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The histone acetyltransferase hMOF suppresses hepatocellular carcinoma growth

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ABSTRACT

Males absent on the first (MOF) is a histone acetyltransferase belongs to the MYST (MOZ, Ybf2/Sas3, Sas2 and TIP60) family. In mammals, MOF plays critical roles in transcription activation by acetylating histone H4K16, a prevalent mark associated with chromatin decondensation. MOF can also acetylate transcription factor p53 on K120, which is important for activation of pro-apoptotic genes; and TIP5, the largest subunit of NoRC, on K633. However, the role of hMOF in hepatocellular carcinoma remains unknown. Here we find that the expression of hMOF is significantly down-regulated in human hepatocellular carcinoma and cell lines. Furthermore, our survival analysis indicates that low hMOF expression predicts poor overall and disease-free survival. We demonstrate that hMOF knockdown promotes hepatocellular carcinoma growth *in vitro* and *in vivo*, while hMOF overexpression reduces hepatocellular carcinoma growth *in vitro* and *in vivo*. Mechanically, we show that hMOF regulates the expression of SIRT6 and its downstream genes. In summary, our findings demonstrate that hMOF participates in human hepatocellular carcinoma by targeting SIRT6, and hMOF activators may serve as potential drug candidates for hepatocellular carcinoma therapy.

1. Introduction

Hepatocellular carcinoma (HCC) causes more than 500,000 deaths per year worldwide [1]. Although patients with chronic hepatitis virus B and C infections or liver cirrhosis are known to be high-risk populations for HCC, measures aiming at preventing HCC development in these patients are limited. In addition, the long-term prognosis after surgical resection of HCC remains poor, owing to the high rate of *de novo* recurrence and the lack of effective preventive therapy [2]. Those facts prompted us to investigate the underling molecular mechanisms for hepatocellular carcinoma development and to identify new prognostic factor.

Human MOF (males absent on the first), as a histone acetyltransferase, is responsible for histone H4K16 acetylation in human cells. Recent studies have shown that the abnormal gene expression of hMOF is involved in certain primary cancers. For instance, MOF overexpression correlates with increased cellular proliferation, oncogenic transformation and tumor growth [3]. Abnormal gene expression of hMOF is involved in certain primary cancers, including breast cancer [4], renal cell carcinoma [5], ovarian cancer [6], medulloblastoma [7], as well as lung cancers [8,9]. hMOF is more frequently highly expressed in non-small cell lung cancer than corresponding normal tissues [8–10]. In addition, up-regulation of H4K16 acetylation is also more frequent in NSCLC than normal tissues [9]. Furthermore, hMOF promotes the cell proliferation, migration and adhesion of NSCLC cell lines [9]. A recent study shows that hMOF facilitates lung cancer by maintaining drug-resistance through acetylating Nrf2 [10]. Low expression of hMOF with clinicopathological features of colorectal carcinoma, gastric cancer and renal cell carcinoma [5,11]. hMOF is frequently down-regulated in primary breast carcinoma and medulloblastoma and constitutes a biomarker for clinical outcome in medulloblastoma [7]. Although, hMOF is down-regulated in those carcinoma and predicts favorite prognosis, it is unknown how hMOF functions in those carcinomas. Those studies indicate that hMOF plays dual roles in carcinogenesis depending upon individual cancer types and targets. However, it remains unknown whether and how hMOF participates in human hepatocellular carcinoma.

SIRT6 belongs to the class III NAD+-dependent deacetylase family. The role of SIRT6 in human carcinoma has been widely investigated, especially in human hepatocellular carcinoma. During the initiation of hepatocellular carcinoma, survival of initiated cancer cells is controlled by c-Jun, independently of p53, through suppressing c-Fos-mediated apoptosis. Mechanistically, c-Fos induces

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SIRT6 transcription, which represses survivin by reducing histone H3K9 acetylation and NF-κB activation. Importantly, increasing the level of SIRT6 or targeting the anti-apoptotic activity of survivin at the initiation stage markedly impairs cancer development [12]. Sirt6-deficient hepatocytes showed up-regulation of established hepatocellular carcinoma (HCC) biomarkers alpha-fetoprotein (Afp), insulin-like growth factor 2 (Igf2), H19, and glypican-3. Furthermore, decreased SIRT6 expression was observed in hepatoma cell lines that are known to be apoptosis-insensitive. Re-expression of SIRT6 in HepG2 cells increased apoptosis sensitivity to CD95-stimulation or chemotherapy treatment. Loss of Sirt6 was characterized by oncogenic changes, such as global hypomethylation, as well as metabolic changes, such as hypoglycemia and increased fat deposition [13]. However, the molecular mechanism by which SIRT6 is controlled in hepatocellular carcinoma and how SIRT6 participate in the development process in addition to cancer initiation are not fully understood.

