Research progress on oncoprotein hepatitis B X-interacting protein (Review)

LEI CHENG[1], LIJUAN GUO[1], TENG ZOU[1], YISONG YANG[1], RAN TAO[2] and SHUANGPING LIU[1]

[1]Chronic Disease Research Center; [2]Department of Anatomy, Medical College, Dalian University, Dalian, Liaoning 116622, P.R. China

Received November 29, 2023; Accepted March 7, 2024

DOI: 10.3892/mmr.2024.13213

Abstract. Hepatitis B X-interacting protein (HBXIP) is a membrane protein located on the lysosomal surface and encoded by the Lamtor gene. It is expressed by a wide range of tumor types, including breast cancer, esophageal squamous cell carcinoma and hepatocellular carcinoma, and its expression is associated with certain clinicopathological characteristics. In the past decade, research on the oncogenic mechanisms of HBXIP has increased and the function of HBXIP in normal cells has been gradually elucidated. In the present review, the following was discussed: The normal physiological role of the HBXIP carcinogenic mechanism; the clinical significance of high levels of HBXIP expression in different tumors; HBXIP regulation of transcription, post-transcription and post-translation processes in tumors; the role of HBXIP in improving the antioxidant capacity of tumor cells; the inhibition of ferroptosis of tumor cells and regulating the metabolic reprogramming of tumor cells; and the role of HBXIP in promoting the malignant progression of tumors. In conclusion, the present review summarized the existing knowledge of HBXIP, established its carcinogenic mechanism and discussed future related research on HBXIP.

Contents

Correspondence to: Professor Ran Tao, Department of Anatomy, Medical College, Dalian University, 10 Xuefu Street, Dalian, Liaoning 116622, P.R. China
E-mail: 598302882@qq.com

Professor Shuangping Liu, Chronic Disease Research Center, Medical College, Dalian University, 10 Xuefu Street, Dalian, Liaoning 116622, P.R. China
E-mail: liushuangping@dlu.edu.cn

Key words: hepatitis B X-interacting protein, transcription, post-transcription, translation, oxidative stress, ferroptosis, review

1. Introduction

Hepatitis B virus X (HBX) protein has a long peptide chain composed of 154 amino acids. The N-terminus of HBX is the negative regulatory domain and the C-terminus is the deactivation domain (1). In 1998, a protein that interacts with the C-terminus of HBX was first identified and named HBX-interacting protein (IP), also known as Lamtor5. HBXIP is encoded by four exons located on human chromosome 1p13.3, and is a conserved protein with a molecular weight of 18 kDa. HBXIP localizes subcellularly to the surface of lysosomes and forms a pentameric regulatory complex with the other four proteins of the Lamtor family to activate mammalian target of rapamycin complex (mTORC1) (2,3). mTORC1 is the major growth regulator in humans and serves a role in cell growth (4,5).

HBXIP is highly expressed in numerous types of cancer, such as breast cancer, gastric cancer and esophageal squamous cell carcinoma, and its expression is associated with certain clinicopathological characteristics (6-14). Furthermore, high levels of HBXIP expression are associated with a poor prognosis.

Research on HBXIP has revealed multiple carcinogenic mechanisms. For example, in cervical cancer, HBXIP can interact with LIM domain 2 and activate the Wnt signaling pathway to promote malignant progression (15). In ovarian cancer, HBXIP can coactivate S-phase kinase-associated protein 2 via transcription factor SP1 to accelerate malignant progression (16). HBXIP can also promote the metastasis of tongue squamous cell carcinoma and regulate the malignant progression of gastric cancer cells through the PI3K/AKT signaling pathway (17,18). Therefore, targeting HBXIP has been suggested as a potential cancer treatment approach. Germacone, a monocyclic sesquiterpene, has been reported to regulate the cell cycle and apoptosis in renal cell carcinoma by inhibiting HBXIP expression (19). Reduction or loss of HBXIP expression increases the number of cells containing single-phase spindles, which impedes the ability of cells to divide (20). Inhibition of HBXIP expression was reported

to reduce tumor drug resistance and knockdown of HBXIP expression sensitized patients with osteosarcoma and liver cancer cell lines to chemotherapy (21).

The carcinogenic mechanism of HBXIP in most tumors has been established, but its role in normal cells has been less well studied. At present, the role of HBXIP in maintaining normal glucose tolerance phenotype and normal embryonic tissue development in mice has been preliminarily studied (22,23). Likewise, HBXIP is involved in DNA damage repair (21). In summary, HBXIP serves roles in both normal and cancer cells. The present review summarizes the current knowledge of HBXIP, including its normal physiological function and role in tumor cells, and provides a reference for subsequent research on HBXIP.

2. Normal physiological role of HBXIP

mTORC1 is a major growth regulator in humans and is activated by translocation to the lysosomal surface in response to numerous cell signals (2). HBXIP is a membrane protein on the surface of lysosomes and forms a pentameric regulatory complex with P18, P14, MEK partner 1 (MP1) and chromosome 7 open reading frame 59 (C7orf59). This complex serves a key role in activating mTORC1. HBXIP and C7orf59 form the core of this pentameric regulatory complex, which is responsible for the initial nucleation of the complex as well as the stabilization of the P18 conformation, which in turn allows the subsequent binding of MP1 and P14 (2,24). Therefore, loss of HBXIP leads to the formation and dysfunction of this complex, which then inhibits mTORC1 activation and impedes the downstream signaling pathways. For example, the self-renewal and differentiation of embryonic stem cells are regulated by mTORC1 signaling. In mice, knockout of HBXIP causes mTORC1 inactivation, which further affects the differentiation of embryonic stem cells and eventually leads to embryonic lethality (23).

HBXIP has also been reported to act as a transcription coactivator of oncoproteins in tumors and has a similar function in normal cells (22,25,26). HBXIP knockout mice have impaired glucose tolerance and reduced insulin production (22). Furthermore, HBXIP is highly expressed in pancreatic islets, acting as a coactivator of pancreatic and duodenal homeobox transcription factor and forming a complex with neurogenic differentiation 1 to upregulate insulin transcription genes and promote insulin secretion (22). Furthermore, the DNA damage response is an intrinsic signaling network in cells that recognizes and repairs DNA damage (27). Ataxia telangiectasia mutated (ATM) is a potential first-step sensor of DNA damage response, which can regulate downstream phosphorylation of p53, murine double minute 2 and checkpoint kinase (Chk) (28). HBXIP delays or blocks cell cycle progression by activating ATM, phosphorylating Chk and activating the G2/M phase DNA damage checkpoint (21). Therefore, patients with high HBXIP expression may be resistant to chemotherapy by regulating DAN damage repair.

In summary, HBXIP may serve a role at several points in the physiological regulation of cells (Fig. 1). When HBXIP expression is dysregulated, it affects the malignant progression of cancer cells. Therefore, an improved understanding of the physiological functions of HXBIP in normal cells will help to elucidate the mechanisms affected by its dysregulation in a more systematic manner.

3. HBXIP and tumors

Prediction of worse survival in patients with tumors and high expression of HBXIP. In the past decade, studies have reported that HBXIP is highly expressed in breast cancer, esophageal squamous cell carcinoma, colorectal, gastric cancer, renal cancer, liver cancer, tongue squamous cell carcinoma and pancreatic cancer, and its expression associated with the clinicopathological characteristics, prognosis and survival of patients (Table I) (6-14). Furthermore, HBXIP expression is associated with tumor metastasis, stage and survival of different tumor types (6-14). Therefore, high expression of HBXIP often predicts a higher degree of malignancy, and promotes tumor cell proliferation and invasion through different mechanisms.

