

The oncoprotein HBXIP – its functions and roles in oncogenesis

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ABSTRACT

Nowadays, Hepatitis B X interacting protein (HBXIP) is an object of scientists' interest worldwide. It is a protein with significant involvement in the development of malignant tumors like breast or ovarian cancer. One of the most important functions of HBXIP is the regulation of cell proliferation, which is related to the progression of a cell cycle. Many studies provide the growing number of evidence that HBXIP plays various important roles, including the regulation of a cell cycle through complexes with survivin, belonging to the inhibitors of apoptosis and interactions with transcriptional factors like STAT4, SP1, TFIID or E2F1. It also has the influence on the promotion of tumor angiogenesis thanks to the association with VEGF and FGF8. Another important role of HBXIP is a reprogramming of glucose metabolism to conditions favorable to growing cancerous cells due

to regulating the activation of SCO2 and PDHA1. Furthermore, it impacts on the complement-dependent cytotoxicity, also, HBXIP affects on lipid metabolism through disturbing of metabolic pathways of FAS. According to recent studies, HBXIP can be used as a prognostic biomarker in many tumors, including cervical cancer, ovarian cancer, and esophageal squamous cell carcinoma thanks to the high expression of this protein noted exclusively in these tumor tissues. What is even more interesting, it significantly correlates with clinical attributes like metastasis to lymph nodes or grading and in some cases can potentially be used as the indicator of prognosis of treatment effectiveness. The paper is review through main functions of HBXIP and its possible applications.

Keywords: HBXIP, survivin, oncoprotein, transcription factor

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INTRODUCTION

Hepatitis B X-interacting protein (HBXIP) is a conserved 18-kDa protein, which was primarily identified in liver cells because of its interaction with hepatitis B virus X protein [1]. Further studies have shown that expression of HBXIP does not restrict exclusively to liver, but also to majority of other tissues [2]. Currently scientists try to explain the role of HBXIP in process of carcinogenesis and determine the value of HBXIP as a prognostic or predictive marker. Additional interesting aspects of this protein are studies that have proven linkage between high expression of HBXIP and development of the malignant tumors like breast or ovarian cancer. HBXIP is commonly named as the oncoprotein controlling growth and migration of cells. Moreover, it regulates cell proliferation, which is related with progression of the cell cycle [3,4].

HBXIP and survivin

Survivin is the smallest member of the inhibitors of apoptosis (IAP), family of proteins, involved in the inhibition of apoptosis and regulation of a cell cycle [5]. Survivin, despite the fact being discovered two decades ago, still remains in the scope of scientific interest. It is linked with various divergent functions, which it performs. In a normal cell it has an impact on proliferation and participates in regulation of a cell cycle. On the other hand, in cancer cells survivin is up-regulated and contributes to regulation of apoptosis. In recent years studies have shown the fact that HBXIP is a co-factor of survivin during restraining of apoptosis in cancerous cells [5,6]. Marusawa et al. described correlation between survivin and HBXIP. It has been proven that the relation between those proteins is an essential condition to reveal antiapoptotic properties of survivin [7]. There is a speculation that HBXIP-survivin complex prohibits composition of apoptosome. Thanks to binding this complex with Apaf-1 it becomes impossible to activate procaspase-9, because it selectively suppresses initiation of apoptosis [7,8]. Lack of expression of HBXIP or survivin yields possibility of cells to execute apoptosis [9].

HBXIP as a coactivator of transcriptional factors

Nowadays HBXIP is defined as oncoprotein having large importance in developing of breast cancer. HBXIP can serve as a coactivator for various transcription factors such as STAT4, SP1, TFIID or E2F1. The nuclear function of HBXIP is an contributing impact on phosphorylation of both HBXIP and c-Fos [10].

