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TRIM59 promotes cell proliferation, migration and invasion in human hepatocellular carcinoma cells

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The human tripartite motif (TRIM) 59 has been implicated in tumorigenesis of many types of cancer. However, the biological function and molecular mechanism of TRIM59 in hepatocellular carcinoma (HCC) remains unknown. In our study, the purpose was to investigate the impact of TRIM59 on the biologic behavior of HCC cells. We observed that TRIM59 was highly expressed in HCC cells compared with a normal human hepatocyte cell line. Lentivirus-mediated knocking down of TRIM59 significantly suppressed the proliferation, migration and invasion of HCC cells, whereas overexpression of TRIM59 enhanced cell growth and metastasis. Furthermore, our study showed that silencing of TRIM59 decreased the expression of E-cadherin and increased N-cadherin and vimentin expression, whereas TRIM59 overexpression had the opposite effects on the above proteins. Finally, we found that p53 protein expression level was regulated by TRIM59, so we proposed that TRIM59 may enhance HCC cell proliferation and metastasis through p53 signaling pathway. In summary, these data indicated that TRIM59 may be a potential biomarker and therapeutic target for the treatment of hepatocellular carcinoma.

1. Introduction

Hepatocellular carcinoma (HCC) is the fifth most common cancer and the second largest contributor to cancer mortality (McGlynn and London 2011). Moreover, the incidence of HCC is consistently increasing in China (Zhu et al. 2016a). Due to the lack of early diagnostic markers, HCC is usually diagnosed at a late stage with poor prognosis, the five-year survival rate less than 7% (Llovet and Bruix 2008). Therefore, a better understanding of the molecular mechanism for hepatocellular tumorigenesis and the development of early diagnosis methods and novel treatment options of HCC is essential.

The TRIM (tripatite motif-containing) family has more than 77 members, which have a TRIM or RBCC motif conprising an amino-terminal RING domain, B-box domains and an associated coiled-coil domain (Sardiello et al. 2008). TRIM family proteins are involved in various biological processes, including proliferation, immunity, transcriptional regulation and cell differentiation (Ikeda and Inoue 2012). Over the past decade, numerous studies focused on the function of TRIM proteins in innate immunity to viral infection. Recently, several members of the TRIM family, such as TRIM13, TRIM19, TRIM24 and TRIM25 have been demonstrated to play crucial roles during human tumorignesis in leukemia, breast, gastric and prostate cancer (Groner et al. 2016; Hatakeyama 2011; Tsai et al. 2010; Zhu et al. 2016b). For instance, TRIM24 has been reported to bind chromatin and estrogen receptor to activate the estrogen-dependent genes, causing breast cancer cell proliferation and tumor development (Tsai et al. 2010). TRIM24 protein was upregulated in gastric cancer specimens and positively correlated with clinical stage and prognosis. The overexpression of TRIM24 increased gastric cell proliferation and chemoresistance via Akt signal pathway (Miao et al. 2015). While TRIM16 inhibits neuroblastoma cell growth and migration *via* modulating cyclinD1 and p27 expression (Bell et al. 2013). TRIM59, a novel TRIM family, has also been reported to be involved in certain types of human cancer (Khatamianfar et al. 2012). TRIM59 exerts oncogenic activities in osteosarcoma which promote cell proliferation and invasion *via* modulating p53 expression (Liang et al. 2016). Similarly, TRIM59 might contribute to gastric carcinogensis *via* promoting ubiquitination and degradation of p53 (Zhou et al. 2014). In addition, TRIM59 promotes non-small cell lung cancer cell growth without affecting the p53 signal pathway (Zhan et al. 2015). However, the specific role of TRIM59 in HCC remained unclear.

In the current study, we focused on the role of TRIM59 in the regulation of cell proliferation, invasion and migration in HCC cell lines. We first found that TRIM59 was significantly upregulated in various HCC cell lines compared with normal human hepatocyte (LO2) cell line. Lentivirus of shTRIM59 or TRIM59 expression plasmid was used to suppress or upregulate TRIM59 expression, respectively. The suppression of TRIM59 significantly inhibited proliferation and metastasis. While overexpression of TRIM59 exerted opposite functions. Our findings provide a novel understanding of the role of TRIM59 in HCC growth and metastasis.

2. Investigations and results

2.1. TRIM59 is upregulated in HCC cell lines

In order to profile the expression of TRIM59 in HCC cell lines, we chose six HCC cell lines including BEL7402, Hep3B, HepG2, Huh7, SMMC7721 and SK-Hep-1. The normal hepatocyte cell line LO2 was used as the control. The mRNA level of TRIM59 was highly expressed in all HCC cells compared with LO2 cell (Fig. 1A). The western blot analysis further confirmed that TRIM59 protein level was also significantly higher in all HCC cell lines than that in LO2 cell line. In addition, the expression of TRIM59 in HepG2 and Huh7 cells was higher than other HCC cell lines.