Here in this study, we show that hMOF is down-regulated in human hepatocellular carcinoma tissues and cell lines. Low hMOF level is significantly correlated with overall and disease-free survival of patients. In addition, hMOF regulates hepatocellular carcinoma cells growth *in vitro* and *in vivo*. Finally, we show that hMOF controls SIRT6 and its downstream genes in hepatocellular carcinoma.

2. Materials and methods

2.1. Patients

Seventy human HCC samples and twenty-four non-HCC samples were collected at Eastern Hepatobiliary Surgery Hospital, Second Military Medical University. All HCC samples were histopathologically re-evaluated independently by two pathologists before further analysis. Healthy liver samples were obtained from donor livers used for transplantation that were pathologically evaluated before transplantation. Further patient information is included in Supplementary Table S1. A written form of informed consent for the use of samples was obtained from all patients before surgery. The Ethical Committee of Second Military Medical University approved the collection and use of human samples.

2.2. Immunohistochemistry

Tissues were fixed with 4% neutral formalin. Cancer or adjacent tissue sections were subjected for immunohistochemical staining with anti-hMOF antibody. Paraffin sections were subjected to high-temperature antigen retrieval, 3 min in a pressure cooker in 0.01 M citrate buffer pH 6.0. Slides were treated with 3% H_2O_2 for 15 min, blocked in 5% normal horse serum in PBS for 20 min, and stained with anti-hMOF antibody in 5% normal goat serum overnight at 4 °C. Secondary antibody was used according to Vectastain ABC kits, followed by DAB staining.

The areas of total cancer and hMOF-positive areas were quantified using ImageJ. The average percentage of hMOF-positive area is 8%. This median value was used to cut off the subgroups of all immunohistochemical variables in our data. The patients were then divided into two groups: hMOF high expression group ($\geqslant$8% hMOF-positive/total tissue cores, $n = 30$) and PHF8 low expression group (< 8% hMOF-positive/total tissue cores, $n = 40$)

2.3. Cell culture and infection

Hepatocellular carcinoma cell lines Huh7, Hep3B, PLC/PRF/5 and hepatoblastoma cell line HepG2 were cultivated as described previously [14]. Human hepatocytes were isolated from specimens obtained from patients undergoing hepatic resections for the therapy of hepatic tumors after informed consent and according to the rules of the ethics committee of the Second Military Medical University. The cells were cultured as described previously [15].

To prepare hMOF-expressing adenovirus, the human MOF cDNA was inserted into D-TOPO vector (Invitrogen). The D-TOPO-MOF plasmid was cloned into the pAd/CMV/V5-DEST vector (Invitrogen) using LR Clonase (Invitrogen). The plasmid was linearized with PacI and was transfected into 293A cells for production of adenovirus. For Ad-Ctrl, the GFP cDNA was inserted into D-TOPO vector instead of MOF cDNA. Control shRNA and specific shRNA targeting hMOF were purchased from Invitrogen, and the packaging procedure is the same to that of overexpression. The sequences targeting hMOF is shown in Table S2. Cells were infected with virus as indicated in the figure legend.

2.4. Western blot

Human tissues and cells were lysed in RIPA lysis buffer with mixture of protease inhibitors (Thermo). 40 μg total proteins were applied to 12% SDS–polyacrylamide gel. After electrophoresis, the proteins were transferred to PVDF membranes, which were then blocked with 5% fat-free milk for 2 h. The membranes were then probed with primary antibody for MOF (Abcam, ab71209), SIRT6 (Abcam, ab62739) or GAPDH (Abcam, ab37168) at 4 °C overnight, and then the membranes were washed and incubated with HRP-conjugated secondary antibodies (Zhongsanjinqiao) for 2 h and finally visualized using Chemiluminescent ECL reagent (Beyotime).