Liu et al. proved the influence of HBXIP on the promoting growth and migration of breast cancer through the influence of that protein on

STAT4. The interaction of HBXIP with a signal transducer and an activator of transcription 4 (STAT4) up-regulates S100A4 [11]. The intensified expression of S100A4 has an effect on the growth of breast cancer. Other studies have shown a strict correlation between S100A4 protein and progression and metastasis of tumors on various organs, such as esophagus, thyroid gland, large intestine, pancreas or prostate [12-15]. HBXIP has an impact on the reduction of PTEN protein's expression. The lowering of the level of PTEN is possible thanks to the elevation of the expression of DNMT1 protein and hypermethylation of promotor PTEN. Decreased expression of PTEN leads to higher expression of Akt protein (signal transduction PTEN/PI3K/AKT), which may lead to the increase of S100A4 and the growth of breast cancer [16].

Yue et al. reports that HBXIP is a oncoprotein due to the activation of transcriptional regulatory protein LIM-only protein 4 (LMO4) via Sp1 [17]. LMO4 is transcription regulator having an effect on the progression of a cell cycle, indirectly increases the quantity of cyclin C and cyclin D [18,19]. It has been shown that there is an overexpression of LMO4 in breast cancer and squamous cell oral carcinoma. Moreover, a higher expression correlates with worse prognosis [20-22]. Transcript factor Sp1 (specificity protein 1) plays an important role in the interaction between HBXIP and LMO4. This binding factor Sp1 and HBXIP leads to the activation of LMO4 promotor. The consequence of that process is the increased expression of LMO4, which has an important role in the development of breast cancer. Thus, Yue et al. suggest the major role of HBXIP in tumor progression [17].

Furthermore, HBXIP increases proliferation of breast cancer cells co-activator of transcription factor II D (TFIID) [23]. TFIID is one part of composing the RNA polymerase pre-initiation complex. It is bound with TATA box in order to begin transcription. The connection of HBXIP and TFIID results in the activation of promotor Lin28B. It has been reported that Lin28B acts as a oncogene promoting proliferation of cancer cells. It blocks selectively miR-let-7 [24-27]. Liu et al. speculate about the cooperation of oncogenes HBXIP and Lin28B, which leads to a stimulation of tumor cells growth. Furthermore, these authors suggest influence of Lin28 on high level of HBXIP [23].

Skp2 (S-phase kinase-associated protein 2) is a member of the F-box family that plays a crucial role in the coordination of a cell cycle [28,29]. It was noted, that Skp2 can suppress apoptosis through p53 [30]. Skp2 is being considered as an oncogenic protein because of its involvement in the mechanism of degradation of the cyclin-dependent

kinase (CDK) inhibitor p27(Kip1) [31]. According to the latest research Skp2 expression is correlated with HBXIP expression. Skp2 is one of the factors, that are responsible for the migration of the ovarian cancer cells [32]. Xu F et al. suggest that HBXIP mediates in this process through the interaction with transcriptional factor Sp1, what makes connection with promotor Skp2 possible [33]. Furthermore, HBXIP can influence on Skp2 expression through E2F1 [34]. E2F1 is the transcriptional factor, which belongs to the family E2F taking part in a cell cycle control [35]. Promotor Skp2 contains active site for E2F1. Binding E2F1 factor with HBXIP yields the activation of Skp2's promotor. [34]. The reports suggest an active input of HBXIP in promoting of cancer cells migration. Thus, HBXIP is regarded as an essential co-activator of transcriptional factors in cancerous cells.

Correlation with angiogenesis in tumors

Angiogenesis is a formation of new vascular channels (e.g. capillaries) from preexisting ones and may occur as a part of pathological process during the development of malignant tumor [36]. In microenvironment of tumor multiple signal particles with an impact on angiogenesis can be found. Malignant cells have an ability to release the growth factors and cytokines activating various signal pathways leading to creation of the new blood vessels [37]. Important growth factors connected with angiogenesis are agents from sub-families FGF and VEGF [38,39]. The level of expression of FGF8 have been tested in tissues with confirmed breast cancer. Those studies have proven the correlation between FGF8 and HBXIP. Moreover, inhibition of expression HBXIP reduced level of FGF8. That fact suggests the influence of HBXIP on activity of FGF8 promotor [40]. The Vascular endothelial growth factor (VEGF) is a modulator of angiogenesis, it stimulates mitosis and migration of endothelium cells. Its high expression is connected with bad prognosis during the treatment of breast cancer [39,41]. Wang et al. reported that HBXIP does not have an impact on the activity and the expression of VEGF in hepatoma cells. The increased intensity of angiogenesis in hepatoma is rather considered with the increased activation of eNOS signaling pathway [42]. On the other hand, Liu et al. proved that HBXIP increases the level of VEGF in breast cancer cells through suppression of miRNA-503 [40]. It has been suggested that HBXIP increases expression both of FGF8 and VEGF, which promotes angiogenesis in tumor environment.

