

The aspartyl (asparaginy)l beta-hydroxylase in carcinomas

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1. ABSTRACT

Aspartyl-(asparaginy)l- β -hydroxylase (AAH) is a member of the α -ketoglutarate-dependent dioxygenase family that catalyzes the hydroxylation of aspartyl and asparaginy residues epidermal growth factor (EGF)-like domains of protein. In human tumorous cell lines from main systems of body, including tumor cells of kidney, throat, breast, liver, bladder, cervical and ovary, the AAH can be detected at both the transcriptional level and the translational level, and moreover, the AAH expression is usually increased, which is associated with the development and progression of carcinomas. Thus, AAH may play an important role in different carcinomas and may be a potential hub in carcinogenesis. In this review, we will discuss the role of AAH in carcinomas, focusing on liver cancers and other digestive tumors, lung cancers, and tumors of nervous system.

2. INTRODUCTION

Aspartyl-(asparaginy)l- β -hydroxylase (AAH) is a 2 transmembrane protein and a member of the α -ketoglutarate-dependent dioxygenase family that catalyzes the hydroxylation of aspartyl and asparaginy residues in epidermal growth factor (EGF)-like domains (1) of proteins such as Notch and Jagged (2,3). AAH can interact with both Notch and Jagged (4). The Jagged is the ligand for Notch (5,6), and is the substrate for AAH hydroxylation (7). In

human tumorous cell lines, including tumor cells of kidney, throat, breast, liver, bladder, cervical and ovary, the AAH can be detected at both the transcriptional level and the translational level (8). The expression of AAH in human tumor tissues, such as hepatocellular carcinoma (HCC), lung cancer, kidney cancer, cholangiocarcinoma, prostate cancer, breast cancer and glioblastoma can be detected by AAH-specific monoclonal antibody (9). Later, Yang and colleagues (10) investigated several tumor cell lines and human tissues, finding an increased expression of AAH in a variety of carcinomas and an association between AAH over-expression and the development and progression of carcinomas. Thus, AAH over-expression may be a biomarker in malignant disease. In this review, we will discuss the relationship between AAH and human tumors, and we will focus primarily on tumors in liver, lung, and nervous system.

3. AAH IN LIVER CANCERS

Cholangiocarcinoma is a highly epithelial cell malignancy arising from varying locations within the biliary tree showing markers of cholangiocyte differentiation (11), and is the second most common primary hepatobiliary malignancy with a global increasing incidence (12). Cholangiocarcinoma can be classified into intrahepatic cholangiocarcinoma

(ICC) and extrahepatic cholangiocarcinoma. In ICC, an increased expression of AAH was associated with tumor size, infiltrative growth pattern, aggressive histological grade, vascular invasion and poor prognosis, suggesting an important role of AAH in regulating invasive or metastatic tumor cell growth of human ICC and predicting poor outcome (13). In addition to human tumor tissues, in cholangiocarcinoma cell lines, AAH was increasingly expressed in cells derived from moderately or poorly differentiated compared with well-differentiated tumors, and promoted the infiltrative growth pattern of cholangiocarcinoma cells by promoting motility (14). In contrary, the AAH is undetectable during bile duct proliferation in both human and rat models of non- cholangiocarcinoma as compared with cholangiocarcinoma, suggesting that over-expression of AAH is associated with cellular transformation of biliary epithelial cells into malignancy (15). Moreover, in a rat model of ICC, immunization with AAH-loaded dendritic cells has antitumor effects that these dendritic cells have cytotoxicity against cholangiocarcinoma cells *in vitro*, suppressed growth and metastasis of intrahepatic tumor, and were also associated with increased CD3+ T cells infiltration into the tumors (16). However, whether AAH is involved into extrahepatic cholangiocarcinoma onset and development hasn't been reported, and may be investigated in future to provide more understanding on the role of AAH in cholangiocarcinoma.

In addition to cholangiocarcinoma, human AAH is also over-expressed in HCC (17). HCC is the predominant type of hepatic carcinoma, accounting for 90% of liver primary malignant tumors (18-20). The HCC development is involved the accumulation of genetic and epigenetic alterations, which is associated with liver damage, chronic inflammation and the hyperproliferative hepatocytes status (21-30). The AAH is one of the best expressed tumor antigenic precursor proteins in HCC specimens (31). The over-expression of AAH in HCC predicts a poor prognosis of patients with a higher tumor recurrence and lower survival rates as compared with AAH under-expression (32).

