Technology in Cancer Research & Treatment
Volume 20: 1-7

DOI: 10.1177/15330338211033063
journals.sagepub.com/home/tct
SAGE

Low Expression of KAT6B May Affect Prognosis in Hepatocellular Carcinoma

Junjie Jiang[1,2,3,4], Hui-Ju Wang[2,3], Xiao-Zhou Mou[2,3], Huanqing Zhang[1,2,3,4], YiZhen Chen[1,2,3,4], and Zhi-Ming Hu[4]

Abstract

Aims: Lysine acetyltransferase 6B (KAT6B), is a histone acetyltransferase implicated to have a role in tumor suppression. However, the relationship between KAT6B and hepatocellular carcinoma (HCC) is unclear. The purpose of this study was to detect the expression of KAT6B in HCC tissues and analyze its connection with the clinicopathological features of HCC. **Methods:** First, we performed immunohistochemical staining on 250 HCC tissues and 222 non-tumor liver tissues to examine the expression of KAT6B.Then the relation between KAT6B expression and clinicopathological parameters was analyzed by chi-square test, and the overall survival analysis was conducted by Kaplan-Meier survival method. In addition, based on the Oncomine expression array online and the UALCAN database, we compared KAT6B expression differences between normal liver tissues and HCC tissues more broadly. **Results:** Compared with normal tissues, KAT6B expression was significantly lower in HCC tissues. Low KAT6B expression was found to be related to gender, AFP level, and tumor size. According to the online database, KAT6B expression was found to be decreased in HCC tissues and high in normal tissues. **Conclusions:** Lower expression of KAT6B is associated with poor prognosis of HCC, and KAT6B may be a potential tumor suppressor in liver cancer.

Keywords

KAT6B, MYST, ING5, immunohistochemistry, hepatocellular carcinoma

Received: December 31, 2020; Revised: June 09, 2021; Accepted: June 28, 2021.

Introduction

HCC has become the sixth most commonly diagnosed cancer and the fourth leading cause of cancer death worldwide (Mortality rate 8.2%), with about 841,000 new cases and 782,000 deaths annually.[1] It is also the fourth most commonly diagnosed cancer in China and the leading cause of cancer death among Chinese men.[2] Although hepatectomy can significantly reduce tumor recurrence and metastasis, most patients have been diagnosed in the middle-late stage and are still at risk of recurrence and metastasis. Therefore, how to improve the early screening and diagnosis rate of high-risk groups of liver cancer, improve the drug sensitivity of cancerous tissues and improve the patient quality of life has become an urgent need of the society.

MYST proteins is the largest and most diversiform family of the different HAT (histone acetyltransferase) families that have been characterized to date.[3] The family currently comprises 5 human HATs: Tip60, MOZ, MORF, HBO1 and MOF,[4] known as Lysine acetyltransferases (KATs). Which can catalyze lysine acetylation, a reversible protein modification implicated in a wide variety of disease states.[5] In addition, acetylation of histones by KATs is indispensable for regulating gene expression, DNA repair, cell cycle homeostasis.[6] As an important cofactor of p53, ING5 contains a highly conserved carboxy-terminal plant homeodomain (PHD) finger, which can

[1] Second Clinical Medical College, Zhejiang Chinese Medical University, Hangzhou, Zhejiang, China
[2] Clinical Research Institute, Zhejiang Provincial People's Hospital (People's Hospital of Hangzhou Medical College), Hangzhou, Zhejiang Province, China
[3] Key Laboratory of Tumor Molecular Diagnosis and Individualized Medicine of Zhejiang Province, Zhejiang Provincial People's Hospital (People's Hospital of Hangzhou Medical College), Hangzhou, Zhejiang Province, China
[4] Department of Hepatobiliary and Pancreatic Surgery, Zhejiang Provincial People's Hospital (People's Hospital of Hangzhou Medical College), Hangzhou, Zhejiang Province, China

Corresponding Author:
Zhi-Ming Hu, Department of Hepatobiliary and Pancreatic Surgery, Zhejiang Provincial People's Hospital (People's Hospital of Hangzhou Medical College), Hangzhou, Zhejiang Province 310014, China.
Email: huzhiming4199@163.com

combine with histones to regulate chromatin mediated transcriptional.[7] KAT6B (MYST4/MORF) forms a stable complex with the tumor suppressor ING5 and the Bromodomain PHD finger protein 1/2/3, thereby specifically acetylating histone 3(H3). KAT6B has been proved to have tumor suppressive effect in many recent reports. For example, it was discovered that KAT6B consumption promoted small cell lung cancer growth.[8] In contrast, overexpression of KAT6B caused tumor suppression.[8] Similarly, the chromosomal translocation of KAT6B has been identified in a variety of cancers, including leiomyoma,[9] breast cancer[10] and castration-resistant prostate cancer.[11] However, the relation between the expression level of KAT6B and the clinical treatment of liver cancer is not clear, and its biological function is not as well-known as that of other KATs family members. Therefore, it is necessary to further study the mechanism of KAT6B as a tumor suppressor during the occurrence and development of liver cancer tumors, as well as its potential as a target molecule in the treatment of liver cancer tumors.