2.2. TRIM59 regulates HCC cells growth

We then investigated the biological function of TRIM59 in HCC cells. Firstly, the stable TRIM59 knockdown HepG2 cell and Huh7 cell lines were established using lentivirus infection. As shown in Fig. 2A, both shTRIM59-1 and shTRIM59-2 lentivirus

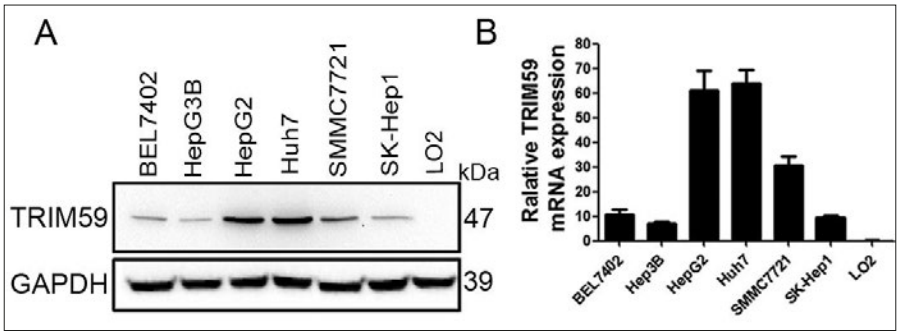

Fig. 1: TRIM59 is upregulated in HCC cell lines. (A)The mRNA levels of TRIM59 in HCC cell lines (BEL7402, Hep3B, HepG2, Huh7, SMMC7721 and SK-Hep-1) and normal hepatocyte cell line LO2 were determined using qRT-PCR analysis. (B) The protein levels of TRIM59 in HCC cell lines and LO2 cells were measured using western blot analysis. All values were represented as means ± SD calculated from three independent experiments. $^{**}p< 0.01$

infections significantly reduced the TRIM59 expression in HepG2 and Huh7 cells. Then colony formation and MTT assays were performed. Colony formation assays showed that knockdown of TRIM59 dramatically reduced colony formation ability (Fig. 2B). Consistently, the MTT results also confirmed that knockdown of TRIM59 inhibited cell proliferation of HepG2 and Huh7 cells (Fig. 2C). On the contrary, TRIM59 overexpression plasmid transfection was performed in HepG2 and Huh7 cells (Fig. 2D). The overexpression of TRIM59 caused a significant increase in colony formation ability and cell proliferation of HepG2 and Huh7 cells (Fig. 2E-F). These data demonstrated that TRIM59 promotes HCC cells growth.

We further assessed the role of TRIM59 on HCC cells migration and invasion using wound healing assay and transwell assay, respectively. As shown in Fig. 3A, after 48 h, the wound was almost healed by migrated cells in shControl group, while knockdown of TRIM59 attenuated the healing of the open area. Moreover, overexpression of TRIM59 promoted cell metastasis by wound healing assay in HepG2 and Huh7 cells (Fig. 3B). Transwell assay indicated that the number of invasion cells was significantly decreased by TRIM59 knockdown (Fig. 3C), whereas TRIM59 overexpression had the opposite affects that promoted the migration and invasion ability of HepG2 and Huh7 cells (Fig. 3D). Therefore, our results suggested that TRIM59 contributes migration and invasion of HCC cells.

2.3. TRIM59 regulates the expression of E-cadherin, N-cadherin and vimentin

To investigate the molecular mechanism of TRIM59 in modulation of cell migration and invasion, western blot was used to determine the protein levels of E-cadherin, N-cadherin and vimentin which play crucial roles in cell metastasis. As shown in Fig. 4A, knockdown of TRIM59 significantly reduced E-cadherin