Tumor-promoting mechanism of HBXIP

HBXIP regulates expression of key proteins in tumors at multiple stages. The regulation process from DNA to protein is called gene expression regulation (29), which is ordered in time and space. Gene expression is regulated at multiple stages, including at the chromatin, transcription, post-transcription, translation and post-translation stage. Dysregulation of any of these stages can lead to changes in the protein levels in the cell and affect related physiological processes. HBXIP has been reported to influence the malignant progression of tumor cells at multiple levels (Fig. 2).

i) HBXIP regulates chromatin and transcriptional processes. Nucleosomes are composed of histones and DNA and are the basic units of chromatin. When transcription occurs, the structure of chromatin is altered in such a way as to allow transcription factors to bind to DNA. Thus, transcriptional activation is closely related to the chromatin environment, and histone H3 modification is the primary mode of chromatin remodeling (30). c-Myc is an oncoprotein that binds to the E-box on the DNA sequence and affects the transcription of thousands of human genes (31). Studies have reported that HBXIP mediates demethylation of the c-Myc histone H3K4 by lysine-specific demethylase 1, with the support of long noncoding RNA (lncRNA) HOX transcript antisense RNA. This causes local DNA oxidation and drives the assembly of the c-Myc transcription initiation complex (32). Promoters are DNA sequences with transcriptional initiation specificity and their methylation is associated with transcriptional inhibition (33). HBXIP induces methylation of the microRNA (miRNA/miR)-18b promoter, thereby inhibiting its transcription and then affecting the expression of subsequent proteins, such as up-regulation of mouse double-minute 2 (MDM) expression, which ultimately degrades P53 and promotes the development of breast cancer (34). HBXIP also directly interacts with promoters to affect the expression of related proteins. Mitogen-activated protein kinase kinase kinase (MEKK) 2 is a member of the MEKK family, which activates extracellular signal-regulated kinase (ERK) 1/2 (35). Chromatin immunoprecipitation has shown that HBXIP directly binds

Table I. Association between cancer type and clinicopathological features with high expression of hepatitis B X-interacting protein.

First author/s, year	Tumor type	Clinicopathological feature					Mechanism	(Refs.)
		Differentiation	Invasion	Stage	Survival	Age		
Zhou *et al*, 2019	Pancreatic ductal carcinoma	Association	Association	Association	Association	Negative	Unknown. Cancer cell metastasis is promoted by	(6)
Wang *et al*, 2020	Colorectal cancer	Not shown	Association	Association	Association	Not shown	epithelial-mesenchymal transition	(7)
Piao *et al*, 2017	Gastric cancer	Not shown	Association	Association	Association	Not shown	Cancer cell metastasis is promoted by regulating metabolism and post-transcriptional translation	(8)
Li *et al*, 2017	Cervical cancer	Association	Association	Association	Association	Not shown	Tumor progression is promoted via the Wnt signaling pathway	(9)
Wang *et al*, 2017	Ovarian cancer	Not shown	Association	Association	Association	Not shown	Co-activation of transcription factors promotes cancer progression	(10)
Xia *et al*, 2017	Esophageal squamous cell carcinoma	Not shown	Association	Association	Association	Not shown	Cancer progression is influenced through translational level regulation	(11)
Cheng *et al*, 2014	Breast cancer	Not shown	Association	Association	Association	Negative	Promotes breast cancer via metabolism and co-activation of transcription factors	(12)
Guo *et al*, 2021	Liver cancer	Association	Association	Association	Association	Association	Promotes liver cancer by regulating level of RNA modification and translation	(13)
Wang *et al*, 2017	Non-small cell lung cancer	Not shown	Association	Association	Association	Not shown	Promotes non-small cell cancer cells via MEPK signaling pathway	(14)

to the promoter of MEKK2 to upregulate its expression and activate downstream ERK 1/2 to regulate the invasion and proliferation of breast cancer cells (36).

ii) HBXIP affects post-transcriptional regulation of related proteins. Eukaryotic transcription products undergo a series of processing and modification steps. Common modifications

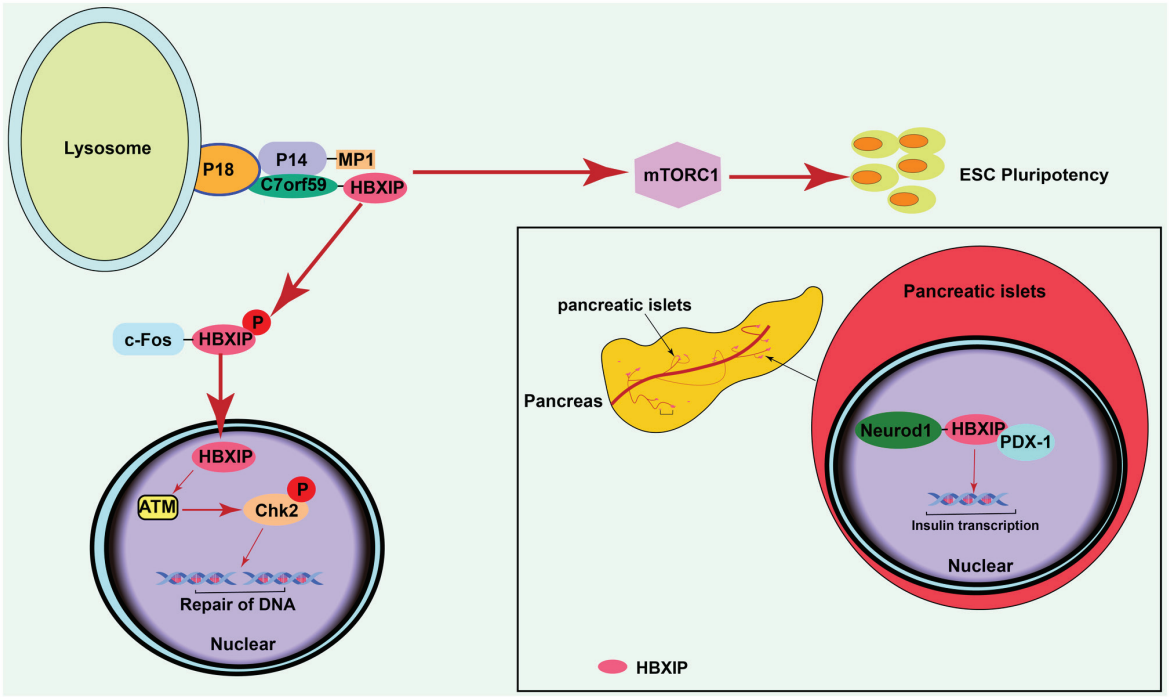

Figure 1. Normal physiological effects of HBXIP. Activation of mTORC1 signaling promotes normal differentiation of ESCs. HBXIP is involved in DNA damage repair by activating ATM. In the normal adult pancreas, HBXIP is highly expressed in the pancreatic islets in comparison with other pancreatic tissue and promotes the transcription of insulin. HBXIP, hepatitis B X-interacting protein; mTORC1, mammalian target of rapamycin complex 1; ESCs, embryonic stem cells; ATM, ataxia telangiectasia mutated; Chk2, checkpoint kinase; c-Fos, c-Fos proto-oncogene protein; PDX-1, programmed cell death 1 ligand 1; Neurod1, neuronal differentiation 1Gene; P, phosphorylated.

