Low Expression of KAT6B May Affect Prognosis in Hepatocellular Carcinoma

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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

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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. It is also the fourth most commonly diagnosed cancer in China and the leading cause of cancer death among Chinese men. 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. The family currently comprises 5 human HATs: Tip60, MOZ, MORF, HBO1 and MOF, known as Lysine acetyltransferases (KATs). Which can catalyze lysine acetylation, a reversible protein modification implicated in a wide variety of disease states. In addition, acetylation of histones by KATs is indispensable for regulating gene expression, DNA repair, cell cycle homeostasis. As an important cofactor of p53, ING5 contains a highly conserved carboxy-terminal plant homeodomain (PHD) finger, which can

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combine with histones to regulate chromatin mediated transcriptional. 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. In contrast, overexpression of KAT6B caused tumor suppression. Similarly, the chromosomal translocation of KAT6B has been identified in a variety of cancers, including leiomyoma, breast cancer and castration-resistant prostate cancer. 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.

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 α = 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.**

| Samples            | KAT6B expression |       |       |       | P-value |
|--------------------|------------------|-------|-------|-------|---------|
| Normal liver tissues | Low              | 72    | 32.4% | 150   | 67.6%   | 222     | 100%   | 0.045 |
| HCC tissues        | High             | 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 (Invitrogen, 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, MAS Liver, Roessler Liver 2, TCGA Liver, Guichard Liver.
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.

**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.

**Table 2. Relationship Between KAT6B Expression and Pathological Parameters of HCC and Relationship Between Pathological Parameters of HCC and Survival.**

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

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

*The total number of cases is less than 250 because of incomplete pathological data.
Discussion

HCC is the fourth most commonly diagnosed cancer in China and the leading cause of cancer death among Chinese men. KAT6B is a lysine acetyltransferase which regulates chromatin organization and function. The KAT6B genes is repeatedly mutated in leukemia, non-hematologic malignancies, and multifarious other abnormalities. 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.

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. KAT6B contains many acetylated subunits: MORF, ING5, BRPF1/2/3 and EAF6. 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. As an important co-factor of p53, the ING tumor suppressor family regulates DNA repair, apoptosis and cell cycle. 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. Thus they are closely related to the pathogenesis of different types of cancer as well as tumor growth (angiogenesis) and metastasis. 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 3. Kaplan-Meier survival curves of the HCC patients with high or low KAT6B expression.

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. Recent research have shown that ING5 is decreased in many malignant tumors, such as breast cancer, gastric cancer, lung cancer, etc. Most importantly, its expression in HCC cell lines decreased significantly. 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, is closely correlated with tumor proliferation. KAT6B low expression in gastric cancer, tongue squamous cell carcinoma, and small cell lung cancer 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.

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

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