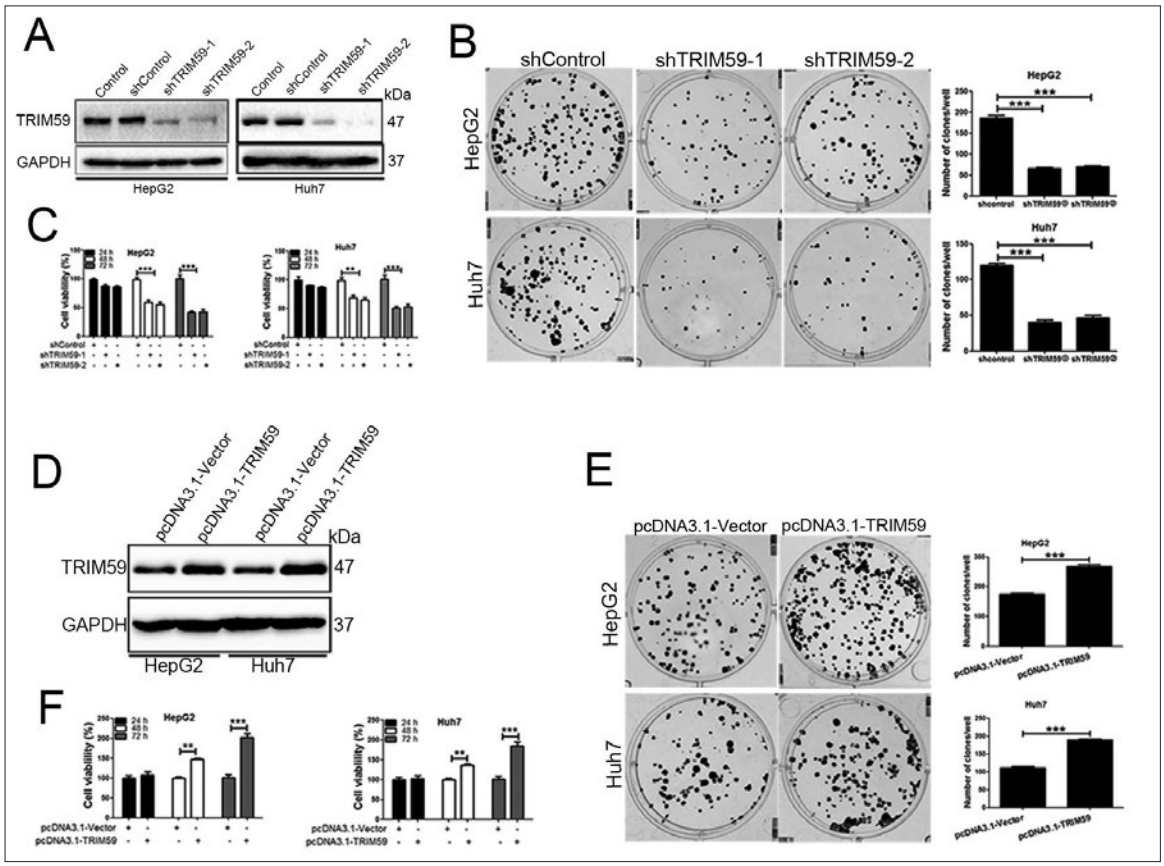

Fig. 2: Biological function of TRIM59 on HCC cells growth. (A) HepG2 and Huh7 cells were infected with shControl, shTRIM59-1 or shTRIM59-2 lentivirus for the establishment of TRIM59 knockdown stable cell lines and shControl cell lines. The protein levels of TRIM59 were determined using Western blot. (B) TRIM59 knockdown reduced the ability of colony formation of HepG2 and Huh7 cells. (C) TRIM59 knockdown inhibited cell proliferation of HepG2 and Huh7 cells. (D) HepG2 cells and Huh7 cells were transfected with pcDNA3.1-Vector or pcDNA3.1-TRIM59 expression plasmid for 48 h, western bolt analyzed the protein levels of TRIM59. (E) TRIM59 overexpression promoted the ability of colony formation of HepG2 and Huh7 cells. (F) TRIM59 overexpression accelerated cell proliferation of HepG2 and Huh7 cells. All values were represented as means ± SD calculated from three independent experiments. $^{**}p< 0.01$, $^{***}p< 0.001$ versus shControl or Vector control.

expression while increased N-cadherin and vimentin expression in HepG2 and Huh7 cells. In contrast, overexpression of TRIM59 upregulated E-cadherin expression and decreased N-cadherin and vimentin expression. These findings indicated that TRIM59 regulates HCC cells metastasis by affecting E-cadherin, N-cadherin and vimentin.