As similar as that in ICC, the AAH stimulation results in the development of antigen-specific CD4+ T cells, and the immunization with AAH-loaded dendritic cells can reduce the risk of HCC recurrence in mice HCC model (33). In HepG2 cells, AAH expression can be induced by insulin and IGF-1 via Erk MAPK and phosphoinositol-3-kinase(PI3K)-Akt

pathways, and activated by over-expression of insulin-receptor substrate type 1 (IRS-1), leading to motility and invasiveness in HepG2 cells, which can be reduced by siRNA inhibition of AAH expression (34) (Figure 1). In the liver of transgenic mice, the hepatitis Bx+/IRS-1+ double transgenic liver had an increased hepatocellular dysplasia and developed HCC, which have selectively increased expression of AAH (35). On the other hand, inhibition of AAH activity can inhibit HCC tumor growth *in vivo* using orthotopic and subcutaneous murine models via inhibiting Notch signaling cascade in HCC (36).

4. AAH IN OTHER TUMORS OF DIGESTIVE SYSTEM

In the study by Yang and colleagues (10), among 19 kinds of human tumor tissues, tumors from digestive system, such as pancreatic carcinoma, gastric carcinoma, colon cancer, cholangiocarcinoma and liver cancer, all have a 100% positive ratio of AAH expression, suggesting a high sensibility of AAH in various kinds of tumors in digestive system in addition to liver tumors. The monoclonal antibodies of human AAH, FB50 and SF25, could distinguish most pancreatic adenocarcinoma from normal pancreas, acting as potential biomarkers of pancreatic adenocarcinoma (37), suggesting the special expression of AAH in pancreatic adenocarcinoma. In diagnosis of bile duct cancer, when combined with both human AAH and homeobox B7, the overall diagnostic sensitivity to 82 %, suggesting a potential of AAH for the diagnosis of bile duct carcinoma (38).

However, knowledge on the relationship between AAH and color cancer is rare. Only Wang and colleagues (39) reported that no relationship between AAH and tumor grade or survival of patients with colon cancer, but humbug can serve as a prognostic biomarker of TNM stage II colon cancers, and moreover humbug can lead to an increased level of FB50 monoclonal antibodies in tumor tissue. Humbug and AAH are alternatively spliced protein products of the AAH messenger RNA, so humbug is a truncated homolog of AAH that lacks a catalytic domain (40). Over-expression of humbug increases intracellular calcium levels by promoting its release from intracellular stores (41). Both AAH and humbug are expressed in most tissues under the regulation of the P1 promoter, which is involved into Sp and USF DNA interaction and transcription activity (42). As similar in colon cancer, humbug is over-expressed in during the malignant progression of human gastric

