between HYOU1 overexpression and poor prognostic histological parameters. Its association with factors, such as regional lymph node metastasis and lymphatic infiltration, suggests that HYOU1 may play a role in metastasis.[50]

The Anti-Apoptotic Role and the Mechanism

Low glucose-induced HYOU1 expression reduced the apoptosis of breast cancer MCF-7 cells.[43]

Proteasome inhibitors have antitumor activity against hematological malignancies and solid tumors. Proteasome inhibitors that interfere with the normal degradation of these proteins are likely to make tumor cells prone to apoptosis.[51] The study found that the proteasome inhibitor MG132 induced HYOU1 expression in thyroid cancer cells, and its expression was stronger in insensitive thyroid cancer cells than in sensitive cells. Among them, activating transcription factor 4 (ATF4) was involved in the upregulation of HYOU1 induced by MG132. Up-regulation of HYOU1 reduced apoptosis by inhibiting the expression of C/EBP homologous protein (CHOP), thereby reducing the anti-tumor activity of MG132.[45] In order to understand the molecular basis of proteasome inhibitor induction of HYOU1 in thyroid cancer, the study found that MG132 induced the expression of HYOU1 via the activation of −421/-307 and −243/+53 regions of HYOU1. Nuclear factor E2-related factor 2 (Nrf2) induced HYOU1 expression in thyroid cancer. Nrf2 directly activated the HYOU1 gene by binding to the −421/-307 region of HYOU1 as a direct transcription activator. Nrf2 also promoted the recruitment of ATF4 to the HYOU1 promoter at −243/+ 53 activates HYOU1 indirectly.[52] In human gastric cancer cells, celecoxib up-regulated the expression of HYOU1 by inducing an increase in intracellular Ca2 + concentration, activating the ATF4 and ATF6 pathways, inhibited CHOP expression, and reduced apoptosis, thereby reducing the potential antitumor activity of celecoxib.[46] Although the research of HYOU1 in tumor cells is extensive, the specific molecular mechanism of action still needs further study (Figure 1).

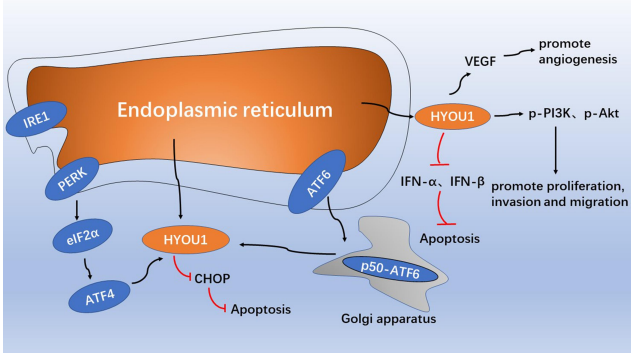

Figure 1 The role model of intracellular HYOU1 in tumor development. The endoplasmic reticulum stress response up-regulates the expression of HYOU1 through the PERK-eIF2α-ATF4 pathway and the active form of the p50-ATF6 pathway, and inhibit the expression of CHOP and reduce apoptosis. HYOU1 promotes tumor angiogenesis by promoting VEGF secretion. HYOU1 promotes cell proliferation, invasion and migration by up-regulating the expression of p-PI3K and p-Akt. HYOU1 reduces apoptosis by down-regulating the expression of IFN-α and IFN-β.

Role of HYOU1 in Anti-Tumor Immunity

The application of human cancer vaccines has become one of the main goals of basic and clinical cancer research. Studies have confirmed that HSPs such as Hsp70, Hsp90, GRP94 and binding immunoglobulin protein (BiP) can trigger effective tumor-specific cytotoxic T lymphocyte (CTL) responses.[53,54] The HSP-Ag complex enters the class I antigen presentation pathway and causes CD8 + T cell stimulation, which is cross-presentation.[55] The mechanism of HSP-mediated cross-presentation may be: (1) HSP can promote the main CD8 + T cell response and MHC class I-restricted epitope cross-presentation and (2) HSPs can stimulate innate immune responses that are not related to tumor antigens. The glycosylated form of HYOU1 is used as a potential anti-tumor vaccine.