Role of HBXIP in glucose metabolism

The glucose metabolism reprogramming is a necessary element of a growing cancerous cell.

Tumor tends to favor metabolism through anaerobic glycolysis rather than oxidative phosphorylation pathway. Among others, synthesis of cytochrome c oxidase 2 (SCO2) participates in the process of a modulation of the balance between the utilization of respiratory and glycolytic pathways [43]. Disruption of SCO2 in cancer cell results in switching the metabolic balance from oxidative phosphorylation to glycolysis. Fabao Liu et al. proved that a higher activity of HBXIP increased the level of intracellular glucose and lactase through downregulating SCO2 and PDHA1 in breast cancer cells. PDH E1 alpha (PDHA1) is a subunit of pyruvate dehydrogenase (PDH) complex, which provides the connection between glycolysis and the tricarboxylic acid cycle. PDHA1 knockdown enhances glucose intake, elevates the rate of glycolysis and lactate production. Hence influence of HBXIP on the glucose metabolism favors cancer cell to grow and proliferate [44]. Recently published paper suggests that HBXIP may depress gluconeogenesis. The suppression of PCK1 (Phosphoenolpyruvate carboxykinase 1), main enzyme of gluconeogenesis through HBXIP promotes hepatocarcinogenesis [45]. Reprogramming of a metabolism of glucose via HBXIP seems to be an important part of carcinogenesis.

Influence on aberration of lipid metabolism

Dysfunctional metabolism of lipids is a characteristic attribute of a growing tumor. The activity of some oncogenes or hypoxia can become the root of changes in lipid biosynthesis [46]. Cancer cells have the ability to reprogram metabolic pathways in order to survive [47]. FAS (fatty acid synthase) is an enzyme taking part in biosynthesis of fatty acids. High activity of FAS has been noticed in some types of cancerous cells. Moreover, high expression of *fasn* correlated with unfavorable prognosis [48,49]. The increased activity of FAS has been also noticed in precancerous state cells [50]. Zhao et al. researched the influence of HBXIP on abnormal metabolism of lipids during carcenogenesis. In their paper they tested the expression of HBXIP and FAS [51]. In breast cancer cells there was shown a correlation between FAS and HBXIP expression, whereas the decreased level of HBXIP expression in colon cancer cells had an effect on the lowering of FAS expression. The relationship between HBXIP and FAS is a consequence of SREBP-1c transcription factor activation. HBXIP has an ability to connect with LXR α/β , which has potential to induce some of the lipogenesis genes [52]. Right after the connection of HBXIP with LXR α/β it comes to activation of SREBP-1c promotor, which is responsible for the regulation of hepatic fatty acids synthesis. Zhao et al. proved the connection between the incorrect lipid metabolism and HBXIP,

which has the ability to activate LXR/SREBP-1c/FAS [51].

Role of HBXIP in Complement-dependent cytotoxicity (CDC)

Complement-dependent cytotoxicity (CDC) is one of the effector mechanisms of monoclonal antibodies. Bounding of the IgG or IgM antibodies with the cluster of designation on a cancerous cell activates classical pathway of the complement system. The result forms a membrane attack complex (MAC). As an effect it comes to lysis of a target cell [53]. Forming of MAC can be controlled through membrane proteins such as CD35, CD46, CD56, CD55, CD59, which are overexpressed in cancerous cells [54,55].

Cui et al. proved that HBXIP has a strong impact on CD46, CD55 and CD59 expression in cancer cells. Overexpression of HBXIP caused the increase of antigen expression. Moreover, the authors suggest that NF- κ B is responsible for upregulation of CD46, CD55 and CD59 [56].