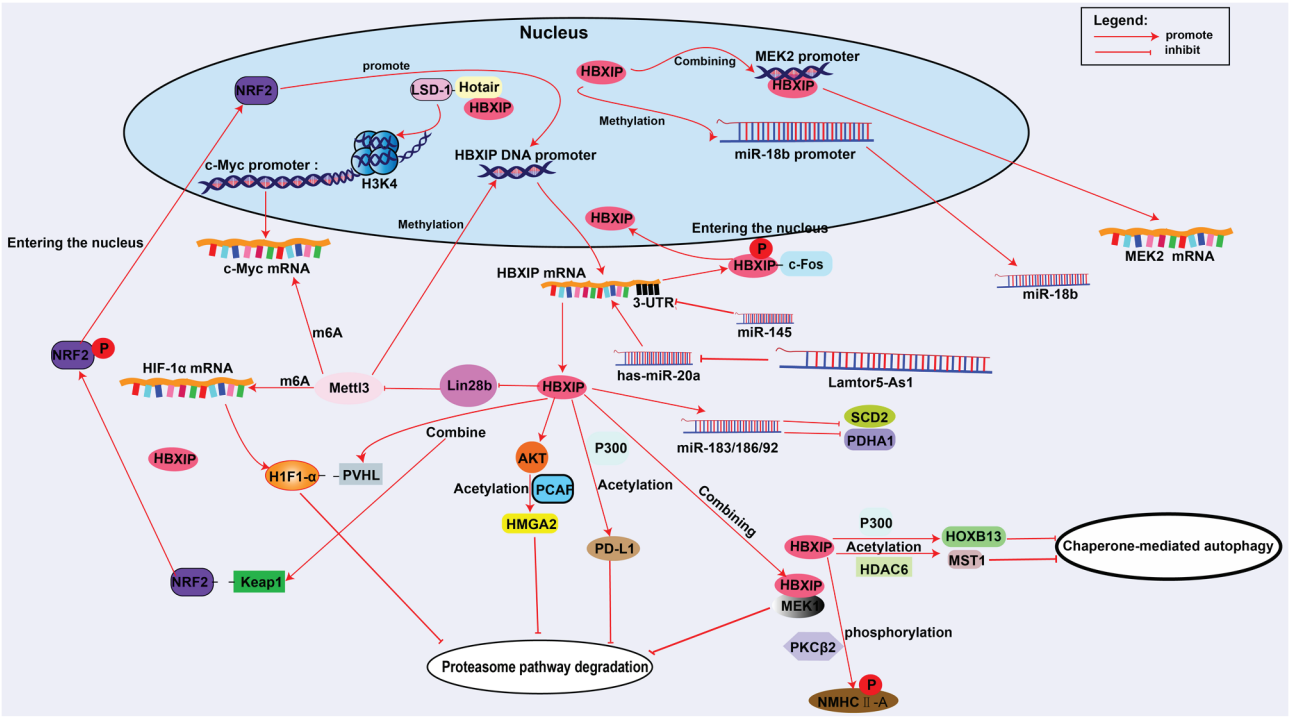

Figure 2. HBXIP regulates tumor cells at multiple levels. HBXIP promotes c-Myc histone demethylation through LSD-1 and binds to the MEK2 promoter to promote transcription. HBXIP directly promotes transcription via the miR-18b promoter. HBXIP modifies HIF-1α and c-Myc mRNA methylation through Mettl3. Micro RNAs and long non-coding RNAs can target or be targeted by HBXIP. HBXIP can regulate the malignant progression of tumors by acetylase, phosphorylase or promoting the separation of target proteins from ubiquitin recognition receptors. LSD-1, lysine-specific demethylase 1; HIF-1α, hypoxia-inducible factor-1α; Mettl3, methyltransferase-like 3; HBXIP, hepatitis B X-interacting protein; Keap1, Kelch-like ECH associated protein 1; PVHL, The von-Hippel Lindau tumor suppressor; MEK2, MAP Kinase Kinase2; MEK1, MAP Kinase Kinase1; PD-L1, programmed death ligand 1; PCAF, P300/CBP-associated factor; m6A, N6-methyladenosine; c-Myc, Cellular-myelocytomatosis viral oncogene; c-Fos, c-Fos proto-oncogene protein; HMGA2, The high mobility group protein 2; Hotair, HOX transcript antisense RNA; HDAC6, Histone deacetylase 6; HOXB13, Homeobox B13; MST, STE20-like kinase 1; NMHC-IIA, non-muscle heavy chain myosin IIA; SCD2, synthetic cytochrome c oxidase 2; PDHA1, pyruvate dehydrogenase A1; H3K4, histone H3 Lysine 4 trimethylation; PKCβII, protein kinase βC.

Table II. Hepatitis B X-interacting protein regulates protein post-translational modifications through different mechanisms.

First author/s, year	Type of tumor	Enzyme	Target protein	Residue	Effect	(Refs.)
Ye *et al*, 2020	Esophageal squamous cell carcinoma	PCAF	HMGA2	K26	Blocking ubiquitination-proteasome pathway degradation	(56)
Zhang *et al*, 2021	Non-small cell carcinoma	None	MEK1	Binding		(58)
Xu *et al*, 2021	Breast cancer	P300	PD-L1	K270		(57)
Liu *et al*, 2015		None	PVHL and H1F-1α	Promote dissociation		(45)
Zhou *et al*, 2019		None	Keap1 and Nrf2	Promote dissociation		(60)
Liu *et al*, 2018		P300	HOXB13	K277	Prevent degradation by the	(62)
Li *et al*, 2015		HDAC6	MST1	L35	lysosomal pathway	(63)
Zhang *et al*, 2023		PKCβII	NMHC-IIA	S1916	Enhanced aggressiveness of cancer cells	(64)

PCAF, P300/CBP-associated factor; HDAC6, Histone deacetylase 6; HOXB13, Homeobox B13; MST, STE20-like kinase 1; NMHC-IIA, non-muscle heavy chain myosin IIA; MEK1, MAP Kinase Kinase1; PD-L1, programmed death ligand 1; HBXIP, hepatitis B X-interacting protein; Keap1, Kelch-like ECH associated protein 1; NRF2, nuclear factor-erythroid 2-related factor 2; PVHL, von-Hippel Lindau tumor suppressor; H1F-1α, hypoxia-inducible factor-1; PKCβII, protein kinase βC.

include N1 methyladenosine, 5-methylcytosine, pseudouracil and N6-methyladenosine (m6A) (37,38). Of these, m6A is the most common in mammals (39) and is mediated by methyltransferase-like 3 (Mettl3). The negative regulation of Mettl3 by miR-let-7g is attenuated by HBXIP through the oncogene Lin-28 Homolog B, thereby increasing the level of Mettl3 in cells. There is also an m6A site in the promoter sequence of HBXIP, which can be modified by Mettl3 to promote transcription of HBXIP and thus produce positive feedback (40). Furthermore, HBXIP mediates the mRNA methylation of several proteins involved in the malignant progression of tumors through the regulation of Mettl3. For example, HBXIP mediates the level of m6A modifications in hypoxia-inducible factor (HIF)-1α mRNA via Mettl3 to promote the metabolic reprogramming of hepatocellular carcinoma (41). Likewise, in gastric cancer, HBXIP modifies the level of methylation of c-Myc mRNA via Mettl3 and promotes expression of c-Myc (42).