HYOU1 played an important role in delivering tumor antigens to specialized antigen-presenting cells for cross-presentation, resulting in the generation of anti-tumor immune response that depend on cytotoxic $CD8^+$ T cells. HYOU1 can be used as an immunostimulant adjuvant for the development of recombinant vaccines for the treatment of cancer.[32]

Increasing knowledge suggests that prostate stem cell antigen (PSCA) is a promising candidate for immunotherapy of advanced prostate cancer. P. Gao et al had demonstrated that HYOU1 formed a molecular chaperone complex with tumor-associated antigen PSCA during heat shock. The HYOU1-PSCA chaperone complex can enhance T cell-mediated immune responses, thereby significantly inhibiting tumor growth and prolonging the life span of tumor-bearing mice, which may be an effective method for the treatment of prostate cancer.[56] Transgenic cancer cells with the ability to produce secret HYOU1 had been successfully tested as a cell-based vaccine that produces a therapeutic anti-tumor response to established tumors in mice.[56,57] The delivery of secreted HYOU1 in tumors by adenovirus can promote the antitumor efficacy of melanoma differentiation-related gene 7 (mda-7), a cancer-specific therapeutic cytokine, by installing a systemic anti-tumor immune system.[58] Early studies had shown that animals immunized with HYOU1 purified from various murine tumors such as colon tumors, melanomas, and fibrosarcomas had shown a strong anti-tumor immune response. Recombinant chaperone complexes of HYOU1 and melanoma-associated antigen gp100 had been used in the field of oncology. HYOU1 and anti-tumor immunity as a targeted

vaccine can produce a robust anti-tumor immune response to invasive, poorly immunogenic B16 melanoma in mice.[59] The above results confirm the important role of tumor-derived HYOU1 and Ag complexes associated with GRP tumors in stimulating antigen and tumor-specific immune responses.

HYOU1 can not only be used as an anti-tumor vaccine, but also plays a role in primary immunodeficient diseases. It has been reported that a patient with mutations in HYOU1 is generally sensitive to bacterial and herpes infections and hypoglycemic episodes.[60]

It is implied that HYOU1 may be targeted to develop an effective anti-tumor vaccine, but in-depth research is required to fully explore the anti-cancer potential.

Role of HYOU1 in Other Diseases

Role of HYOU1 in Diabetes

HYOU1 plays an important role in diabetes.[36] Studies have found that the expression of HYOU1 is observed in the serum of patients with diabetic nephropathy and is accompanied by an increase in proteinuria and VEGF expression. The results show that HYOU1 is involved in the regulation of proteinuria by mediating VEGF.[16] In the vitreous samples of patients with proliferative diabetic retinopathy (PDR), a significant increase in VEGF and HYOU1 expression was observed and there was a significant positive correlation between the two.[24] The study investigated 91 patients with type 1 diabetes and 37 healthy individuals, and measured anti-HYOU1 autoantibody levels in their serum.[36] They found that serum anti-HYOU1 autoantibodies were significantly increased in diabetic patients compared to healthy non-diabetic patients. MIN6 is a known model of insulinoma cell line, HYOU1 has been shown to be highly expressed in mouse MIN6 beta cells under normal oxygen conditions. The study found that the expression of the HYOU1 gene is higher in the insulin resistance library transcription profile than those obtained from insulin-sensitive individuals. Studies on obese diabetic C57BL/KsJ-db/db and non-diabetic C57BL6 mice have shown that overexpression of HYOU1 reduces insulin resistance in diabetic mice and significantly improves glycemic control.[61] The increased expression of HYOU1 resulted in a significant increase in the phosphorylation of IRS-1 and Akt and the decrease of expression levels of PEPCK and G6Pase accordingly.[61] Studies have shown that in the case of type 2 diabetes, HYOU1 can play a role in improving insulin sensitivity of skeletal muscle and liver, but does not participate in insulin secretion. Moreover, systemic overexpression of HYOU1 delayed the onset of disease in homozygous HYOU1/Akita mice and improved insulin sensitivity. On the contrary, the destruction of the HYOU1 gene promotes the development of diabetes and promotes insulin resistance. These findings indicate that ER stress is a key factor in the course of diabetes. Therapies aimed at reducing or enhancing the mechanism of ER stress may become potential treatments for diabetes. As a key mediator of ER stress state, HYOU1 is considered to play an important role in relieving the symptoms of diabetes, but the molecular mechanism and pathway of the specific effect are still not entirely clear.