In consideration of the high incidence of HCC and the multiple effects of KAT6B, we wanted to probe the impact of KAT6B in HCC. In order to explore the relation between KAT6B expression and the clinicopathological parameters of HCC and survival rate of overall, we went through immunohistochemical staining to research the expression of KAT6B in 250 HCC tissues and 222 para-carcinoma tissue. We found that the expression of KAT6B was linked to tumor size, serum AFP level, gender. We delved into the available datasets from the Oncomine and UALCAN Expression Array databases to appraise KAT6B expression in HCC. We found the expression of KAT6B was significantly decreased in HCC. This study might provide further insight into the mechanism of action of KAT6B in HCC cancers.

Materials and Methods

Patients and Tissue Samples

All the human tissue samples were acquired from HCC patients at Zhejiang Provincial People's Hospital (Hangzhou, China). This research was approved by the Ethics Committee of Zhejiang Provincial People's Hospital (Hangzhou, China). All the patients afforded written informed consent.

In this study, the collection time of medical records was 77 months, and the follow-up time was 60 months. We estimate the sample size by Log-Rank test, according to the test power of 0.1, the unilateral $\alpha = 0.025$, and the dropout rate was not more than 5% in each group. The minimum sample sizes for the 2 groups are 116 and 117 respectively. This study included 250 HCC patients from Zhejiang provincial people's hospital from April 2008 to September 2014. 250 paraffin-embedded HCC tissue samples and 222 non-tumor liver tissue samples were obtained in the aggregate. Non-tumor liver tissues were paracancer tissues, which were not paired samples of the HCC tissues. Survival time was calculated according to the time between the date of surgery and the end of follow-up or the date of death. All the tissue samples were used for the tissue microarray (TMA) analysis which constructed by Shanghai Biochip Co., Ltd (Shanghai, China).

Table 1. Expression of KAT6B in HCC and Non-Cancerous Liver Tissues.

	KAT6B expression			
Samples	Low	High	Total	*P*-value
Normal liver tissues	72 (32.4%)	150 (67.6%)	222 (100%)	0.045
HCC tissues	104 (41.6%)	146 (58.4%)	250 (100%)	
Total	176 (37.3%)	296 (62.7%)	472 (100%)	

Immunohistochemical Staining and Evaluation

Immunohistochemical staining was performed taking advantage of Histostain-Plus IHC Kit (Invetrogen, USA), following the manufacturer's instructions. We heated 5 μm sections from TMA at 70°C for 2 hours, then dewaxed them in xylene, rehydrated them using a gradient of ethanol concentrations and boiled them in TE buffer using a pressure cooker for 3 minutes to recover the antigen. After that, the sections were sealed with 3% H2O2 for 15 minutes to refrain endogenous peroxidase activity, and then incubated with 10% goat non-immune serum for 20 minutes to decrease background non-specific staining. Afterward, the sections were incubated with the Rabbit anti-kat6b polyclonal antibody (Abcam, Cambridge, UK, ab58823, 1:1000 dilution) overnight at 4°C, then added biotin-labeled secondary antibody for incubation for 20 minutes at room temperature, and HRP-conjugated streptavidin antibiotics were used to incubate the sections for 30 minutes at room temperature. Furthermore, DAB Kit (ZSGB-BIO, China) was used for color development. In the end, the sections were counterstained with hematoxylin, dehydrated, cleared, and fixed.

The immunohistochemical stain of KAT6B was scored independently by 2 pathologists, according to the proportion of positively stained cells and the intensity of staining. Staining intensity was evaluated with a four-stage scoring system: 0 = negative, 1 = weak, 2 = moderate, and 3 = strong. With regard to the percentage of positive cells: 0 for no cell stained, 1 for 1%-25% of cells stained, 2 for 26%-50% of cells stained, 3 for 51%-75% of cells stained, 4 for >75% of cells stained. Scores for intensity and percentage of positive cells were multiplied to give an overall evaluation. Scores <3 was used to indicate low KAT6B expression and scores ≥ 3 for high KAT6B expression.