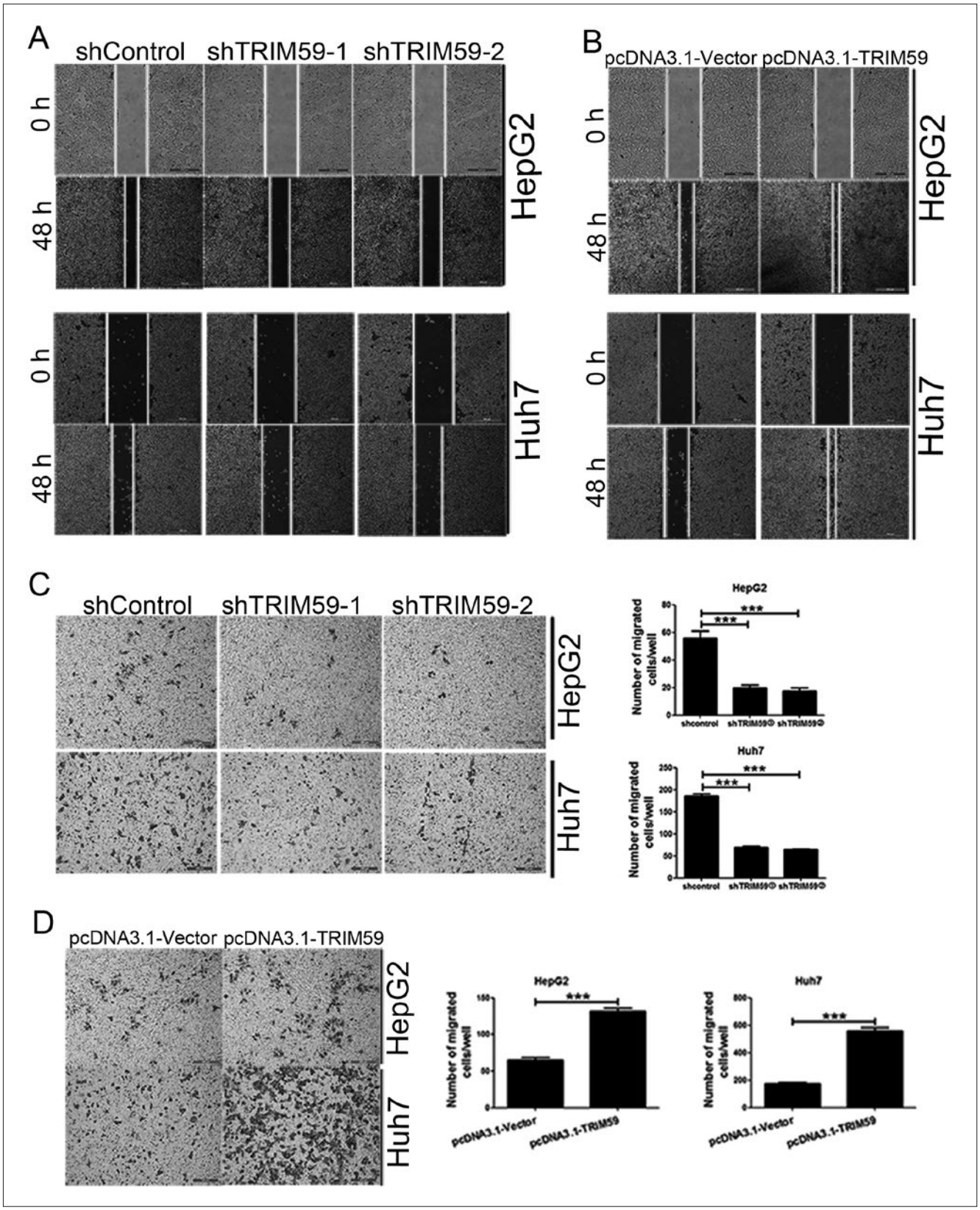

Fig. 3: Biological functions of TRIM59 on HCC cells migration and invasion. (A, B) Wound healing assay. The stable HepG2 and Huh7 cell lines with shTRIM59-1, shTRIM59-2 or shControl (A) and HepG2 and Huh7 cells that transfected with pcDNA3.1-Vector or pcDNA3.1-TRIM59 expression plasmid (B) were cultured to create a confluent monolayer with 90-100% confluence. Then the monolayer was scraped in a scraped in a straight line to create a scratch wound. (C, D) The stable HepG2 and Huh7 cell lines of shTRIM59-1, shTRIM59-2 and shControl (C) and HepG2 and Huh7 cells that transfected with pcDNA3.1-Vector or pcDNA3.1-TRIM59 expression plasmid (D) were cultured in transwell chambers coated with Martrigel for 24h, then cells were fixed, stained and counted in five random views, Results are shown in the right panel. All values were represented as means±SD calculated from three independent experiments. $^{**}p< 0.01$, $^{***}p< 0.001$ versus shControl or vector control.