Role of HYOU1 in Neurodegenerative Diseases

HYOU1 signaling plays an essential role in neurodegenerative diseases.[25,37–39] The common symptom of many neurodegenerative diseases is the accumulation of misfolded proteins in the lumen of nerve cells, especially Alzheimer's disease and Parkinson's disease.[62] The study found that in post-mortem brain tissues and cell culture models, upregulation of ER stress markers was observed in diseases such as Alzheimer's disease and Parkinson's disease. Studies have also shown that endoplasmic reticulum stress and endoplasmic reticulum partner molecules have a direct role in the pathogenesis of Alzheimer's disease.[63,64] HYOU1 is involved in maintaining neuronal cell homeostasis and the survival of vulnerable neurons, and is susceptible to excitatory stimulation.[65–67] The expression of HYOU1 has been identified in the human hippocampus in human brain tissue after alginate injection after seizures. In addition, the up-regulation of HYOU1 expression in the gerbil brain inhibited the delayed death of nerve cells after ischemia, indicating its cytoprotective effect.[68] Studies had found that Aβ42 in Alzheimer's disease can be prevented by inhibiting HYOU1 or activating the E3-ligase activity of CHIP.[37] Over-expression of HYOU1 under stress can protect neurons from cell death. The data indicate that endoplasmic reticulum stress may be the main cause of neuronal cell death, and HYOU1 may become a promising neuroprotective mediator.[65,69,70] However, in-depth research is still needed to fully clarify the role and exact therapeutic potential of HYOU1 in neurodegenerative diseases.

Role of HYOU1 in Cardiovascular Diseases

The study found that HYOU1 autoantibodies have been detected in the serum of patients with severe atherosclerosis. Oxidized low density lipoproteins (oxLDLs) are known to induce apoptosis and promote atherosclerosis. OxLDL enhances the expression of HYOU1 in cultured vascular endothelial cells and smooth muscle cells, and HYOU1 protects endothelial cells from oxLDL-induced apoptosis. Studies have also shown that after incubation of HMEC-1 cells with oxLDL, ER stress markers and ER chaperone proteins GRP78, GRP94 and HYOU1 are clearly expressed. Down-regulation of HYOU1 enhances caspase-3 activation and oxLDL-induced cytotoxicity, while overexpression of HYOU1 in HMEC cells reduces oxLDL-induced caspase-3 activation and IRE1 and c-Jun N-terminal kinase (JNK) phosphorylation. In addition, the down-regulation of HYOU1 leads to inhibition of Akt phosphorylation.[71] Studies have also shown that the anti-ER stress and anti-apoptotic effects of HYOU1 occur downstream of AMPK signaling in liver cell lines. The enhanced expression of HYOU1 plays an important role in preventing apoptosis events of macrophages, vascular cells and cardiomyocytes.

Conclusion

HYOU1 is an endoplasmic reticulum chaperone protein, belonging to the HSP70 family, induced by a variety of stress conditions, such as hypoxia, glucose deficiency, reducing agents and tunicamycin. In general, HYOU1 inhibits apoptosis, maintains calcium homeostasis, and exhibits cytoprotective effects by preventing endoplasmic reticulum stress.[29] The anti-apoptotic effects of HYOU1 include: (1) Attenuation of ER stress-related apoptosis pathways, such as reduced phosphorylation of IRE1 and JNK and down-regulation of XBP1, XBP1s and CHOP expression, (2) through HYOU1 and ER stress sensor PERK, the possible combination of ATF6 and IRE1 keeps them inactive, thereby inhibiting UPR, and (3) activation of Akt phosphorylation as part of the survival phosphatidylinositol 3-kinase/Akt signal transduction pathway.[27] Preliminary studies indicate that HYOU1 directly binds to PERK, ATF6 and IRE1. The results show that GRP78 may not be the only molecule that binds to the UPR sensor, and HYOU1 may be another protein that can bind to the UPR sensor receptor to inhibit or reduce the response of unfolded proteins, but further in-depth analysis and research are needed to solve this problem. Although HYOU1 has been the topic of extensive research since its emergence, its molecular mode of action in cancer biology is still unclear. It is necessary to further explore its specific mechanisms of action and further explore the potential of HYOU1 in clinical treatment.

Abbreviations

HYOU1, hypoxia-upregulated 1; ER, the endoplasmic reticulum; PERK, proteins-protein kinase-like ER kinase; IRE1α, inositol-requiring enzyme 1; ATF6α, activating transcription factor 6α; GRP78, 78 kDa glucose-regulated protein; Hsp70, heat shock protein 70; MHC-1, major histocompatibility complex class-1; ORP150, 150 kDa oxygen-regulated protein; ERSE, ER stress response element; NBD, N-terminal nucleotide binding domain; VEGF, vascular endothelial growth factor; PFS, progression-free survival; OS, overall survival; p-PI3K, phosphorylated phosphoinositide 3-kinase; p-Akt, phosphorylated protein kinase B; EMT, epithelial-mesenchymal transition; MMP-2, metalloproteinase-2; KSHV, Kaposi's sarcoma-associated herpes virus; JAK, janus kinase; STAT, signal transducer and activator of transcription.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors declare that they have no competing interests.

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