2.5. Quantitative PCR (q-PCR)

Total RNA from fresh samples was extracted with TRIzol (Invitrogen) and cDNA was synthesized using 1 μg RNA with the Advantage RT-for-PCR kit (BD Biosciences). We quantified relative mRNA level with PCR amplifications using SYBR Green PCR Master Mix (TaKaRa). The q-PCR primers used in this study are listed in Table S3.

2.6. Cell proliferation assay

Cell proliferation was monitored by a 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) Cell Proliferation/Viability Assay kit (R&D SYSTEMS) in according to the guidelines.

2.7. Soft sugar colony formation assay

Cancer cells were suspended in 1.5 ml complete medium supplemented with 0.45% low melting point agarose (Invitrogen). The cells were placed in 35 mm tissue culture plates containing 1.5 ml complete medium and agarose (0.75%) on the bottom layer. The plates were incubated at 37 °C with 5% CO_2 for 2 weeks. Cell colonies were stained with 0.005% crystal violet and analyzed using a microscope. The colony number in each well was calculated.

2.8. Xenograft mice experiment

Xenograft mice experiments were performed as described previously [16]. The tumor weight was evaluated at the terminal of experiments. $N = 10$ in each group.

2.9. Chromatin immunoprecipitation (ChIP) assay

The ChIP assay and SIRT6 promoter primer was described previously [12].

2.10. Luciferase reporter assay

The luciferase assay and sequence information for SIRT6 promoter was described previously [12].

2.11. Statistical analysis

All values are expressed as the means ± SEM of at least three independent experiments if no additional information is indicated. Statistical differences among groups were determined using either Student's *t* test or one-way ANOVA. The Kaplan–Meier method was used to estimate overall survival. Survival differences according to PHF8 or miR-125b expression were analyzed by the log-rank test. Linear regression analysis was performed to analyze the correlation between hMOF and SIRT6 levels. *p* values of less than 0.05 were considered statistically significant.

3. Results

3.1. hMOF is down-regulated in human hepatocellular carcinoma and cell lines

In order to investigate the potential role of hMOF in human hepatocellular carcinoma, we checked the expression profile of hMOF in human hepatocellular carcinoma tissues and cell lines. We recruited 70 cases of hepatocellular carcinoma in this study, 24 cases of adjacent non-cancer liver tissues were used as control. Our immunohistochemical and Western blot results revealed the down-regulation of hMOF protein in human hepatocellular carcinoma tissues compared to adjacent normal tissues (Fig. 1A–B). To explore whether hMOF level changes at the transcription level, we extracted RNA and performed q-PCR analysis. We found that hMOF was significantly decreased at the mRNA level (Fig. 1C), indicating that hMOF reduced at the transcription level. Furthermore, we compared the levels of hMOF in primary human hepatocytes and

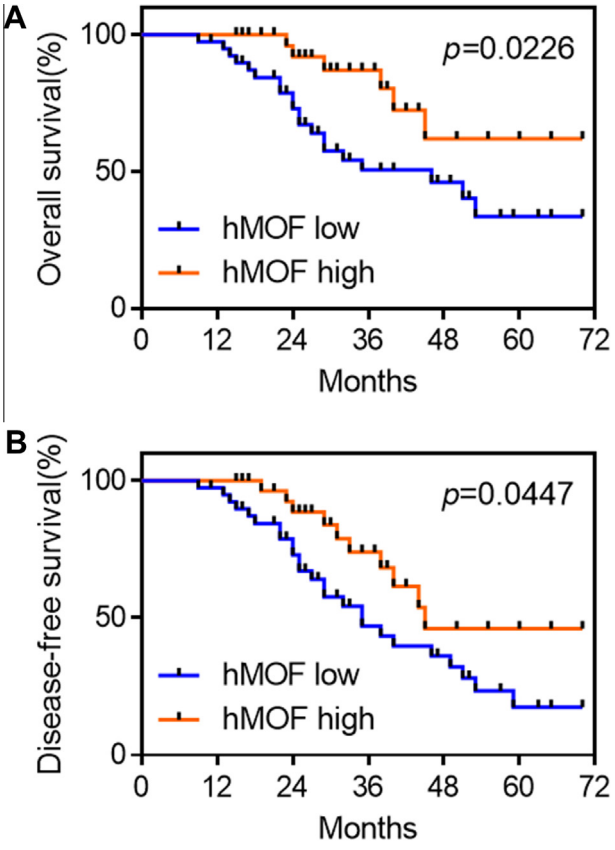

Fig. 2. hMOF predicts overall and disease-free survival. Kaplan–Meier curve showing overall or disease-free survival rates in patients with high and low levels of hMOF expression according to the IHC results. (A) Low hMOF level predicts poor overall survival. (B) Low hMOF level predicts poor disease-free survival. $N = 40$ in hMOF low group and $n = 30$ in hMOF high group.