Oncomine Database Analysis

We conducted a comprehensive Analysis of the existing data set in the Oncomine Expression Array database (www.oncomine.org) to compare the difference expression of KAT6B between HCC and Normal tissues, using the following terms: "KAT6B," "Cancer vs. Normal Analysis." Five relevant data sets were finalized, including wurmbach Liver,[12] MAS Liver,[13] Roessler Liver 2,[14] TCGA Liver, Guichard Liver.[15]

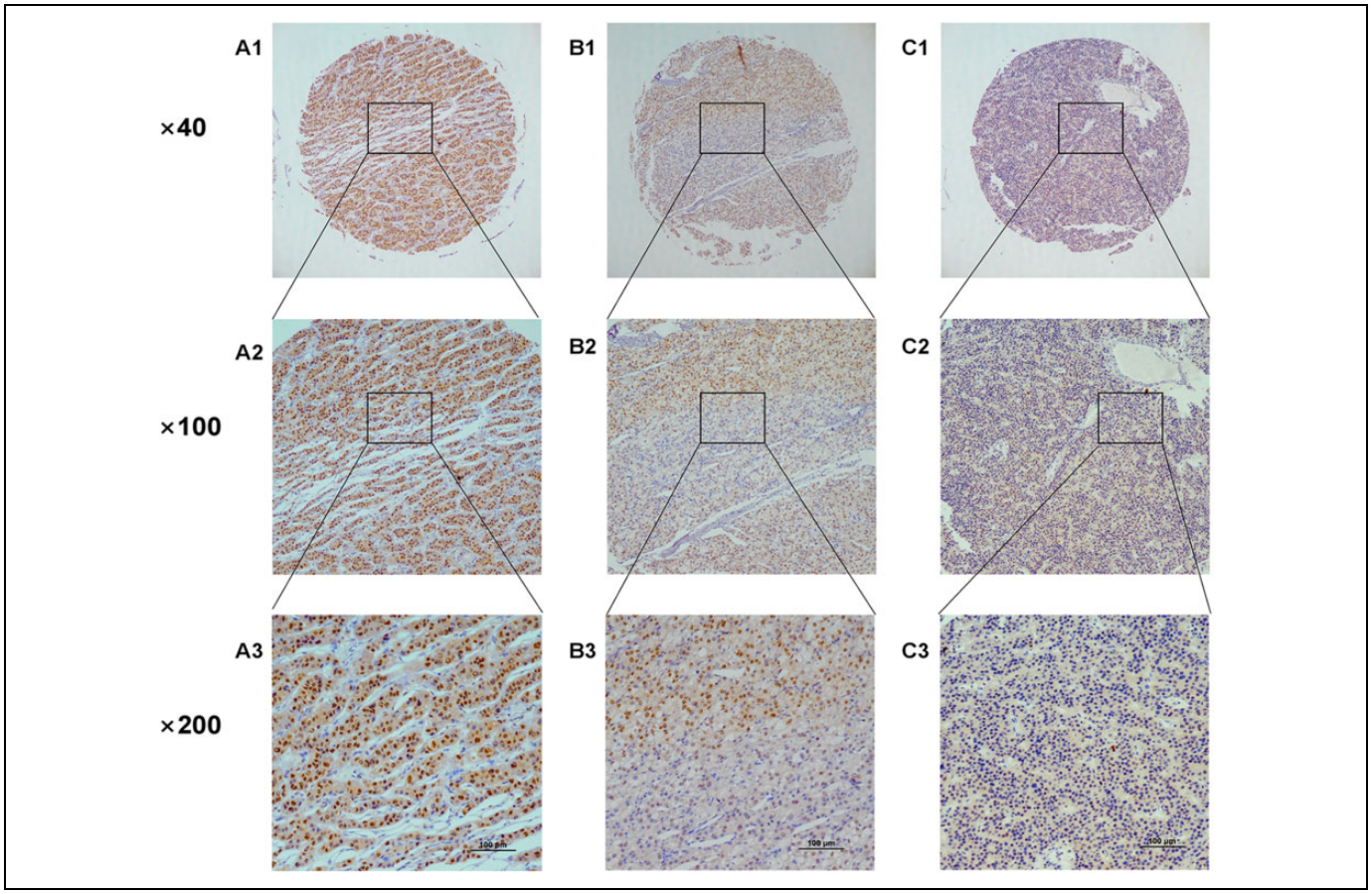

Figure 1. Strong (A), Moderate (B), and Negative (C) expression of KAT6B in HCC tissues.