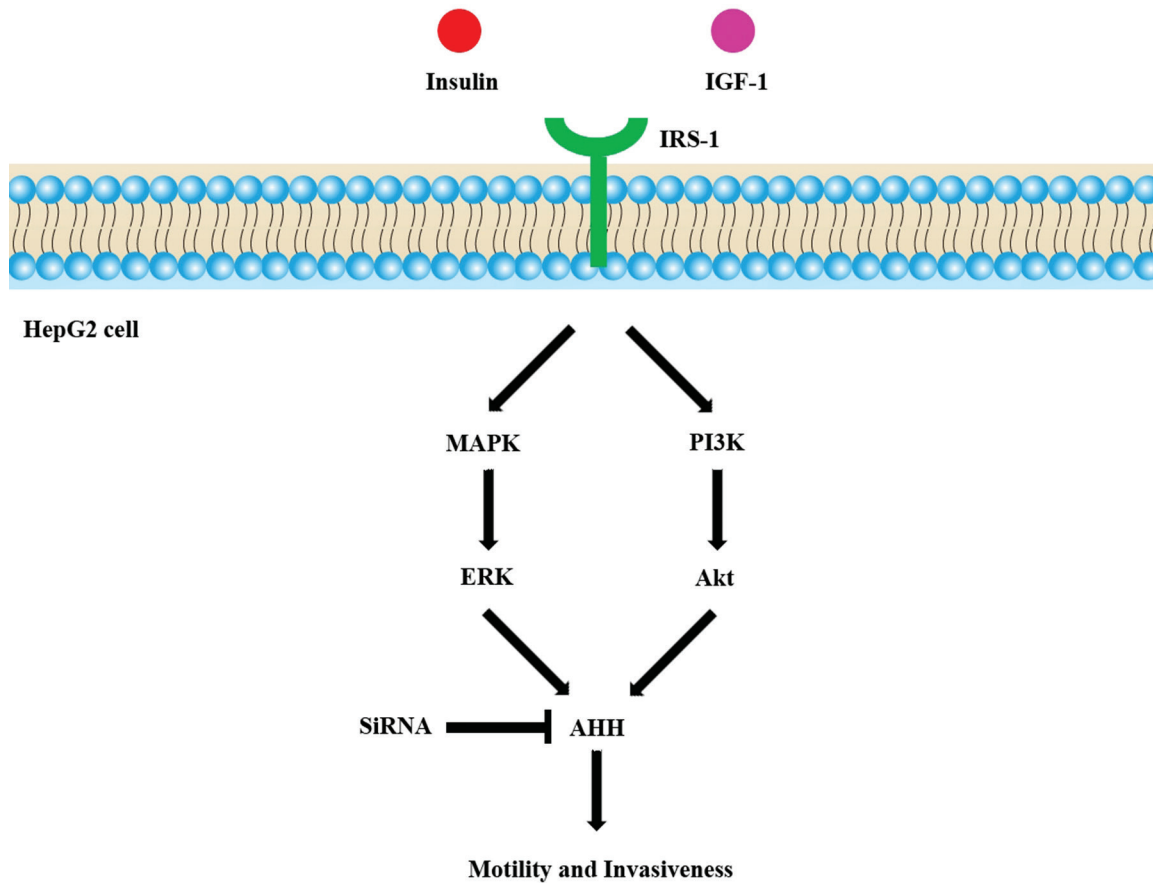


Figure 1. Aspartyl-(asparaginyl)-β-hydroxylase (AAH) leads to motility and invasiveness in hepatocellular carcinoma (HCC). In HepG2 cells, AAH expression can be induced by insulin and IGF-1 via Erk MAPK and phosphoinositol-3-kinase-Akt (PI3K-Akt) pathways, and activated by over-expression of insulin-receptor substrate type 1 (IRS-1), leading to motility and invasiveness in HepG2 cells, which can be reduced by siRNA inhibition of AAH expression

cancer cells, and moreover it can play a role as a metastasis-inducing gene (43).

5. AAH IN LUNG CANCER

In lung cancer, AAH has been observed to associate with the disease, but only with the non-small cell lung cancer type, especially squamous cell carcinoma. In non-small cell lung cancer, AAH and humbug show a prognostic potential in clinic implication. Among paraffin-embedded tumor tissues of adenocarcinomas, bronchioloalveolar carcinomas, squamous cell carcinomas and large cell carcinomas, only non-small cell lung carcinoma can be recognized by FB50 monoclonal antibody, the monoclonal antibodies of human AAH, which was an independent predictor of survival with squamous cell carcinoma and correlate with poor prognosis in non-small cell lung

cancer, particularly squamous cell carcinoma subtype (44). However, the mechanism of AAH in squamous cell carcinomas development is still unclear. The study *in vitro* or *in vivo* is needed in future to explore the precise role of AAH in biological behaviors of squamous cell carcinoma, such as proliferation, invasion and migration, which in turn may be help to explain the prognostic role of AAH in this disease.

In human adenocarcinomas cell line, A549 tumors, the phosphorothioate antisense oligonucleotides differentially down-regulated AAH and humbug at the mRNA and protein level, but the biological function of these proteins *in vivo* with nude mice bearing A549 tumor xenografts was limited by the poor uptake properties of phosphorothioate (45). Future study may be get new findings when the bottleneck in technology is break through.