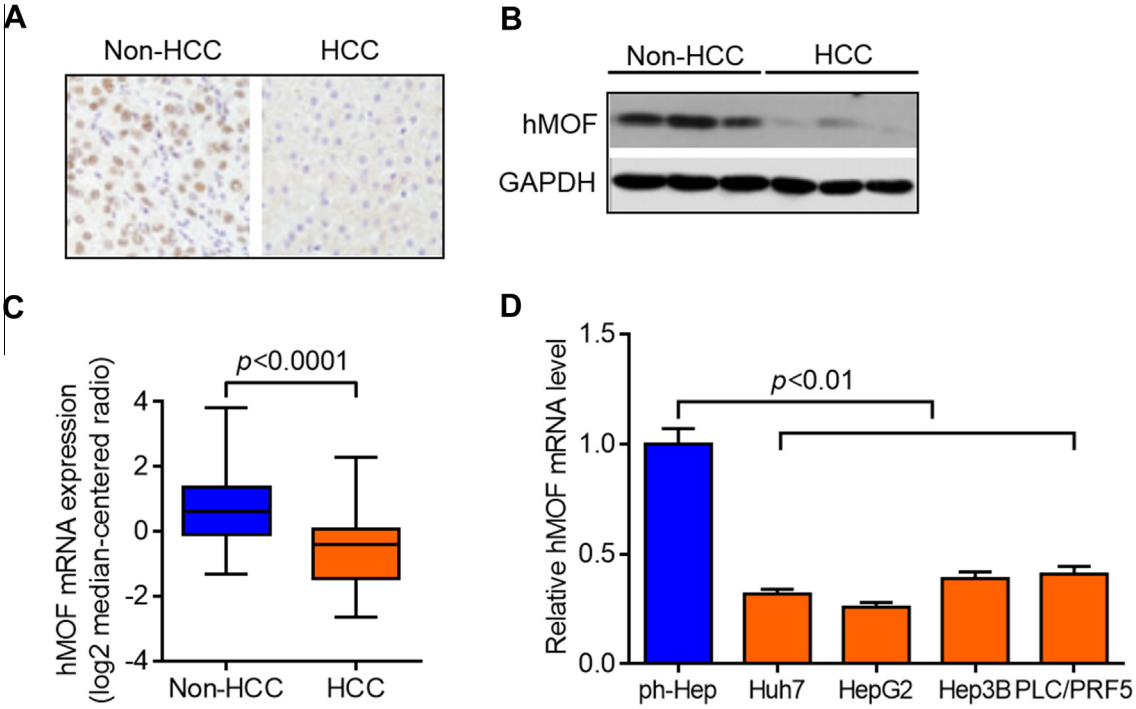

Fig. 1. hMOF is down-regulated in HCC tissues and cell lines. (A) hMOF protein level is up-regulated in human hepatocellular carcinoma (HCC) tissues. Paraffin sections of adjacent and cancer tissues of HCC patients were subjected to IHC analysis with anti-hMOF antibody. (B and C) Total protein and RNA were extracted from HCC and adjacent and cancer tissues and subjected to Western blot (B) and q-PCR (C) analyses, respectively. $N = 24$ in non-HCC group and $n = 70$ in HCC group in (C). (D) mRNA level of hMOF was analyzed in 4 hepatoma cell lines by q-PCR. Primary human hepatocytes (ph-Hep) were used as a reference.

four hepatoma cell lines (Huh7, HepG2, Hep3B, AND PLC/PRF5) by q-PCR. The results indicated that hMOF mRNA level was lower in hepatoma cells than normal hepatocytes (Fig. 1D). In summary, hMOF is down-regulated in human hepatocellular carcinoma tissues and cell lines.