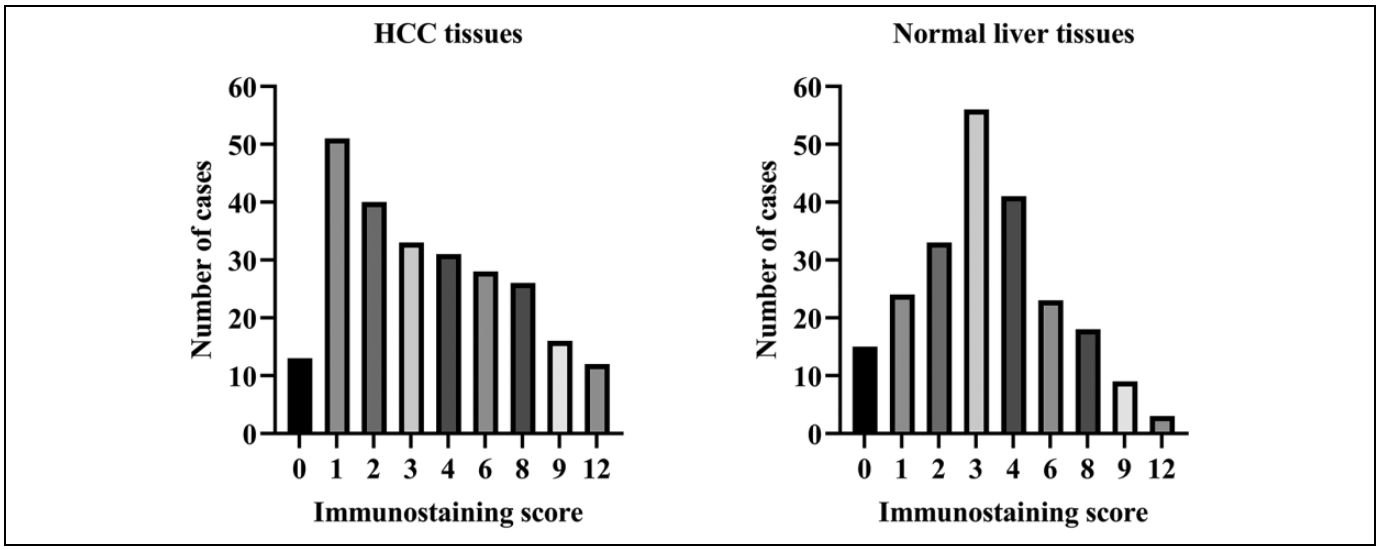

Figure 2. The distribution of immunohistochemical scores of HCC and Normal liver tissues.

Statistical Analysis

Statistical analysis was performed by using SPSS v13.0 (SPSS Inc., Chicago, IL, USA). Chi-square test was performed to evaluate the statistical significance of the relationship between KAT6B expression and clinicopathological parameters. The Kaplan-Meier method was used to estimate the survival curves

and the logarithmic rank test was used to calculate the differences between these curves. $P < 0.05$ was considered as a threshold of statistical significance.

Results

Expression of KAT6B in HCC and Adjacent Non-Cancerous Tissues

Immunostaining of KAT6B was mainly detected in the nucleus of HCC and non-cancerous liver tissues, but absent in the cytoplasm. The expression of KAT6B was detected in 150 of the 222 (67.6%) samples of adjacent non-cancerous liver tissues. However, high expression of KAT6B was found in 146 of 250 (58.4%) HCC tissues (Table 1, Figures 1 and 2, $P = 0.045$).

Relationship Between KAT6B Expression and Clinicopathologic Parameters

The relation between the expression of KAT6B and clinical variables in HCC was shown in Table 2. KAT6B expression was significantly associated with gender, tumor size, and AFP. The expression of KAT6B is significantly reduced in tumor of male, large size and high AFP level. Aside from that, there was no evident relationship between KAT6B expression and else clinicopathologic parameters.

Relationship Between Clinicopathological Parameters and Survival

Table 2 indicates the relationship between HCC patients' clinicopathological parameters and their survival conditions. Through Log Rank (Mantel-Cox) test, HCC patients with distant metastasis, microvascular invasion, and Edmondson Grade III undergo poor survival conditions ($P < 0.05$). However, other clinicopathological parameters did not exhibit significant relationship with survival condition in this database.

Table 2. Relationship Between KAT6B Expression and Pathological Parameters of HCC and Relationship Between Pathological Parameters of HCC and Survival.[a]

		KAT6B			
Clinical parameters	All cases	Low	High	*P* value	Log rank
Age (years)				0.294	0.257
< 55	96	44	52		
> 55	154	60	94		
Gender				0.024	0.683
Male	206	79	127		
Female	44	25	19		
Size				0.010	0.216
< 5	135	45	90		
≥5	111	55	56		
Tumor number				0.705	0.807
Single	207	85	122		
Multiple	43	19	24		
Edmondson grade				0.352	0.007
I + II	152	59	93		
III	96	43	53		
Metastasis				0.477	0.003
M0	227	94	133		
M1	18	9	9		
Microvascular invasion				0.328	0.013
Absence	98	38	60		
Presence	94	43	51		
HBs antigen				0.377	0.487
Negative	51	24	27		
Positive	194	78	116		
Cirrhosis				0.198	0.251
Negative	81	29	52		
Positive	169	75	94		
AFP(ng/mL)				0.004	0.394
< 50	111	35	76		
≥ 50	85	44	41		
Status				0.000	/
Alive	84	25	59		
Dead	26	18	8		

Abbreviations: HBs antigen, hepatitis B surface antigen; AFP, alpha fetoprotein.