Most genes in the eukaryotic genome do not encode proteins, and their transcript products are called noncoding (nc)RNAs, which serve a role in normal physiological and pathological states. For example, miRNAs are members of the ncRNA family, which regulate the expression of target proteins by targeting and interacting with the 3' untranslated regions of mRNA. This induces the degradation or inhibition of translation of mRNA and affects many processes such as cell proliferation and differentiation, and serves a role in promoting or suppressing cancer (43,44). There is a close relationship between miRNAs and HBXIP levels in tumors. For example, both miR-let-7g and miR-18b are downregulated by HBXIP to promote tumor development (34,40). HBXIP can also inhibit the synthesis of human synthetic cytochrome c oxidase 2 and pyruvate dehydrogenase A1 by upregulating the miR-183/182/96 cluster, thereby reprogramming the glucose metabolism of tumor cells to promote malignant progression (45). Certain miRNAs directly affect the mRNA of HBXIP and serve a role in cancer inhibition. For example, miR-145 targets the noncoding region of HBXIP mRNA, inhibiting its translation and preventing malignant progression of breast cancer (46). Similarly, both miR-520b and miR-548p inhibit HBXIP-induced breast and liver cancer (47,48). lncRNAs are another member of the ncRNA family. LncRNAs are >200 nucleotides in length and serve a role in the degradation and regulation of mRNA or protein stability through numerous mechanisms (49). LAMTOR5-AS1 is a lncRNA located next to the HBXIP gene. LAMTOR5-AS1 expression is positively associated with the age of patients with colorectal cancer. LAMTOR5-AS1 may also affect the expression of HBXIP mRNA by inhibiting the miRNAs hsa-let-7b and hsa-miR-20a (50).

iii) HBXIP regulates the expression of related proteins through post-translational modifications (PTMs). Protein PTMs are the addition of moieties, catalyzed by relevant enzymes, to ≥1 amino acid residues to alter the biochemical properties of a protein (51). Common PTMs include acetylation, ubiquitination and phosphorylation, which can change the stability and activity of proteins (52-54). HBXIP affects the malignant progression of tumor cells by altering the acetylation or ubiquitination of target proteins through several mechanisms, thereby regulating their intracellular abundance and activity (Table II). The ubiquitination-proteasome pathway is one of the major pathways of protein degradation (55). HBXIP can prevent this pathway in three ways: i) The first mechanism is though the activation of acetylases. In esophageal squamous cell carcinoma, HBXIP activates the acetylase PCAF via AKT to acetylate a specific lysine

residue of HMGA2, preventing ubiquitination at this site and thereby enhancing its stability (56). HBXIP also maintains the stability of programmed death ligand 1 (PD-L1) by increasing the level of acetylation through the acetylase P300. Notably, HBXIP inhibits the degradation of PD-L1 to increase its intracellular levels. HBXIP also acts as a coactivator of the transcription factor ETS2 which upregulates the expression of PD-L1 (57). However, the mechanism by which HBXIP activates P300 remains unclear; ii) HBXIP can directly bind to the target protein to prevent proteasome-mediated degradation. In non-small cell carcinoma, HBXIP binds to MEK1 preventing its degradation by the proteasome (58); and iii) HBXIP prevents the binding of target proteins to ubiquitin ligase. The von-Hippel Lindau tumor suppressor (pVHL) is a tumor suppressor protein which is part of the E3-ubiquitin ligase complex. PVH2 binds the target protein allowing it to be ubiquitinated (59). A study reported that HBXIP abrogates the interaction between pVHL and H1F-1α inhibiting the ubiquitination and therefore degradation of HIF-1α (45). Similarly, HBXIP reduces binding of E3 ubiquitin ligase adaptor protein Kelch-like ECH associated protein 1 (KEAP1) to nuclear factor erythroid 2-related factor 2 (NRF2) and inhibits ubiquitin regulated degradation of NRF2 (60).

Another major pathway of protein degradation is chaperon-mediated autophagy. This selectively transports proteins to the lysosomes for degradation (61). HBXIP is also involved in this pathway. Unlike the ubiquitin-proteasome pathway, HBXIP mainly regulates the acetylation of target proteins by modulating acetylases. For example, tissue chip technology showed that HBXIP expression in tumor cells was related to HOXB13 and STEM20 like kinase1 (MST1) (62,63); further research into the mechanism found that HBXIP can change the acetylation levels of HOXB13 and tumor suppressor proteinMST1 via the acetylase P300 and Histone deacetylase 6 (HDAC6) to regulate chaperone-mediated autophagy HBXIP also recruits protein kinase CβII to stimulate phosphorylation of non-muscle heavy chain myosin IIA, thereby enhancing breast cancer invasion (64).

HBXIP acts as an oxidative regulator to promote tumor development. Mitochondria are among the main sources of intracellular reactive oxygen species (ROS), which are continuously produced as a byproduct of aerobic metabolism and simultaneously scavenged by the cellular antioxidant mechanisms, thus maintaining a non-toxic levels (65). Under normal physiological conditions, ROS can act as specific molecular regulators of cell signaling and function. For example, one of the more typical modes of ROS regulation is to reversibly oxidize the sulfhydryl group of a target protein to cystine thereby mediating its biological effects. ROS-induced changes in the intracellular oxidation-reduction (redox) status can affect cellular activities, including signaling, metabolism, growth and apoptosis (66,67). However, in pathological conditions, such as when tumors or inflammation occurs, excessive accumulation of ROS usually leads to redox imbalance, causing oxidative stress. Tumor cells increase their antioxidant capacity to adapt to the elevated ROS levels (68,69). HBXIP reduces ROS levels in tamoxifen-resistant breast cancer cells, demonstrating its potential antioxidant capacity (70). The KEAP1-NRF2 signaling pathway is commonly dysregulated in tumor cells to maintain oxidative balance (71). In breast cancer, HBXIP competitively binds to KEAP1 and NRF2, with a significantly higher affinity for KEAP1 than NRF2 (60). Therefore, when HBXIP is highly expressed in tumors, it binds to KEAP1, activates the nuclear displacement of NRF2, and binds to the related antioxidant response element (ARE), thereby improving the antioxidant capacity of tumor cells. Furthermore, there is an ARE sequence in the HBXIP promoter. Therefore, nuclear translocation of NRF2 allows NRF2 to bind to the HBXIP promoter sequence to upregulate HBXIP. The positive feedback between NRF2 and HBXIP increases the antioxidant capacity of tumor cells (72).

HBXIP regulates ferroptosis and promotes tumor development. Ferroptosis induces programmed cell death by catalyzing the lipid peroxidation of unsaturated fatty acids highly expressed on the cell membrane, under the action of divalent iron or ester oxygenase (73). Lipid metabolism disorder is closely related to ferroptosis. Liver X receptor (LXR) is a gene that induces and controls cholesterol homeostasis and adipogenesis. When the LXR receptor binds to its ligands, it recruits nuclear coactivators containing NR motifs to activate target gene transcription. In the absence of ligands, nuclear co-repressors containing (CoRNR) motifs are recruited to repress transcription (74,75). HBXIP, which contains a CoRNR motif in the side chain of the amino acid sequence, activates LXR independently in a ligand-independent manner, thereby upregulating sterol regulatory element-binding protein-1c expression (76). The altered LXR/Sterol regulatory element-binding transcription factor 1 (SREBP-1c) axis can disrupt fatty acid regulation in normal cells, indicating that HBXIP has the potential to regulate cell ferroptosis. Stearyl-CoA desaturase (SCD) catalyzes the conversion of saturated fatty acids to unsaturated fatty acids and its expression prevents ferroptosis (75). HBXIP acts as a coactivator of transcription factor zinc finger protein 263, which binds to the -315/-165 region of the SCD promoter to upregulate SCD expression, prevent ferroptosis and enhance the drug resistance of tumor cells (77). In summary, the relationship between HBXIP and ferroptosis has not been widely assessed, but we hypothesize there is an association between the two and this is worth further exploration.