3.2. hMOF predicts patients' prognosis in human hepatocellular carcinoma

In order to determine whether hMOF expression levels could predict cancer progression and/or survival, we analyzed the IHC results of hMOF expression in samples from hepatocellular carcinoma patients. We found that patients with high levels of hMOF had longer time of survival than those with low levels of hMOF ($p = 0.0226$; Fig. 2A). hMOF expression is associated with recurrence, low hMOF expression predicted adverse disease-free survival ($p = 0.0447$; Fig. 2B). These results suggest that decreased disease-free survival time is associated with low levels of hMOF in patients with hepatocellular carcinoma.

3.3. hMOF regulates hepatocellular carcinoma growth in vitro and in vivo

To further investigate the potential participation of hMOF in human cancer development, we knocked down hMOF or overexpressed hMOF expression in human hepatocellular carcinoma cell line HepG2 cells (Figs. 3A and B; S1A and B). We showed that hMOF knockdown promoted hepatocellular carcinoma cell proliferation and colony formation (Figs. 3A and C; S1A–D), whereas hMOF overexpression reduced hepatocellular carcinoma proliferation rate and colony formation capacity (Fig. 3B and D). In addition, the *in vivo* xenograft mice experiments showed that hMOF can inhibit the growth of hepatocellular carcinoma cells (Fig. 3E and F; Fig. S1E and F). Collectively, we showed that hMOF blunted hepatocellular carcinoma growth *in vitro* and *in vivo*.

3.4. hMOF regulates SIRT6 and its downstream genes in hepatocellular carcinoma

SIRT6 is a histone deacetylase which was recently reported to inhibit hepatocellular carcinoma development. We wanted to investigate whether hMOF can regulate SIRT6 in hepatocellular carcinoma. Firstly, we checked the expression of SIRT6 in hepatocellular carcinoma and normal tissues. We found that SIRT6 mRNA was significantly down-regulated in human hepatocellular carcinoma tissues (Fig. 4A). Linear regression analysis was performed to explore the correlation between hMOF and SIRT6. Markedly, SIRT6 mRNA was positively correlated with hMOF mRNA level (Fig. 4B). To further text whether SITT6 serves as a downstream of hMOF, we knocked down or overexpressed hMOF in HepG2 cells. We found that hMOF can significantly increase the protein and mRNA levels of SIRT6 (Fig. 4C and data not shown). Next, we performed ChIP experiment and showed that hMOF can bind to the promoter or SIRT6 (Fig. 4D). In addition, the luciferase report assay revealed that hMOF enhanced the promoter activity of SIRT6 (Fig. 4E). Finally, we tested the effect of hMOF on SIRT6 target genes in hepatocellular carcinoma. The results showed that hMOF inhibited the expression of SIRT6 target genes in HepG2 cells (Fig. 4F).

4. Discussion

Here in the present work, we found that hMOF was decreased in human hepatocellular carcinoma and low hMOF level predicted poor overall and disease-free survival. We demonstrated that hMOF repressed hepatocellular carcinoma growth with *in vitro*