[a]The total number of cases is less than 250 because of incomplete pathological data.

Survival Analysis

The 5 year cumulative survival rate of patients with low KAT6B expression was 58.1%, and that of patients with high KAT6B expression was 88.1% based on a Kaplan-Meier survival analysis. Patients with low KAT6B expression had an average survival time of 40.047 ± 3.645 months, which was significantly shorter than that of patients with high KAT6B expression group (54.425 ± 1.877, $P < 0.001$). This difference indicated that low expression of KAT6B was related with poor overall survival (Figure 2).

Based on the Kaplan-Meier survival analysis, patients with low KAT6B expression had a 5-year accumulate survival rate of 58.1%, and those with high KAT6B expression had a 5-year accumulate survival rate of 88.1%. The average survival time of patients with high KAT6B expression was 54.425 ± 1.877 months, which was obviously longer than that of patients with low KAT6B expression group (40.047 ± 3.645 months, $P < 0.001$). This difference manifested that low expression of KAT6B was related to inferior overall survival (Figure 3).

Analysis of KAT6B Expression According to Oncomine Databases

In order to compare the expression of KAT6B in hepatocellular carcinoma with normal tissues, we analyzed the Oncomine database. What we discovered was that KAT6B expression was lower in HCC tissues in comparison with normal controls (Figure 4, all $P = 0.007$). These data highlight that KAT6B may be a potential inhibitor of HCC.

Discussion

HCC is the fourth most commonly diagnosed cancer in China and the leading cause of cancer death among Chinese men.[2] KAT6B is a lysine acetyltransferase which regulates chromatin organization and function.[16] The KAT6B genes is repeatedly mutated in leukemia, non-hematologic malignancies, and multifarious other abnormalities.[17] In this study, we analyzed the expression of KAT6B in hepatocellular carcinoma. A meta-analysis of the online Oncomine Expression Array database showed that KAT6B Expression in 494 HCC tissues was significantly lower than that in 394 normal liver tissues. Besides, in the outlier dataset, most of the case reports still showed decreased expression of KAT6B in HCC patients. In subsequent immunohistochemical staining, the staining results also confirmed that KAT6B was highly expressed in normal liver tissue. These results suggest that KAT6B may be a potential tumor suppressor in HCC.

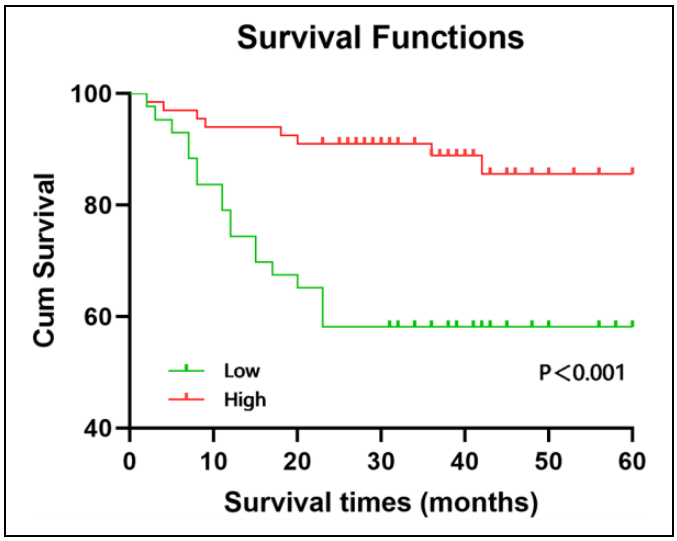

Figure 3. Kaplan-Meier survival curves of the HCC patients with high or low KAT6B expression.

It has been confirmed that KAT6B is available for targeted inhibition by a variety of miRNAs to promote the proliferation of gastric cancer, tongue squamous cell carcinoma and other tumors. However, it is still unclear how KAT6B regulates the development of HCC. Previous proteomics studies of catalytic enzyme complexes have shown that acetylated proteins are usually subunits of the KATs complex.[18] KAT6B contains many acetylated subunits: MORF, ING5, BRPF1/2/3 and EAF6.[19] MORF can form a stable complex to specifically acetylate histone H3 with tumor suppressor ING5 and PHD-finger motif. The deficiency of MOZ /MORF may destroy ING5 complex and lose the ability to regulate p53 function, leading to the cause of tumorigenesis.[20] As an important co-factor of p53, the ING tumor suppressor family regulates DNA repair, apoptosis and cell cycle.[21-23] All ING proteins include plant homologous domains (PHD), which have been identified as binding motifs of DNA, RNA and proteins that bind histones in a methylated sensitive manner to regulate chromatin structure.[7,24,25] Thus they are closely related to the pathogenesis of different types of cancer as well as tumor growth (angiogenesis) and metastasis.[26] Although all ING family (Ing1-Ing5) proteins have similar phylogenetic conserved structures, ING5 is unique as part of the HAT complex of HBO1 (MYST subgroup containing zinc finger structures), which is involved in