The connection among regulation of CD59 expression and NF- κ B was researched also by Du et al. According to their paper, NF- κ B and CREB (as an enhancer-binding protein) have the influence on an induced expression of CD59 [57]. HBXIP contributes to the immune escape of a carcinoma cell from CDC by up-regulating the expression of CD46, CD55 and CD59.

HBXIP as a new prognostic tumor marker

Cervical cancer. Cervical cancer is one of the most common female tumors worldwide. Data from 2012 says about 528,000 new cases and 266,000 deaths due to this type of cancer in the world [58]. In the developing countries high mortality is connected with delayed diagnosis and high-level risk of metastasis [59,60].

It seems to be reasonable to identify new, specific biomarkers, with practical application, novel predictive indicators, in the case of cervical cancer as therapeutic targets. Li et al. tested the expression of HBXIP protein in cervical cancer and cervical intraepithelial neoplasia (CIN). HBXIP protein was not expressed in healthy cervical epithelium. On the other hand, HBXIP expression has been noticed in atypical cells: CIN, gland and epithelium from squamous cell carcinoma (SCC). High expression occurred only in atypical cells, not in regular neighbor cells. HBXIP was located mostly in cytoplasm. Moreover, its expression is correlated with clinical level and metastasis. It was also noted, that high expression of this protein is connected with lower overall survival (OS) [61].

Potentially, HBXIP may be the indicator of prognosis in the treatment effectiveness of cervical cancer. Tests suggest usefulness of HBXIP as a new diagnostic and prognostic marker in the

treatment of SCC. However, there is the need for complex analysis of molecular mechanisms in order to recognize an exact biological function of HBXIP in carcinogenesis.

Ovarian cancer. The morbidity rate of ovarian cancer is estimated on about 240,000 new cases and is cause of 150,000 deaths per year [62]. Ovarian cancer in over 75% of cases is diagnosed on advanced phase (III/IV stage). The disease diagnosis in advanced stage and difficulties in early diagnosis are main reasons of high mortality rate of this type of tumor [63]. Despite the improvement of treatment possibilities, prognosis still remains unsatisfying [64].

There were attempts of estimation of connection between HBXIP expression and ovarian cancer progression. Scientists demonstrated positive expression HBXIP in ovarian cancer tissue. In regular tissues its expression did not occur [33].

Wang et al. reported that overexpression of HBXIP is significantly correlated with clinical attribute like metastasis to lymph nodes or grading. That indicates that HBXIP can be used as a potential prognostic marker in ovarian cancer, however there is the necessity of running additional trials to verify those studies [65].

Esophageal squamous cell carcinoma (ESCC). Annually there are over 400,000 diagnosed cases of esophageal cancer [66]. Statistically, male patients suffer more frequently. Among the risk factors, the most common are smoking tobacco and drinking alcohol beverages [67,68].

Scientists tested the correlation between patients' clinical features with ESCC and the expression of HBXIP. In the tissue taken from the patients with z ESCC significantly higher level of HBXIP has been detected. The expression of this protein correlated with TNM stage, histological grade and lymph node metastasis [69].

That fact suggests the potential impact of HBXIP as oncoprotein in ESCC, however these results require further research.

CONCLUSIONS

This review of the functions and role of HBXIP in oncogenesis has been focused largely on data published for the recent few years. According to collected data the oncoprotein HBXIP has many important roles, such as the control of proliferation, growth and migration of cancerous cells. What is even more interesting, HBXIP has also many functions like activation of transcriptional factors, modulation of immune response, regulation of metabolism of glucose and lipids. It also acts as angiogenesis stimulator in cancer cell. Further research can bring thorough knowledge about involvement of HBXIP various processes, what could be useful to find a new role of this protein in

diagnostic or therapy. The question is the high number of the roles, which it plays in different processes, don't exclude this protein as potential therapeutic target. On the other hand, the association of HBXIP with numerous clinical attributes proclaims that this protein can be used as prognostic marker. In the light of the mentioned above facts it is reasonable to run further research to confirm the role of HBXIP as a significant biomarker of carcinogenesis.

Conflicts of interest

The authors declare that they have no conflicts of interest.

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