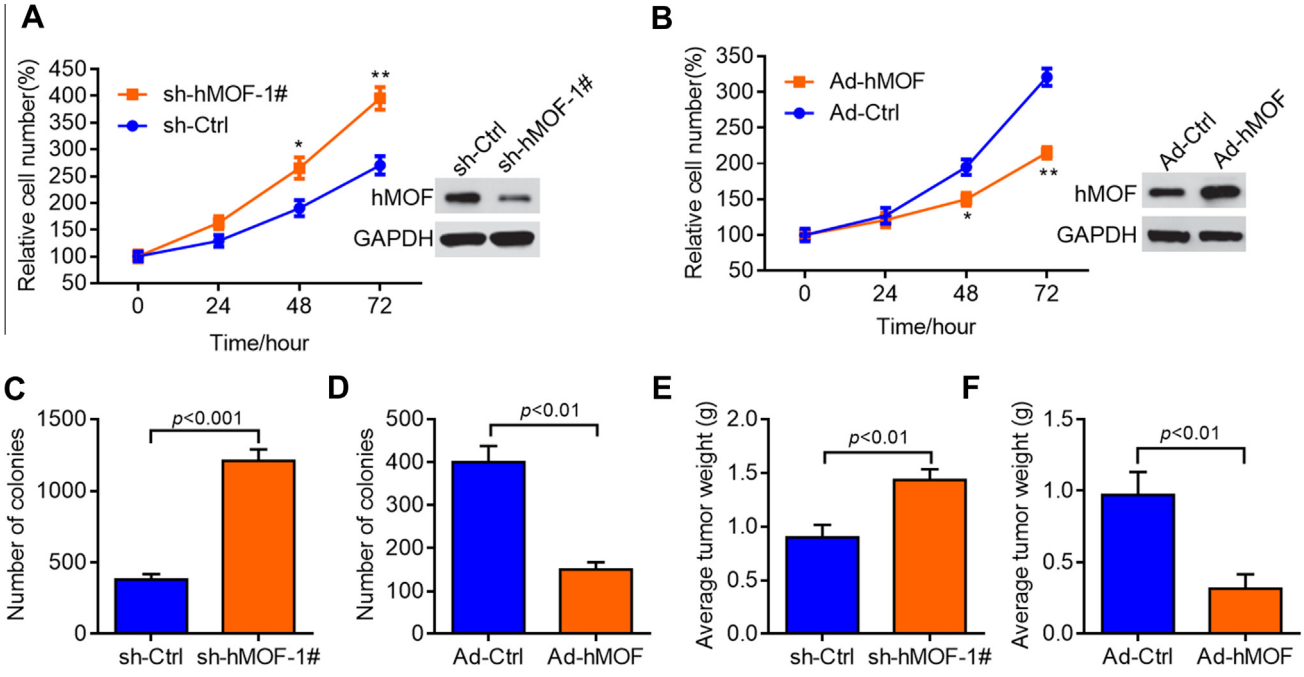

Fig. 3. hMOF inhibits hepatoma cancer cell growth *in vitro* and *in vivo*. (A) hMOF knockdown promotes HepG2 cancer cell proliferation. HepG2 lung cancer cells were infected with retrovirus expressing ctrl shRNA (sh-Ctrl) or shRNA targeting hMOF (sh-hMOF). The relative cell numbers were evaluated with MTT method at the indicated time points. (B) hMOF overexpression inhibits HepG2 cancer cell proliferation. HepG2 cancer cells were infected with adenovirus expressing GFP (Ad-Ctrl) or hMOF (Ad-hMOF). The relative cell numbers were evaluated at the indicated time points. (C) hMOF knockdown promotes HepG2 cancer cell colony formation. HepG2 cells infected with retro-sh-Ctrl or retro-sh-HMOF were subjected to soft sugar colony formation assay. The colony numbers were evaluated two weeks later. (D) hMOF overexpression inhibits HepG2 cancer cell colony formation. HepG2 cells infected with Ad-Ctrl or Ad-hMOF were subjected to soft sugar colony formation assay. The colony numbers were evaluated two weeks later. (E and F) HepG2 cells with hMOF knockdown or overexpression were subjected to xenograft mice experiments. Tumor weight was evaluated at the terminal of the experiments. (E) hMOF knockdown facilitates lung cancer cell growth *in vivo*. (F) hMOF overexpression blunts lung cancer cell growth *in vivo*. $^{*}p < 0.05$; $^{**}p < 0.01$ vs sh-ctrl. # indicates the number, for instance, sh-hMOF-1# indicates the first shRNA targeting hMOF.

and *in vivo* evidence. Finally, we provided data that SIRT6, which was a tumor suppressor, was down-regulated and correlated with hMOF in human hepatocellular carcinoma. hMOF overexpression facilitated SIRT6 expression, which may underling the mechanism by which hMOF regulates hepatocellular carcinoma.