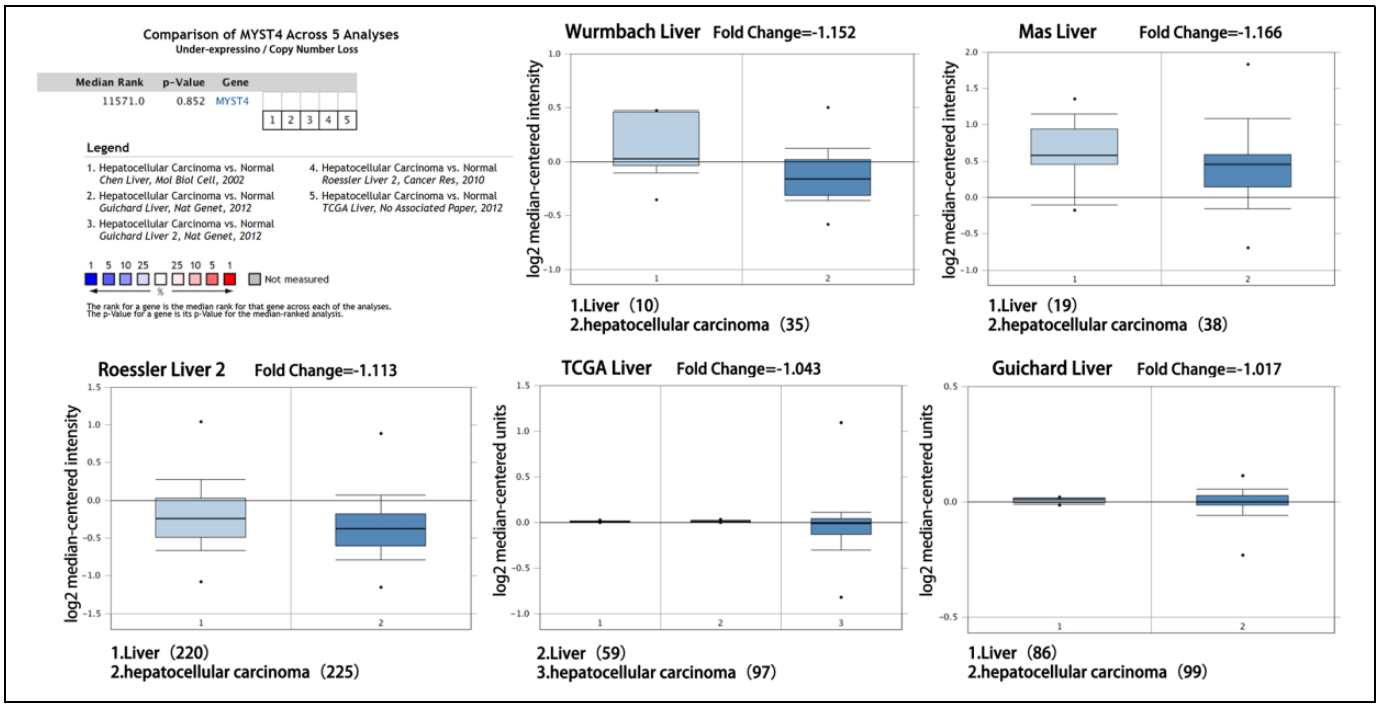

Figure 4. Expression of KAT6B in normal liver and hepatocellular carcinoma tissues based on Oncomine database.

the acetylation of histone H4 and activation of p53.[26,27] Recent research have shown that ING5 is decreased in many malignant tumors, such as breast cancer,[28] gastric cancer,[29] lung cancer,[30] etc. Most importantly, its expression in HCC cell lines decreased significantly.[31] Our study also revealed that the expression of KAT6B in men, larger tumors and tumors with high AFP level significantly decreased, and low KAT6B expression was significantly correlated with poor overall survival. Therefore, it is speculated that KAT6B can inhibit the proliferation of liver cancer via ING5-mediated P53 pathway.

Due to the complicated course of HCC, a lot of factors may result in a poor prognosis. Despite the significant relation between tumor metastasis, microvascular invasion, higher grading and prognosis in our database, as elaborated above, KAT6B mainly involved in gene expression, DNA repair, cell cycle homeostasis,[32] is closely correlated with tumor proliferation. KAT6B low expression in gastric cancer,[33] tongue squamous cell carcinoma,[34] and small cell lung cancer[8] has merely promoted tumor proliferation, without strengthening tumor invasion. KAT6B mainly affects the prognosis by affecting the proliferation and size of the tumor, rather than strengthening the invasiveness of the tumor. It can be found this study that the low expression of KAT6B is also closely related to tumor size. Therefore, we speculate that KAT6B has a closer relation with tumor size in HCC than that with tumor metastasis, vascular complication, and higher grading.