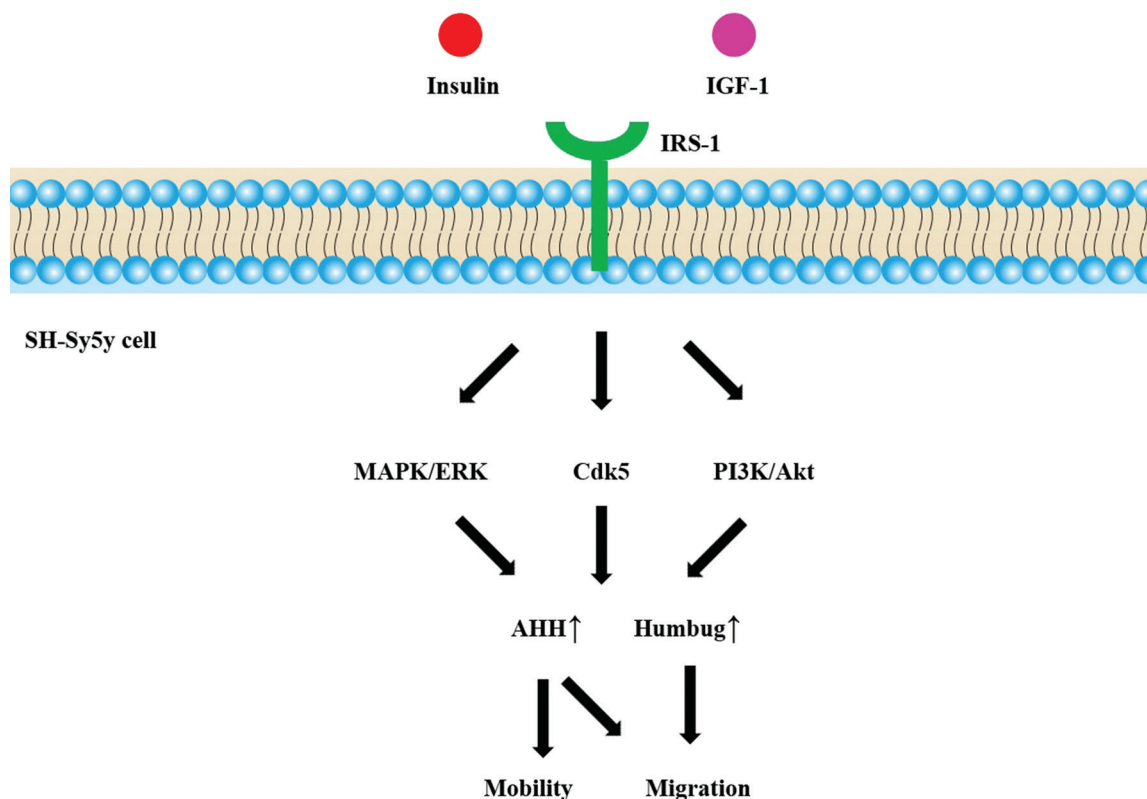


Figure 2. Aspartyl-(asparaginy)-β-hydroxylase (AAH) and humbug in neuroblastoma cells. In SH-Sy5y human neuroblastoma cells, AAH and humbug are over-expressed, which are regulated by mediators of cell migration that insulin/IGF-1 signaling through Erk MAPK, PI3 kinase-Akt, and Cdk-5, but only AAH mediates directional motility in SH-Sy5y neuroblastoma cells.

6. AAH IN TUMORS OF NERVOUS SYSTEM

The AAH is over-expressed in primary human malignant neuroectodermal tumors, including medulloblastomas and neuroblastomas, and Sy5y cells transfected with the human AAH cDNA have an increasing motility and enhancing proliferation, survival, and cell cycle progression (46). Through AAH domain-containing protein 2, a hypoxic niche can regulate glioblastoma stem cells (47).

The insulin-like growth factor (IGF) signaling through these receptors mediates diverse neuronal functions, including motility and survival (48). In cerebellar neuronal cells, the neuronal migration can be impaired by ethanol, which is associated with reduced IGF-I stimulated AAH protein expression, and is mediated by increased GSK-3β phosphorylation and Caspase degradation of AAH (49,50). The IGF signaling can regulate the cross-talk between AAH and hypoxia inducible factor-1 alpha within a hydroxylation-regulated

signaling pathway in regulating neuronal motility (51). In SH-Sy5y human neuroblastoma cells, AAH and humbug are over-expressed, which are regulated by mediators of cell migration that insulin/IGF-1 signaling through Erk MAPK, PI3 kinase-Akt, and Cdk-5, but only AAH mediates directional motility in SH-Sy5y neuroblastoma cells (52) (Figure 2).

7. CONCLUSIONS

In several tumors from main system of the body, AAH has been detected. But only in cholangiocarcinoma and HCC, the function and mechanism of AAH in tumor has been concerned and found the role of AAH in tumor growth and metastasis. AAH in other tumors of digestive system and lung squamous cell carcinoma is recognized as a prognosis biomarker. AAH in nerve system tumor is still need more investigate. Since the important role of AAH in several different kinds of carcinomas, AAH may be a hub in carcinogenesis. However, the role of AAH in these tumors' biological behaviors,

such as tumor growth, migration or invasion, is rarely reported. Further studies *in vivo* or *in vitro* may provide more knowledge on the role of AAH in tumors and give more understanding on the pathogenesis, which may provide a novel therapeutic strategy.

8. ACKNOWLEDGEMENTS

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Abbreviation: AAH: Aspartyl-(asparaginyl)- β -hydroxylase; EGF: epidermal growth factor; HCC: hepatocellular carcinoma; ICC: intrahepatic cholangiocarcinoma; PI3K: phosphoinositol-3-kinase; IRS-1: insulin-receptor substrate type 1; IGF: insulin-like growth factor

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