hMOF plays critical roles in diverse carcinomas. It has been reported that MOF overexpression is correlated with cellular proliferation, oncogenic transformation and tumor growth [3]. Abnormal gene expression of hMOF is involved in certain diverse primary cancers, including breast cancer [4], renal cell carcinoma [5], ovarian cancer [6], medulloblastoma [7], as well as lung cancers [8,9]. hMOF was found to be more frequently highly expressed in NSCLC than corresponding normal tissues [8–10]. Furthermore, hMOF promotes the cell proliferation, migration and adhesion of NSCLC cell lines [9]. A recent study shows that hMOF facilitates lung cancer by maintaining drug-resistance through acetylating Nrf2 [10]. In addition, low expression of hMOF with clinicopathological features of colorectal carcinoma, gastric cancer and renal cell carcinoma [5,11]. hMOF is frequently downregulated in primary breast carcinoma and medulloblastoma and constitutes a biomarker for clinical outcome in medulloblastoma [7]. In human hepatocellular carcinoma, the expression of hMOF is significantly down-regulated (Fig. 1). Low expression of hMOF predicts poor overall and disease-free survival, indicating that hMOF may participate both in hepatocellular carcinoma development and recurrence (Fig. 2). By utilizing *in vitro* and *in vivo* evidence, we demonstrate that hMOF facilitates hepatocellular carcinoma cell growth (Fig. 3). The dual roles of hMOF in carcinomas largely depend upon the individual type of carcinoma itself cellular environment and the certain factors that hMOF may target. Further work is critically essential to profile how hMOF prevents the development of a certain carcinoma other than hepatocellular carcinoma, and how hMOF expression is regulated in different carcinomas.

As a member of the family of histone acetyltransferases (HATs), hMOF is the major enzyme that catalyzes the acetylation of histone H4 K16. Acetylation of H4K16 is a prevalent mark associated with chromatin decondensation. MOF has recently been shown to play an essential role in maintaining normal cell functions. In mammals, MOF is ubiquitously expressed and is clearly targeted to all chromosomes. Loss of MOF gene in mice causes peri-implantation lethality, as a result of massive disruptions of chromatin architecture in a wide range of cells [3,17]. In addition, by maintain normal chromatin structure, MOF is important for ATM-dependent cell-cycle checkpoint control [18], and transcription activation of Hox genes in coordination with the H3K4 methyltransferase MLL [19]. Loss of MOF leads to a global reduction of H4K16 acetylation, severe G2/M cell cycle arrest, massive chromosome aberration, and defects in ionizing radiation-induced DNA damage repair by both nonhomologous end-joining (NHEJ) and homologous recombination (HR) [20,21]. All those effects are mediated by the HAT activity of MOF on H4K16. MOF was also reported to acetylate non-histone proteins. Until now, three non-histone substrates of MOF have been identified. Sykes et al. [22] reported that hMOF can acetylate p53 on its DNA-binding domain (K120) and help to distinguish the cell-cycle arrest and apoptotic functions of p53. Another non-histone substrate of MOF is the TIP5 (K633) subunit of the NoRC chromatin-remodeling complex [23]. Reversible acetylation of NoRC is required for non-coding RNA-dependent silencing. Recently, Chen et al. [10] showed that hMOF can acetylate Nrf2