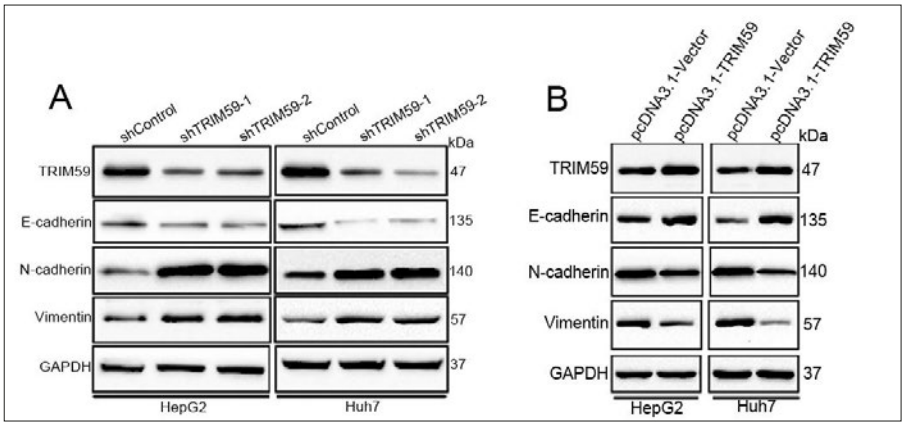

Fig. 4: TRIM59 regulates the expression of E-cadherin, N-cadherin and vimentin. (A) Western blot analyzed the expression of E-cadherin, N-cadherin and Vimentin in the stable HepG2 and Huh7 cell lines with shTRIM59-1, shTRIM59-2 or shControl. (B) Western blot analyzed the expression of E-cadherin, N-cadherin and Vimentin in pcDNA3.1-Vector or pcDNA3.1-TRIM59 transiently transfected HepG2 cells and Huh7 cells. All values were represented as means ± SD calculated from three independent experiments.**p< 0.01, ***p< 0.001 versus shControl or vector control.

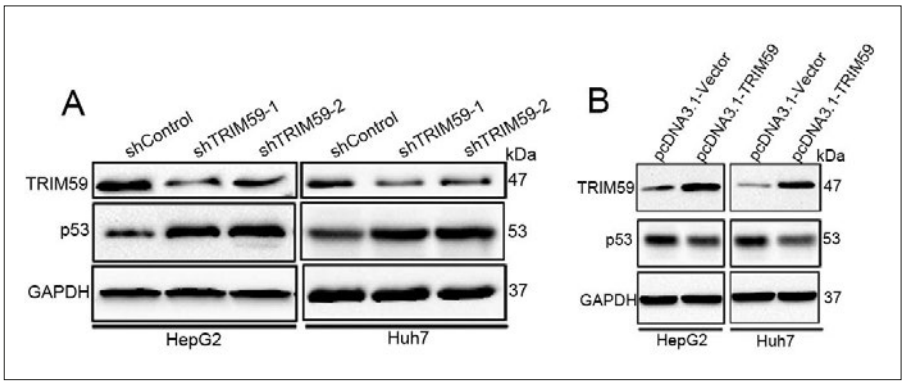

Fig. 5: TRIM59 promotes HCC cells growth and metastasis through p53 signal pathway. (A)Western blot analyzed the expression of p53 in the stable HepG2 and Huh7 cell lines with shTRIM59-1, shTRIM59-2 or shControl. (B) Western blot analyzed the expression of p53 in pcDNA3.1-Vector or pcDNA3.1-TRIM59 transiently transfected HepG2 cells and Huh7 cells. All values were represented as means±SD calculated from three independent experiments. **p< 0.01, ***p< 0.001 versus shControl or vector control.

2.4. TRIM59 promotes HCC cells growth and metastasis via modulating p53 signaling pathway

P53 is generally known as a tumor suppressor (Hong et al. 2014). Recently it has been reported that TRIM59 shows several effects on p53 expression, e.g. TRIM59 promotes p53 degradation in gastric tumor and osteosarcoma (Liang et al. 2016; Zhou et al. 2014), while does not affect p53 expression in NSCLC cells (Zhan et al. 2015). To investigate whether the biological function of TRIM59 on HCC cells is associated with p53 pathway, we determined the expression of p53 response to TRIM59 knockdown or overexpression. As shown in Fig. 5, the p53 protein levels were upregulated by TRIM59 knockdown in HepG2 and Huh7 cells, meanwhile overexpression of TRIM59 downregulated p53 protein expression. In summary, these data indicate that TRIM59 promotes HCC cells growth and metastasis through the p53 pathway.