Other mechanisms of HBXIP tumor regulation. i) Involvement in the regulation of metabolic reprogramming of tumor cells. HBXIP regulation of glucose metabolism reprogramming in tumor cells has been previously elucidated and its mechanisms of action are as follows: First, HBXIP targets the PI3K/AKT axis and its downstream molecule mTOR to regulate glucose metabolism reprogramming in gastric and bladder cancer (18,78); second, HBXIP, as a coactivator of the transcription factor E2F1, directly induces the transcription of pyruvate kinase, which promotes glycolysis (26); third, HBXIP mediates the m6A levels of HIF-1α mRNA to promote transcription and reduces ubiquitination and degradation of HIF-1α, which increases HIF-1α protein levels in cells to modulate glucose metabolism in tumor cells (41,45); and fourth, HBXIP regulates lipid metabolism in tumor cells through the LXR/SREBP-1c/FAS signaling cascade (76).

ii) HBXIP is a co-activator of multiple transcribed genes. Following phosphorylation at Ser26, HBXIP interacts with

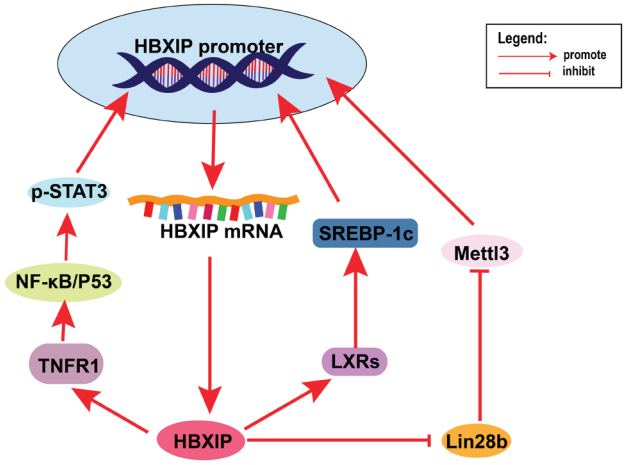

Figure 3. Multiple positive feedback processes involving HBXIP. After HBXIP upregulates TNFR1, this activates the NF-κB pathway, which activates STAT3 in the nucleus and activates the HBXIP promoter. After HBXIP upregulates LXRs, activated SREBP-1c stimulates the HBXIP promoter. HBXIP inhibits the inhibitory effect of Lin28b on Mettl3, which methylates the HBXIP promoter to promote HBXIP expression. HBXIP, hepatitis B X-interacting protein; Lin28b, Lin-28 homolog B; TNFR1, tumor necrosis factor receptor 1; NF-κB, nuclear factor-kB; STAT3, signal transducer and activator of transcription 3; LXRs, liver X receptor; Mettl3, methyltransferase-like 3; SREBP-1c, sterol regulatory element-binding transcription factor 1.

the leucine zipper domain of c-Fos and translocates from the cytoplasm to the nucleus (79). The leucine zipper domain of HBXIP binds to transcription factors, allowing HBXIP to act as a coactivator to regulate the transcription of downstream related proteins and signaling pathways (79). For example, transcription factors such as E2F1, SP1, c-Myc, STAT4 and CREB have been reported to bind to HBXIP and act on downstream-related genes and proteins to promote tumor development (25,26,80,81).

iii) Involvement in endoplasmic reticulum (ER) stress. When the demand for protein folding exceeds the limit of the ER, ER stress is triggered and the unfolded protein response (UPR) is activated to maintain ER homeostasis (82). Appropriate ER stress can promote the survival of tumor cells (83). HBXIP is a novel UPR factor that can bind to the ER stress protein sensor inositol-requiring transmembrane kinase/endoribonuclease 1α, thereby regulating UPR in the appropriate range to promote tumor cell survival (70).

iv) High expression of HBXIP can cause abnormal activation of multiple signaling pathways: Abnormal activation of the PI3K/AKT signaling pathway in liver, stomach cancer, breast cancer and tongue squamous cell carcinoma promotes the malignant progression of tumor cells (17,18,80,84); the MAPK/ERK signaling pathway can be aberrantly activated by HBXIP in non-small cell lung cancer and breast cancer, thereby promoting tumor cell invasion inhibiting targeting by the immune complement system (36,58); and knockdown of HBXIP can block the Wnt signaling pathway and inhibit the malignant progression of cervical cancer (15).

v) Positive feedback signaling in tumors. HBXIP has positive feedback signaling in multiple types of tumors (Fig. 3). For example, HBXIP upregulates the expression of Mettl3, which methylates HBXIP promoter to upregulate HBXIP protein expression. HBXIP also upregulates the expression of tumor necrosis factor receptor 1, which in turn increases the expression of HBXIP by activating the NF-kB/STAT3 signaling pathway (40,85). In summary, such a positive feedback mechanism could enhance the role of HBXIP in promoting tumor cell proliferation and invasion, or other molecular mechanisms of malignant progression.

4. Discussion

HBXIP is a membrane protein localized on the surface of lysosomes and is encoded by the Lamtor gene. Under normal physiological conditions, the pentameric complex that includes HBXIP serves an important role in the regulation of mTORC. HBXIP is essential for the normal development of mouse embryos and HBXIP promotes the transcription of insulin transcription factors, thereby maintaining normal cellular glucose metabolism. As an oncoprotein, HBXIP is highly expressed in numerous tumor types and is associated with poor clinicopathological features. Moreover, drug resistance is associated with a high expression of HBXIP protein in different tumors. For example, in estrogen-receptor-positive breast cancer, HBXIP enhances interleukin-6 transcription and maintains appropriate estrogen receptor activation to confer tamoxifen resistance. Furthermore, doxorubicin acts as a tumor suppressor by regulating DNA damage response and inducing apoptosis. However, high expression of HBXIP increase of DNA damage repair and thus serves a role in resistance to doxorubicin-induced DNA damage. In summary, the carcinogenic mechanism of HBXIP should be further studied.

In the present review, three types of mechanisms by which high expression of HBXIP promotes tumor progression were discussed: i) HXBIP promotes tumor development by regulating transcriptional, post-transcriptional and translational processes; ii) HBXIP promotes tumor development as a regulator of oxidative stress; and iii) HBXIP prevents ferroptosis of tumor cells and promotes tumor development. The reprogramming of tumor cell metabolism by HBXIP was also discussed, as well as its role as a coactivator of transcription factors and as a novel effector of UPRs.

Over the past decade, HBXIP has been studied; however, further research is still required to elucidate the relationship between HBXIP and ferroptosis to determine whether HBXIP regulates ferroptosis-related proteins, such as glutathione peroxidase 4 and solute carrier family 7 member 11 to inhibit ferroptosis of tumor cells. Furthermore, the protein function of HBXIP may be involved in interference of the Keap1-NRF2 signaling pathway. In previous studies, direct targeting of the Keap1-Nrf2-ARE signaling pathway was the main strategy to inhibit or activate oxidative stress. For example, the natural compound curcumin enhances cellular antioxidant capacity by directly disrupting Keap1 and thereby activating NRF2 in the nucleus (86). However, the fact that HBXIP competes with NRF2 to bind Keap1 brings new considerations for modulating with this pathway. Future studies should assess a mechanism to inhibit the binding of HBXIP and Keap1, to regulate the level of NRF2 in the nucleus to indirectly regulate the ROS levels to kill tumor cells. Moreover, further research on the interaction between HBXIP and PTM is required.

HBXIP can affect the expression of related proteins through acetylation, ubiquitination and phosphorylation. The diversity and universality of HBXIP, through the different modifications demonstrated in several types of tumors are worthy of further evaluation. The present review demonstrated that the expression of HBXIP and different PTM enzymes verified by tissue chip technology has a good preliminary screening effect, and subsequent testing in different tumor types should be considered to expand knowledge of the relationship between HBXIP and PTM. For the development of drugs targeting HBXIP. Although the mechanism of action of HBXIP in numerous malignant tumors has been established, research on drugs targeting HBXIP is scarce. At present, Germacrone extracted from the traditional herbal medicine *Curcuma zedoaria*, was reported by Fang *et al* (19) to inhibit the expression of HBXIP. Therefore, considering traditional Chinese herbal medicine may be a potential direction for the selection of HBXIP targeted drugs in the future. Further research should develop natural or synthetic compounds for the clinical treatment of HBXIP-related tumors.

In conclusion, HBXIP can promote the proliferation, invasion and migration of tumor cells through numerous mechanisms. Inhibition of HBXIP expression has potential therapeutic significance for cancers. Finally, HBXIP has therapeutic potential in tumors, and more in-depth studies are required to further explore its carcinogenic mechanisms.