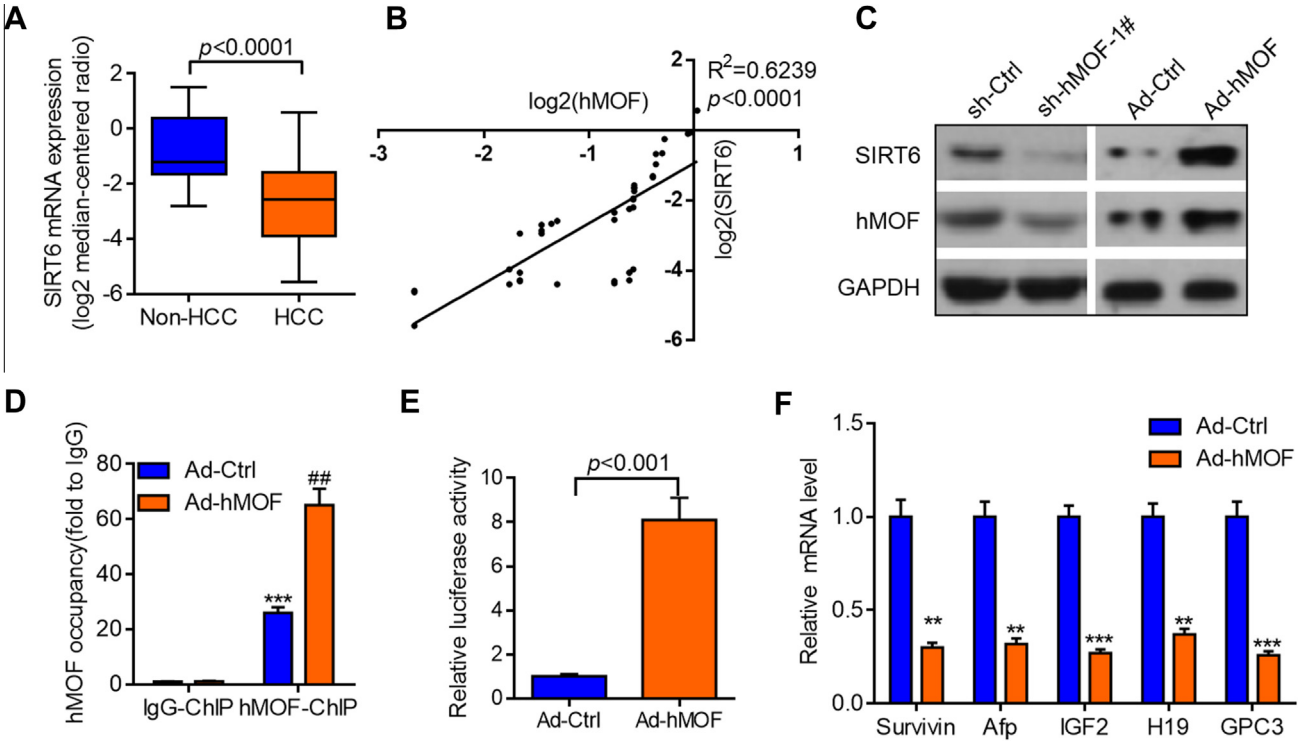

Fig. 4. hMOF regulates SIRT6 in hepatocellular carcinoma cells. (A) SIRT6 is down-regulated in human HCC. RNA was extracted from HCC and adjacent and cancer tissues and subjected to q-PCR analysis. $N = 18$ in normal group and $n = 44$ in HCC group. (B) hMOF level is correlated with SIRT6 level. Linear regression analysis was performed to analyze the correlation between hMOF and SIRT6 mRNA levels. (C) hMOF promotes SIRT6 expression. HepG2 cells were infected with retrovirus carrying sh-Ctrl or sh-hMOF or adenovirus carrying Ctrl or hMOF sequence for 48 h. Protein was extracted and subjected to Western blot with indicated antibodies. (D) hMOF binds to the promoter of SIRT6. HepG2 cells were infected with ad-hMOF for 48 h and ChIP assay was performed. The immunoprecipitates were subjected to q-PCR analysis with primers targeting SIRT6 primer. (E) Luciferase assay showing that hMOF overexpression decreases SIRT6 promoter activity. (F) hMOF suppresses the expression of SIRT6-target genes. HepG2 cells were infected with ad-hMOF for 48 h and RNA was subjected to q-PCR analysis with indicated primers. *** indicates $p < 0.001$ vs IgG-ChIP; ## indicates $p < 0.01$ vs Ad-Ctrl; ** indicates $p < 0.01$ while *** indicates $p < 0.001$ vs Ad-Ctrl.

and facilitate Nrf2 nucleus retention and transcription activation. In the present study, we showed that hMOF is correlated with SIRT6 level. hMOF binds to the promoter and promotes the transcription activity of SIRT6, and subsequently inhibits the expression of SIRT6 target genes (Fig. 4). Those effects are more likely attribute to the acetylation of H4K16, as the luciferase results revealed hMOF enhances SIRT6 promoter activity.

SIRT6 plays critically roles in liver functions. Depletion of SIRT6 results in diverse dysfunction of the liver, including fatty liver [24], liver inflammation [25], and hepatic steatosis [26], all of those pathoses are risk factors of hepatocellular carcinoma. In addition, SIRT6 critically participates in the initiation of hepatocellular carcinoma by maintaining genome stability [12]. Those facts implicate that hMOF may be important for maintaining the normal function of the liver, partly by targeting SIRT6. Abnormal of hMOF may result in liver diseases that increase cancer risk, while SIRT6 plays a key role in this process.

In summary, we show here that hMOF is down-regulated in human hepatocellular carcinoma and may be a potential prognostic marker predicting favorite outcome. We identify a novel role of hMOF in liver system to control hepatocellular carcinoma *via* targeting SIRT6. Those findings reveal that hMOF may be a prognostic factor and potential target for interventions.

Conflict of interest

None.

Acknowledgment

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.bbrc.2014.08.122.

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