3. Discussion

Hepatocellular carcinoma (HCC) is one of the most common cancers in the world and its prognosis of HCC patients is extremely poor (McGlynn and London 2011). TRIM proteins play important roles in HCC. As a result of genomic deletion and gene hypermethylation, TRIM35 is downregulated in HCC tissues and the expression level of TRIM35 is negatively correlated with tumor grade, tumor size, and serum AFP level of patients (Jia et al. 2011). TRIM16 inhibited ZEB2 expression, which in turn inhibited transcription of the pivotal ZEB2 target gene E-cadherin in HCC cells (Li et al. 2016). Germline inactivation of TRIM24 in mice leads to the development of HCC *via* disrupting RA-signaling in HCC (Herquel et al. 2011). TRIM26 is a novel tumor suppressor modulating multiple metabolism-related pathways in HCC (Wang et al. 2015). Over-expression of TRIM37 promotes cell migration and metastasis in hepatocellular carcinoma by activating Wnt/b-catenin signaling (Jiang et al. 2015). Although researchers have found that many TRIM proteins in HCC contribute to the malignant behavior, novel molecular makers are still urgently needed.

TRIM59 is a novel multiple cancer biomarker and may be used as specific cobiomaker (Khatamianfar et al. 2012). Valiyeva et al. (2011) found TRIM59 upregulation in the cytoplasm in all 37 tumor types of 291 human cancer cases (Valiyeva et al. 2011). Recent research indicated that TRIM59 exerts oncogenic activators in osteosarcoma, gastric and non-small cell lung cancers (Liang et al. 2016; Miao et al. 2015; Zhan et al. 2015). We characterized that mRNA or protein level of TRIM59 was overexpressed in HCC cells. This data is required to aid in the discovery of novel diagnostic and prognostic biomarkers. We further proposed the biological function of TRIM59 in HCC cells. Lentivirus-mediated silencing of TRIM59 significantly suppressed the proliferation, colony formation, migration and invasion of HCC cells. On the contrary, overexpression of TRIM59 enhances oncogenic activates in HCC cells. Thus, it is suggested that TRIM59 is a key mediator of HCC progression.

In hepatocellular carcinoma cancer studies it was reported that epithelial–mesenchymal transition (EMT) plays an important role in tumor invasion and metastasis (Maheswaran and Rushbrook 2012; van Zijl et al. 2009). E-Cadherin plays a pivotal role in epithelial cell-cell adhesion, and the loss of E-cadherin is considered a hallmark of EMT (Kalluri and Weinberg 2009). Recent researches observed that TRIM37 promotes cell migration in hepatocellular carcinoma by activating Wnt/β-catenin signaling (Jiang et al. 2015), while TRIM35 inhibits the Warburg effect and tumorigenicity in hepatocellular carcinoma (Chen et al. 2015). In this study, western blot was used to determine the protein levels of E-cadherin, N-cadherin and vimentin which play crucial roles in cell metastasis. We found that knockdown of TRIM59 significantly suppressed the expression of the epithelial marker (E-cadherin) and promoted the expression of the mesenchymal markers (N-cadherin and vimentin), whereas overexpression of TRIM59 increased the expression of E-cadherin and inhibited the expression of N-cadherin and vimentin. These data indicate that TRIM59 could promote the migration and invasion by enhancing EMT through upregulating EMT-inducing genes in HCC cells.

Interestingly, knockdown of TRIM59 leads to a significant increase of p53 protein, while TRIM59 overexpression decreased the protein levels of p53. TRIM59 belongs to the E3 unbiquitin ligase family, which enhances ubiquitin-induced degradation of

target proteins (Kondo et al. 2012). Human homolog of MDM2 is a well-known E3 ubiquitin ligase that promotes p53 degradation in cancer (Haupt et al. 1997; Honda et al. 1997). This structural similarity between TRIM59 and MDM2 additionally suggests a similar regularity mechanism on p53 ubiquitination (Liang et al. 2016; Zhou et al. 2014). Whether TRIM59 possesses E3 ligase activity for p53 *in vivo* and works synergistically with MDM2 will be interesting to explore in the future.

In summary, we found that TRIM59 expression is upregulated in HCC cells. Lentivirus-mediated knocking down of TRIM59 significantly inhibited the proliferation, migration and invasion of HCC by activating the p53 pathway. On the contrary, when TRIM59 was overexpressed in HCC cells, increased cell proliferative rates, migratory and invasive abilities were observed. The regulation of p53 by TRIM59 may suggest that TRIM59 enhances HCC cells progression by degradation of p53. However, the *in vivo* physiological role and mechanism of TRIM59 protein need to be further investigated.

4. Experimental

4.1. Cell culture and transfection

All cell lines used in this paper were purchased from the American Type Culture Collection (ATCC). Huh7 cells were cultured in DMEM (GIBCO). Hep3B, HepG2 and SK-Hep1 cells were maintained in EMEM (GIBCO). BEL7402, LO2 and SMMC7721 cells were maintained in RPMI 1640 cell culture media (GIBCO). All culture media were supplemented with 10% fetal bovine serum (FBS)(GIBCO) and 1% penicillin/streptomycin (Beyotime Institute of Biochnology). Cells were cultured in a humidified incubator in 5% CO_2 at 37 °C. Plasmids into all cells were performed using Lipofectamine 3000 (Invitrogen), according to the manufacturer's instructions.