Acknowledgements

Not applicable.

Funding

No funding was received.

Availability of data and materials

Not applicable.

Authors' contributions

The original draft of the manuscript was written by LC, manuscript editing and review was performed by LG, TZ and YY. SL and RT revised and edited the final version of the manuscript. All authors have read and approved the final version of the manuscript. Data authentication is not applicable.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

References

1. Chaturvedi VK, Singh A, Dubey SK, Hetta HF, John J and Singh MP: Molecular mechanistic insight of hepatitis B virus mediated hepatocellular carcinoma. Microb Pathog 128: 184-194, 2019.
2. Bar-Peled L, Schweitzer LD, Zoncu R and Sabatini DM: Ragulator Is a GEF for the Rag GTPases that signal amino acid levels to mTORC1. Cell 150: 1196-1208, 2012.
3. Xiu M, Zeng X, Shan R, Wen W, Li J and Wan R: The oncogenic role of HBXIP. Biomed Pharmacother 133: 111045, 2021.
4. Giguère V: Canonical signaling and nuclear activity of mTOR-a teamwork effort to regulate metabolism and cell growth. FEBS J 285: 1572-1588, 2018.
5. Villa E, Sahu U, O'Hara BP, Ali ES, Helmin KA, Asara JM, Gao P, Singer BD and Ben-Sahra I: mTORC1 stimulates cell growth through SAM synthesis and m(6)A mRNA-dependent control of protein synthesis. Mol Cell 81: 2076-2093. e9, 2021.
6. Zhou X, Wang X, Duan J, Sun W, Chen Z, Li Q, Ou Z, Jiang G, Ren X and Liu S: HBXIP protein overexpression predicts the poor prognosis of pancreatic ductal adenocarcinomas. Pathol Res Pract 215: 343-346, 2019.
7. Wang X, Feng Q, Yu H, Zhou X, Shan C, Zhang Q and Liu S: HBXIP: A potential prognosis biomarker of colorectal cancer which promotes invasion and migration via epithelial-mesenchymal transition. Life Sci 245: 117354, 2020.
8. Piao JJ, Li N, Wang YX, Lin ZH and Liu SP: HBXIP expression in gastric adenocarcinoma predicts poor prognosis. Zhonghua Bing Li Xue Za Zhi 46: 88-92, 2017 (In Chinese).
9. Li N, Wang Y, Che S, Yang Y, Piao J, Liu S and Lin Z: HBXIP over expression as an independent biomarker for cervical cancer. Exp Mol Pathol 102: 133-137, 2017.
10. Wang Y, Sun J, Li N, Che S, Jin T, Liu S and Lin Z: HBXIP overexpression is correlated with the clinical features and survival outcome of ovarian cancer. J Ovarian Res 10: 26, 2017.
11. Xia H, Ma L, Li J, Bai H and Wang D: Elevated HBXIP expression is associated with aggressive phenotype and poor prognosis in esophageal squamous cell carcinoma. Am J Cancer Res 7: 2190-2198, 2017.
12. Cheng D, Liang B and Li Y: HBXIP expression predicts patient prognosis in breast cancer. Med Oncol 31: 210, 2014.
13. Guo ZY, Jiang LP and Zhu ZT: High HBXIP expression is related to poor prognosis in HCC by extensive database interrogation. Eur Rev Med Pharmacol Sci 25: 6196-6207, 2021.
14. Wang Y, Li N, Che S, Jin T, Piao J, Liu S and Lin Z: HBXIP suppression reduces cell proliferation and migration and its overexpression predicts poor prognosis in non-small-cell lung cancer. Tumour Biol 39: 1010428317709675, 2017.
15. Gao X and Yang L: HBXIP knockdown inhibits FHL2 to promote cycle arrest and suppress cervical cancer cell proliferation, invasion and migration. Oncol Lett 25: 186, 2023.
16. Xu F, Zhu X, Han TAO, You X, Liu F, Ye L, Zhang X, Wang X and Yao Y: The oncoprotein hepatitis B X-interacting protein promotes the migration of ovarian cancer cells through the upregulation of S-phase kinase-associated protein 2 by Sp1. Int J Oncol 45: 255-263, 2014.
17. Meng X and Liu W: The effects of HBXIP on the biological functions of tongue squamous cell carcinoma cells and correlation with PI3K/Akt. Transl Cancer Res 9: 3375-3384, 2020.
18. Qiu L, Lu F, Zhang L, Wang G, Geng R and Miao Y: HBXIP regulates gastric cancer glucose metabolism and malignancy through PI3K/AKT and p53 signaling. Onco Targets Ther 13: 3359-3374, 2020.
19. Fang X, Tan T, Gao B, Zhao Y, Liu T and Xia Q: Germacrone regulates HBXIP-Mediated cell cycle, apoptosis and promotes the formation of autophagosomes to inhibit the proliferation of gastric cancer cells. Front Oncol 10: 537322, 2020.
20. Fujii R, Zhu C, Wen Y, Marusawa H, Bailly-Maitre B, Matsuzawa S, Zhang H, Kim Y, Bennett CF, Jiang W and Reed JC: HBXIP, cellular target of hepatitis B virus oncoprotein, is a regulator of centrosome dynamics and cytokinesis. Cancer Res 66: 9099-9107, 2006.
21. Fei H, Zhou Y, Li R, Yang M, Ma J and Wang F: HBXIP, a binding protein of HBx, regulates maintenance of the G2/M phase checkpoint induced by DNA damage and enhances sensitivity to doxorubicin-induced cytotoxicity. Cell Cycle 16: 468-476, 2017.