Conclusion

In short, our results suggest that KAT6B may be a potential inhibitor of HCC. Decreased expression of KAT6B was associated with gender, AFP level, tumor size, poor overall survival, and poor prognosis in HCC.

Authors' Note

Junjie Jiang and Hui-Ju wang contributed equally to this work. JJ, HZ and CY wrote and revised the manuscript; HW critically revised and corrected the manuscript; and ZH conceived the idea for the review, collected and interpreted the studies included, reviewed the manuscript and contributed significantly to the writing the manuscript. All authors read and approved the final manuscript. The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request. The research was allowed by Review Board of Hospital Ethics Committee, and the informed consent from every patient was obtained before we collected the data (2021QT179).

Acknowledgments

This work was supported by the grants from the General research projects of Education Department of Zhejiang Province (Y20204460).

Declaration of Conflicting Interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Funding

The author(s) disclosed receipt of the following financial support for the research, authorship, and/or publication of this article: This work was supported by the grants from the General research projects of Education Department of Zhejiang Province (Y20204460).

ORCID iDs

Junjie Jiang https://orcid.org/0000-0002-2539-2325
Huanqing Zhang https://orcid.org/0000-0002-2495-8438

References

1. Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, Jemal A. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA Cancer J Clin*. 2018;68(6):394-424. doi:10.3322/caac.21492
2. Chen W, Zheng R, Baade PD, et al. Cancer statistics in China, 2015. *CA Cancer J Clin*. 2016;66(2):115-132. doi:10.3322/caac.21338
3. Shanmugam MK, Dharmarajan A, Warrier S, et al. Role of histone acetyltransferase inhibitors in cancer therapy. *Adv Protein Chem Str*. 2021;125:149-191. doi:10.1016/bs.apcsb.2020.08.002
4. Zhang LX, Lemire G, Gonzaga-Jauregui C, et al. Further delineation of the clinical spectrum of KAT6B disorders and allelic series of pathogenic variants. *Genet Med*. 2020;22(8):1338-1347.
5. Huang F. New KAT6 inhibitors induce senescence and arrest cancer growth. *Synth Syst Biotechnol*. 2018;3(4):244-245. doi:10.1016/j.synbio.2018.10.006
6. McCullough CE, Marmorstein R. In vitro activity assays for MYST histone acetyltransferases and adaptation for high-throughput inhibitor screening. *Method Enzymol*. 2016;573:139-160. doi:10.1016/bs.mie.2016.01.016
7. Zhang T, Meng J, Liu X, et al. ING5 differentially regulates protein lysine acetylation and promotes p300 autoacetylation. *Oncotarget*. 2018;9(2):1617. doi:10.18632/oncotarget.22176
8. Simó-Riudalbas L, Pérez-Salvia M, Setien F, et al. KAT6B is a tumor suppressor histone H3 Lysine 23 acetyltransferase undergoing genomic loss in small cell lung cancer. *Cancer Res*. 2015;75(18):3936-3945. doi:10.1158/0008-5472.CAN-14-3702
9. Yang X. MOZ and MORF acetyltransferases: molecular interaction, animal development and human disease. *Biochimt Biophys Acta (BBA)*. 2015;1853(8):1818-1826. doi:10.1016/j.bbamcr.2015.04.014
10. Lynch H, Wen H, Kim YC, et al. Can unknown predisposition in familial breast cancer be family-specific? *Breast J*. 2015;19(5):520-528. doi:10.1111/tbj.12145
11. Grasso CS, Wu YM, Robinson DR, et al. The mutational landscape of lethal castration-resistant prostate cancer. *Nature*. 2012;487(7):239-243. doi:10.1038/nature11125
12. Wurmbach E, Chen YB, Khitrov G, et al. Genome-wide molecular profiles of HCV-induced dysplasia and hepatocellular carcinoma. *Hepatology*. 2017;45(4):938-947. doi:10.1002/hep.21622
13. Mas VR, Maluf DG, Archer KJ, et al. Genes involved in viral carcinogenesis and tumor initiation in hepatitis C virus-induced hepatocellular carcinoma. *Mol Med*. 2009;15(3-4):85-94. doi:10.2119/molmed.2008.00110