4.2. Antibodies, plasmids and lentivirus

Anti-TRIM59 was purchased from Santa Cruz. Anti-E-Cadherin, N-Cadherin, vimentin, p53 and GAPDH were obtained from Cell Signaling Technology. TRIM59 was amplified by PCR from a mouse E17 Cdna library (Clontech Laboratories). The resulting fragments containing TRIM59 cDNA were subcloned into pcDNA3.1 vector with a FLAG-tag which was obtained from Addgene. The lentiviral constructs of TRIM59 was purchased from Santa Cruz. Lentiviral particles were used to directly infect HepG2 and Huh7 cells. Stable clones were then selected using puromycin (Sigma). The selected cell populations were subjected to immunoblotting to investigate the knockdown efficiency.

4.3. Quantitative real-time polymerase chain reaction (qRT-PCR)

Total RNA was extracted from the cells using an RNeasy Mini Kit (QIAGEN) according to the manufacturer's instructions. Quantitative Real-Time Polymerase Chain Reaction (qRT-PCR) for TRIM59 and for the housekeeping gene β-actin were performed in a final volume of 10 µl, which contained 5 µl of SsoFast™ EvaGreen Supermix (Bio-Rad Laboratories), 1 µl of cDNA, and 1 mM each of the forward and reverse primers. The primers for the TRIM59 were 5'-tac gag agc agc agc ttg aa-3' and 5'-acg ggt tga acc tca gga ag-3'. Primers for β-actin were 5'-agt act ccg tgt gga tcg gc-3' and 5'-gct gat cca cat ctg ctg ga-3'. qRT-PCR was performed on an Applied Biosystems 7500 real-time PCR cycler. The expression of the target gene was normalized to the housekeeping gene level. The results were expressed as normalized TRIM59 mRNA levels.

4.4. Cell proliferation and colony formation assays

Cell proliferation assay was performed using the MTT (3-(4, 5-dimethyl-2-thiazolyl)-2,5-diphenyl tetrazolium bromide) assay according to the manufacturer's protocol. Briefly, cells were seeded in 96-well culture plates for 24, 48 and 72 h, then treated with MTT solution during the last 4 h of the culture. Optical density of the wells was measured at 450 nm using a microplate reader. To determine colony formation, the cells were cultured in complete medium at 37 °C in 5% CO_2. Colonies (containing 50 or more cells) were stained with 0.1% crystal violet and counted by light microscopy after 14 days. Three independent experiments were performed.

4.5. Immunoblotting

Total proteins from cell lines were extracted in lysis buffer (Roche) and quantified using the Bradford method. The protein was separated by SDS–PAGE. After transferring, the nitrocellulose filter (NC) membranes (PALL) were incubated with the primary antibodies, horseradish peroxidase conjugated antibodies to mouse or rabbit immunoglobulin G and an enhanced chemiluminescence system (ECL, Bio-Rad Laboratories) and GAPDH is the loading control. To quantify changes, the densitometries of protein bands were determined with a calibrated GS-670 densitometer. All IB experiments were performed as three independent experiments.

4.6. Transwell assay

Cell suspensions (200 µL) were seeded at 1×10^5 cells/well to the upper chamber coated with Martrigel (Corning), while media containing 10% FBS (650 G) was added to the lower chamber. After 24 h, the non-penetrated cells were removed using a cotton swab. Cells that had invaded to the back of the membrane of the trans-well chamber were stained with 0.1% crystal violet after fixed by 4% formaldehyde. The invasive capacity of cells was defined according to the total number of cells in randomly selected fields by light microscopy.

4.7. Scratch assay

HepG2 and Huh7 cells were seeded at 4.0×10^5 cells/mL. After one day, confluent monolayer cells were linearly scratched using a 20-µL pipette chip. The scratched region was photographed immediately or 48 h after scratching using a microscope equipped with a camera. Data were analyzed by imageJ software.

4.8. Statistical analysis

Data were expressed as means±SD of at least three independent experiments. The Student's t-test was used to compare other data in SPSS 17.0 software (SPSS Inc., Chicago, IL, USA). A value of $p < 0.05$ was considered statistically significant.

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Conflict of interest: None declared.

References

Bell JL, Malyukova A, Kavallaris M, Marshall GM, Cheung BB (2013) TRIM16 inhibits neuroblastoma cell proliferation through cell cycle regulation and dynamic nuclear localization. Cell Cycle 12: 889-998.