22. Li H, Wang Z, Li Y, Fang R, Wang H, Shi H, Zhang X, Zhang W and Ye L: Hepatitis B X-interacting protein promotes the formation of the insulin gene-transcribing protein complex Pdx-1/Neurod1 in animal pancreatic β-cells. J Biol Chem 293: 2053-2065, 2018.
23. Qin Y, Ni P, Zhang Q, Wang X, Du X, Yin Z, Wang L, Ye L and Chen L: Hbxip is essential for murine embryogenesis and regulates embryonic stem cell differentiation through activating mTORC1. Development 149: dev200527, 2022.
24. Yonehara R, Nada S, Nakai T, Nakai M, Kitamura A, Ogawa A, Nakatsumi H, Nakayama KI, Li S, Standley DM, *et al*: Structural basis for the assembly of the Ragulator-Rag GTPase complex. Nat Commun 8: 1625, 2017.
25. Jiang Y, Wang D, Ren H, Shi Y and Gao Y: Oncogenic HBXIP enhances ZEB1 through Sp1 to accelerate breast cancer growth. Thorac Cancer 9: 1664-1670, 2018.
26. Liu BW, Wang TJ, Li LL, Zhang L, Liu YX, Feng JY, Wu Y, Xu FF, Zhang QS, Bao MZ, *et al*: Oncoprotein HBXIP induces PKM2 via transcription factor E2F1 to promote cell proliferation in ER-positive breast cancer. Acta Pharmacol Sin 40: 530-538, 2019.
27. Haradhvala NJ, Polak P, Stojanov P, Covington KR, Shinbrot E, Hess JM, Rheinbay E, Kim J, Maruvka YE, Braunstein LZ, *et al*: Mutational strand asymmetries in cancer genomes reveal mechanisms of DNA damage and repair. Cell 164: 538-549, 2016.
28. Smith J, Tho LM, Xu N and Gillespie DA: The ATM-Chk2 and ATR-Chk1 pathways in DNA damage signaling and cancer. Adv Cancer Res 108: 73-112, 2010.
29. Holoch D and Moazed D: RNA-mediated epigenetic regulation of gene expression. Nat Rev Genet 16: 71-84, 2015.
30. Easwaran H, Tsai HC and Baylin SB: Cancer epigenetics: Tumor heterogeneity, plasticity of stem-like states, and drug resistance. Mol Cell 54: 716-727, 2014.
31. Pourdehnad M, Truitt M, Siddiqi I, Ducker G, Shokat K and Ruggero D: Myc and mTOR converge on a common node in protein synthesis control that confers synthetic lethality in Myc-driven cancers. Proc Natl Acad Sci USA 110: 11988-11993, 2013.
32. Li Y, Wang Z, Shi H, Li H, Li L, Fang R, Cai X, Liu B, Zhang X and Ye L: HBXIP and LSD1 Scaffolded by lncRNA hotair mediate transcriptional activation by c-Myc. Cancer Res 76: 293-304, 2016.
33. Smith J, Sen S, Weeks RJ, Eccles MR and Chatterjee A: Promoter DNA hypermethylation and paradoxical gene activation. Trends Cancer 6: 392-406, 2020.
34. Li H, Wang Z, Jiang M, Fang RP, Shi H, Shen Y, Cai XL, Liu Q, Ye K, Fan SJ, *et al*: The oncoprotein HBXIP promotes human breast cancer growth through down-regulating p53 via miR-18b/MDM2 and pAKT/MDM2 pathways. Acta Pharmacol Sin 39: 1787-1796, 2018.
35. Maruyama T, Kadowaki H, Okamoto N, Nagai A, Naguro I, Matsuzawa A, Shibuya H, Tanaka K, Murata S, Takeda K, *et al*: CHIP-dependent termination of MEKK2 regulates temporal ERK activation required for proper hyperosmotic response. EMBO J 29: 2501-2514, 2010.
36. Li Y, Zhang Z, Zhou X, Li L, Liu Q, Wang Z, Bai X, Zhao Y, Shi H, Zhang X and Ye L: The oncoprotein HBXIP enhances migration of breast cancer cells through increasing filopodia formation involving MEKK2/ERK1/2/Capn4 signaling. Cancer Lett 355: 288-296, 2014.
37. Halbeisen RE, Galgano A, Scherrer T and Gerber AP: Post-transcriptional gene regulation: From genome-wide studies to principles. Cell Mol Life Sci 65: 798-813, 2008.
38. Sánchez-Vásquez E, Alata Jimenez N, Vázquez NA and Strobl-Mazzulla PH: Emerging role of dynamic RNA modifications during animal development. Mech Dev 154: 24-32, 2018.
39. Zhou Y, Yin Z, Hou B, Yu M, Chen R, Jin H and Jian Z: Expression profiles and prognostic significance of RNA N6-methyladenosine-related genes in patients with hepatocellular carcinoma: Evidence from independent datasets. Cancer Manag Res 11: 3921-3931, 2019.
40. Cai X, Wang X, Cao C, Gao Y, Zhang S, Yang Z, Liu Y, Zhang X, Zhang W and Ye L: HBXIP-elevated methyltransferase METTL3 promotes the progression of breast cancer via inhibiting tumor suppressor let-7g. Cancer Lett 415: 11-19, 2018.
41. Yang N, Wang T, Li Q, Han F, Wang Z, Zhu R and Zhou J: HBXIP drives metabolic reprogramming in hepatocellular carcinoma cells via METTL3-mediated m6A modification of HIF-1α. J Cell Physiol 236: 3863-3880, 2021.
42. Yang Z, Jiang X, Li D and Jiang X: viaHBXIP promotes gastric cancer METTL3-mediated MYC mRNA m6A modification. Aging (Albany NY) 12: 24967-24982, 2020.
43. Fabian MR, Sonenberg N and Filipowicz W: Regulation of mRNA translation and stability by microRNAs. Annu Rev Biochem 79: 351-379, 2010.
44. Shukla GC, Singh J and Barik S: MicroRNAs: Processing, maturation, target recognition and regulatory functions. Mol Cell Pharmacol 3: 83-92, 2011.
45. Liu F, Zhang W, You X, Liu Y, Li Y, Wang Z, Wang Y, Zhang X and Ye L: The oncoprotein HBXIP promotes glucose metabolism reprogramming via downregulating SCO2 and PDHA1 in breast cancer. Oncotarget 6: 27199-27213, 2015.
46. Jiang Y, Wang D, Ren H, Shi Y and Gao Y: MiR-145-targeted HBXIP modulates human breast cancer cell proliferation. Thorac Cancer 10: 71-77, 2018.
47. Zhang W, Lu Z, Kong G, Gao Y, Wang T, Wang Q, Cai N, Wang H, Liu F, Ye L and Zhang X: Hepatitis B virus X protein accelerates hepatocarcinogenesis with partner survivin through modulating miR-520b and HBXIP. Mol Cancer 13: 128, 2014.
48. Hu XM, Yan XH, Hu YW, Huang JL, Cao SW, Ren TY, Tang YT, Lin L, Zheng L and Wang Q: miRNA-548p suppresses hepatitis B virus X protein associated hepatocellular carcinoma by down-regulating oncoprotein hepatitis B x-interacting protein. Hepatol Res 46: 804-815, 2016.
49. Sebastian-delaCruz M, Gonzalez-Moro I, Olazagoitia-Garmendia A, Castellanos-Rubio A and Santin I: The role of lncRNAs in gene expression regulation through mRNA Stabilization. Noncoding RNA 7: 3, 2021.
50. Zaniani NR, Oroujalian A, Valipour A and Peymani M: LAMTOR5 expression level is a biomarker for colorectal cancer and lncRNA LAMTOR5-AS1 predicting miRNA sponging effect. Mol Biol Rep 48: 6093-6101, 2021.
51. Balasooriya ER, Madhusanka D, Lopez-Palacios TP, Eastmond RJ, Jayatunge D, Owen JJ, Gashler JS, Egbert CM, Bulathsinghalage C, Liu L, *et al*: Integrating clinical cancer and PTM proteomics data identifies a mechanism of ACK1 kinase activation. Mol Cancer Res 22: 137-151, 2024.
52. Huang L, Wen X, Jin L, Han H and Guo H: HOOKLESS1 acetylates AUTOPHAGY-RELATED PROTEIN18a to promote autophagy during nutrient starvation in Arabidopsis. Plant Cell 36: 136-157, 2023.
53. Yin X, Wang X and Komatsu S: Phosphoproteomics: Protein phosphorylation in regulation of seed germination and plant growth. Curr Protein Pept Sci 19: 401-412, 2018.
54. Cockram PE, Kist M, Prakash S, Chen SH, Wertz IE and Vucic D: Ubiquitination in the regulation of inflammatory cell death and cancer. Cell Death Differ 28: 591-605, 2021.
55. Pispa J, Mikkonen E, Arpalahti L, Jin C, Martínez-Fernández C, Cerón J and Holmberg CI: AKIR-1 regulates proteasome subcellular function in Caenorhabditis elegans. iScience 26: 107886, 2023.
56. Ye L, Zhang W, Jin T, Zhang L, Wang T, Fu X, Jin T, Zhang W and Ye L: The regulation of acetylation and stability of HMGA2 via the HBXIP-activated Akt-PCAF pathway in promotion of esophageal squamous cell carcinoma growth. Nucleic Acids Res 48: 4858-4876, 2020.
57. Xu FF, Sun HM, Fang RP, Zhang L, Shi H, Wang X, Fu XL, Li XM, Shi XH, Wu Y, *et al*: The modulation of PD-L1 induced by the oncogenic HBXIP for breast cancer growth. Acta Pharmacol Sin 43: 429-445, 2022.
58. Zhang J, Sun B, Ruan X, Hou X, Zhi J, Meng X, Zheng X and Gao M: Oncoprotein HBXIP promotes tumorigenesis through MAPK/ERK pathway activation in non-small cell lung cancer. Cancer Biol Med 18: 105-119, 2021.
59. Min JH, Yang H, Ivan M, Gertler F, Kaelin WG Jr and Pavletich NP: Structure of an HIF-1alpha-pVHL complex: Hydroxyproline recognition in signaling. Science 296: 1886-1889, 2002.
60. Zhou XL, Zhu CY, Wu ZG, Guo X and Zou W: The oncoprotein HBXIP competitively binds KEAP1 to activate NRF2 and enhance breast cancer cell growth and metastasis. Oncogene 38: 4028-4046, 2019.
61. Bopape M, Tiloke C and Ntsapi C: Moringa oleifera and Autophagy: Evidence from in vivo studies on chaperone-mediated autophagy in $HepG_2$ cancer cells. Nutr Cancer 75: 1822-1847, 2023.
62. Liu B, Wang T, Wang H, Zhang L, Xu F, Fang R, Li L, Cai X, Wu Y, Zhang W and Ye L: Oncoprotein HBXIP enhances HOXB13 acetylation and co-activates HOXB13 to confer tamoxifen resistance in breast cancer. Hematol Oncol 11: 26, 2018.