14. Roessler S, Jia HL, Budhu A, et al. A unique metastasis gene signature enables prediction of tumor relapse in early-stage hepatocellular carcinoma patients. *Cancer Res*. 2010;70(24): 10202-10212. doi:10.1158/0008-5472.CAN-10-2607
15. Guichard C, Amaddeo G, Imbeaud S, et al. Integrated analysis of somatic mutations and focal copy-number changes identifies key genes and pathways in hepatocellular carcinoma. *Nat Genet*. 2012;44(6):694-698. doi:10.1038/ng.2256
16. He W, Zhang M, Wang X, et al. KAT5 and KAT6B are in positive regulation on cell proliferation of prostate cancer through PI3K-AKT signaling. *Int J Clin Exp Patho*. 2013;6(12):2864-2871.
17. Borrow J, Stanton VP, Andresen JM, et al. The translocation t(8; 16)(p11;p13) of acute myeloid leukaemia fuses a putative acetyltransferase to the CREB-binding protein. *Nat Genet*.1996;14(1):33-41.
18. Khokhar ES, Borikar S, Eudy E, Stearns T, Young K, Trowbridge JJ. Aging-associated decrease in the histone acetyltransferase KAT6B is linked to altered hematopoietic stem cell differentiation. *Exp Hematol*. 2020;82:43-52. doi:10.1016/j.exphem.2020.01.014
19. Choudhary C, Kumar C, Gnad F, et al. Lysine acetylation targets protein complexes and co-regulates major cellular functions. *Science*. 2000;325(5492):834-840. doi:10.1126/science.1175371
20. Shiseki M, Nagashima M, Pedeux RM, et al. p29ING4 and p28ING5 bind to p53 and p300, and enhance p53 activity. *Cancer Res*. 2003;63(10):2373-2378.
21. Liu N, Wang J, Wang J, et al. ING5 is a tip60 cofactor that acetylates p53 in response to DNA damage. *Cancer Res*. 2013; 73(12):3749-3760. doi:10.1158/0008-5472.CAN-12-3684
22. Linzen U, Lilischkis R, Pandithage R, et al. ING5 is phosphorylated by CDK2 and controls cell proliferation independently of p53. *PLoS One*. 2015;10(4):e123736. doi:10.1371/journal.pone.0123736
23. Xie X, Xu X, Sun C, Yu Z. Hepatitis B virus X protein promotes proliferation of hepatocellular carcinoma cells by upregulating miR-181b by targeting ING5. *Biol Chem*. 2018;399(6):611-619. doi:10.1515/hsz-2018-0178
24. Thalappilly S, Feng X, Pastyryeva S, et al. The p53 tumor suppressor is stabilized by Inhibitor of Growth 1 (ING1) by blocking polyubiquitination. *PLoS One*. 2011;6(6):e21065. doi:10.1371/journal.pone.0021065
25. Peña PV, Davrazou F, Shi X, et al. Molecular mechanism of histone H3K4me3 recognition by plant homeodomain of ING2. *Nature*. 2006;442(7098):100-103. doi:10.1038/nature04814
26. Doyon Y, Cayrou C, Ullah M, et al. ING tumor suppressor proteins are critical regulators of chromatin acetylation required for genome expression and perpetuation. *Mol Cell*. 2006;21(1):51-64. doi:10.1016/j.molcel.2005.12.007
27. Iizuka M, Sarmento OF, Sekiya T, Scrable H, Allis CD, Smith MM. Hbo1 links p53-dependent stress signaling to DNA replication licensing. *Mol Cell Biol*. 2008;28(1):140-153. doi:10.1128/MCB.00662-07
28. Ding X, Zhao S, Yang L, et al. The nucleocytoplasmic translocation and up-regulation of ING5 protein in breast cancer: a potential target for gene therapy. *Oncotarget*. 2017;8(47):81953. doi:10.18632/oncotarget.17918
29. Xing Y, Yang X, Xu X, et al. The altered expression of ING5 protein is involved in gastric carcinogenesis and subsequent progression. *Hum Pathol*. 2011;42(1):25-35. doi:10.1016/j.humpath.2010.05.024
30. Zhao S, Yang X, Shen D, et al. The down-regulated ING5 expression in lung cancer: a potential target of gene therapy. *Oncotarget*. 2016;7(34):54596. doi:10.18632/oncotarget.10519
31. Yang X, Shen D, Zhao S, et al. Expression pattern and level of ING5 protein in normal and cancer tissues. *Oncol Lett*. 2019; 17(1):63-68. doi:10.3892/ol.2018.9581
32. Wiesel-Motiuk N, Assaraf YG. The key roles of the lysine acetyltransferases KAT6A and KAT6B in physiology and pathology. *Drug Resist Update*. 2020;53:100729. doi:10.1016/j.drup.2020.100729
33. Zhu L, Wang C, Lin S, Zong L. CircKIAA0907 retards cell growth, cell cycle, and autophagy of gastric cancer in vitro and inhibits tumorigenesis in vivo via the miR-452-5p/KAT6B axis. *Med Sci Monitor*. 2020;26:e924160. doi:10.12659/MSM.924160
34. Gu Y, Liu H, Kong F, et al. miR-22/KAT6B axis is a chemotherapeutic determiner via regulation of PI3k-Akt-NF-kB pathway in tongue squamous cell carcinoma. *J Exp Clin Canc Res*. 2018; 37(1):164. doi:10.1186/s13046-018-0834-z