63. Li L, Fang R, Liu B, Shi H, Wang Y, Zhang W, Zhang X and Ye L: Deacetylation of tumor-suppressor MST1 in Hippo pathway induces its degradation through HBXIP-elevated HDAC6 in promotion of breast cancer growth. Oncogene 35: 4048-4057, 2016.
64. Zhang L, Zhou X, Liu B, Shi X, Li X, Xu F, Fu X, Wang X, Ye K, Jin T, *et al*: HBXIP blocks myosin-IIA assembly by phosphorylating and interacting with NMHC-IIA in breast cancer metastasis. Acta Pharm Sin B 13: 1053-1070, 2023.
65. Yoneyama M, Kawada K, Gotoh Y, Shiba T and Ogita K: Endogenous reactive oxygen species are essential for proliferation of neural stem/progenitor cells. Neurochem Int 56: 740-746, 2010.
66. Freyre-Fonseca V, Delgado-Buenrostro NL, Gutiérrez-Cirlos EB, Calderón-Torres CM, Cabellos-Avelar T, Sánchez-Pérez Y, Pinzón E, Torres I, Molina-Jijón E, Zazueta C, *et al*: Titanium dioxide nanoparticles impair lung mitochondrial function. Toxicol Lett 202: 111-119, 2011.
67. Cremers CM and Jakob U: Oxidant sensing by reversible disulfide bond formation. J Biol Chem 288: 26489-26496, 2013.
68. Galadari S, Rahman A, Pallichankandy S and Thayyullathil F: Reactive oxygen species and cancer paradox: To promote or to suppress? Free Radic Biol Med 104: 144-164, 2017.
69. Moldogazieva NT, Lutsenko SV and Terentiev AA: Reactive oxygen and nitrogen species-induced protein modifications: Implication in carcinogenesis and anticancer therapy. Cancer Res 78: 6040-6047, 2018.
70. Zhang S, Wang R, Wang X, Guo X, Du Y, Guo X, Zong X, Zhu C and Zhou X: HBXIP is a novel regulator of the unfolded protein response that sustains tamoxifen resistance in ER+ breast cancer. J Biol Chem 298: 101644, 2022.
71. Baird L and Yamamoto M: Immunoediting of KEAP1-NRF2 mutant tumours is required to circumvent NRF2-mediated immune surveillance. Redox Biol 67: 102904, 2023.
72. Zhou X, Li L, Guo X, Zhang C, Du Y, Li T, Tong K, Zhu C and Wang Z: HBXIP induces anoikis resistance by forming a reciprocal feedback loop with Nrf2 to maintain redox homeostasis and stabilize Prdx1 in breast cancer. NPJ Breast Cancer 8: 7, 2022.
73. Tang R, Luo J, Zhu X, Miao P, Tang H, Jian Y, Ruan S, Ling F and Tang M: Recent progress in the effect of ferroptosis of HSCs on the development of liver fibrosis. Front Mol Biosci 10: 1258870, 2023.
74. Zhao C and Dahlman-Wright K: Liver X receptor in cholesterol metabolism. J Endocrinol 204: 233-240, 2010.
75. Cohen RN, Brzostek S, Kim B, Chorev M, Wondisford FE and Hollenberg AN: The specificity of interactions between nuclear hormone receptors and corepressors is mediated by distinct amino acid sequences within the interacting domains. Mol Endocrinol 15: 1049-1061, 2001.
76. Zhao Y, Li H, Zhang Y, Li L, Fang R, Li Y, Liu Q, Zhang W, Qiu L, Liu F, *et al*: Oncoprotein HBXIP modulates abnormal lipid metabolism and growth of breast cancer cells by activating the LXRs/SREBP-1c/FAS signaling cascade. Cancer Res 76: 4696-4707, 2016.
77. Zhang L, Li XM, Shi XH, Ye K, Fu XL, Wang X, Guo SM, Ma JQ, Xu FF, Sun HM, *et al*: Sorafenib triggers ferroptosis via inhibition of HBXIP/SCD axis in hepatocellular carcinoma. Acta Pharmacol Sin 44: 622-634, 2023.
78. Liu X, Li H, Che N, Zheng Y, Fan W, Li M, Li X and Xuan Y: HBXIP accelerates glycolysis and promotes cancer angiogenesis via AKT/mTOR pathway in bladder cancer. Exp Mol Pathol 121: 104665, 2021.
79. Zhang Y, Zhao Y, Li H, Li Y, Cai X, Shen Y, Shi H, Li L, Liu Q, Zhang X and Ye L: The nuclear import of oncoprotein hepatitis B X-interacting protein depends on interacting with c-Fos and phosphorylation of both proteins in breast cancer cells. J Biol Chem 288: 18961-18974, 2013.
80. Liu S, Li L, Zhang Y, Zhang Y, Zhao Y, You X, Lin Z, Zhang X and Ye L: The oncoprotein HBXIP uses two pathways to up-regulate S100A4 in promotion of growth and migration of breast cancer cells. J Biol Chem 287: 30228-30239, 2012.
81. Liu F, You X, Wang Y, Liu Q, Liu Y, Zhang S, Chen L, Zhang X and Ye L: The oncoprotein HBXIP enhances angiogenesis and growth of breast cancer through modulating FGF8 and VEGF. Carcinogenesis 35: 1144-1153, 2014.
82. Clarke HJ, Chambers JE, Liniker E and Marciniak SJ: Endoplasmic reticulum stress in malignancy. Cancer Cell 25: 563-573, 2014.
83. Clarke R, Shajahan AN, Wang Y, Tyson JJ, Riggins RB, Weiner LM, Bauman WT, Xuan J, Zhang B, Facey C, *et al*: Endoplasmic reticulum stress, the unfolded protein response, and gene network modeling in antiestrogen resistant breast cancer. Horm Mol Biol Clin Investig 5: 35-44, 2011.
84. Meng X, Qi XY, Wang QX and Liu WX: Effect of HBXIP on biological function and PI3K/Akt signaling pathway of adenoid cystic carcinoma cell line ACC-M. Shanghai Kou Qiang Yi Xue 26: 389-394, 2017 (In Chinese).
85. Cai X, Cao C, Li J, Chen F, Zhang S, Liu B, Zhang W, Zhang X and Ye L: Inflammatory factor TNF-α promotes the growth of breast cancer via the positive feedback loop of TNFR1/NF-κB (and/or p38)/p-STAT3/HBXIP/TNFR1. Oncotarget 8: 58338-58352, 2017.
86. Zhuang C, Narayanapillai S, Zhang W, Sham Y and Xing C: Rapid identification of Keap1-Nrf2 small-molecule inhibitors through structure-based virtual screening and hit-based substructure search. J Med Chem 57: 1121-1126, 2014.