Chen Z, Wang Z, Guo W, Zhang Z, Zhao F, Zhao Y, Jia D, Ding J, Wang H, Yao M, He X (2015) TRIM35 Interacts with pyruvate kinase isoform M2 to suppress the Warburg effect and tumorigenicity in hepatocellular carcinoma. Oncogene 34: 3946-3956.

Groner AC, Cato L, De THJ, Bernasocchi T, Janouskova H, Melchers D, Houtman R, Cato AC, Tschopp P, Gu L (2016) TRIM24 is an oncogenic transcriptional activator in prostate cancer. Cancer Cell 29: 846-858.

Hatakeyama S (2011) TRIM proteins and cancer. Nature Rev Cancer 11: 792-804.

Haupt Y, Maya R, Kazaz A, Oren M (1997) Mdm2 promotes the rapid degradation of p53. Nature 387: 296-269.

Herquel B, Ouararhni K, Khetchoumian K, Ignat M, Teletin M, Mark M, Bechade G, Van Dorsselaer A, Sanglier-Cianferani S, Hamiche A, Cammas F, Davidson I, Losson R (2011) Transcription cofactors TRIM24, TRIM28, and TRIM33 associate to form regulatory complexes that suppress murine hepatocellular carcinoma. Proc Natl Acad Sci USA 108: 8212-8217.

Honda R, Tanaka H, Yasuda H (1997) Oncoprotein MDM2 is a ubiquitin ligase E3 for tumor suppressor p53. FEBS Lett 420: 25-27.

Hong B, Ap VDH, Prabhu VV, Zhang S, Eldeiry WS (2014) Targeting tumor suppressor p53 for cancer therapy: strategies, challenges and opportunities. Current Drug Targets 15: 80-89.

Ikeda K, Inoue S (2012) TRIM proteins as RING finger E3 ubiquitin ligases. Adv Exp Med Biol 770: 27-37.

Jia D, Wei L, Guo W, Zha R, Bao M, Chen Z, Zhao Y, Ge C, Zhao F, Chen T, Yao M, Li J, Wang H, Gu J, He X (2011) Genome-wide copy number analyses identified novel cancer genes in hepatocellular carcinoma. Hepatology 54: 1227-1236.

Jiang J, Yu C, Chen M, Tian S, Sun C (2015) Over-expression of TRIM37 promotes cell migration and metastasis in hepatocellular carcinoma by activating Wnt/beta-catenin signaling. Biochem Biophys Res Commun 464: 1120-1127.

Kalluri R, Weinberg RA (2009) The basics of epithelial-mesenchymal transition. J Clin Invest 119: 1420-1428.

Khatamianfar V, Valiyeva F, Rennie PS, Lu W, Yang BB, Bauman GS, Moussa M, Xuan JW, Khatamianfar V, Valiyeva F (2012) TRIM59, a novel multiple cancer biomarker for immunohistochemical detection of tumorigenesis. BMJ Open 2: e001410.

Kondo T, Watanabe M, Hatakeyama S (2012) TRIM59 interacts with ECSIT and negatively regulates NF-kappaB and IRF-3/7-mediated signal pathways. Biochem Biophys Res Commun 422: 501-507.

Li L, Dong L, Qu X, Jin S, Lv X, Tan G (2016) Tripartite motif 16 inhibits hepatocellular carcinoma cell migration and invasion. Int J Oncol 48: 1639-1649.

Liang J, Xing D, Li Z, Shen J, Zhao H, Li S (2016) TRIM59 is upregulated and promotes cell proliferation and migration in human osteosarcoma. Mol Med Rep 13: 5200-5206.

Llovet JM, Bruix J (2008) Novel advancements in the management of hepatocellular carcinoma in 2008. J Hepatol 48 Suppl 1: S20–S37.

Maheswaran T, Rushbrook SM (2012) Epithelial-mesenchymal transition and the liver: role in hepatocellular carcinoma and liver fibrosis. J Gastroenterol Hepatol 27: 418-420.

McGlynn KA, London WT (2011) The global epidemiology of hepatocellular carcinoma: present and future. Clin Liver Dis 15, 223-243.

Miao ZF, Wang ZN, Zhao TT, Xu YY, Wu JH, Liu XY, Xu H, You Y, Xu HM (2015) TRIM24 is upregulated in human gastric cancer and promotes gastric cancer cell growth and chemoresistance. Virchows Arch 466: 525-532.

Sardiello M, Cairo S, Fontanella B, Ballabio A, Meroni G (2008) Genomic analysis of the TRIM family reveals two groups of genes with distinct evolutionary properties. BMC Evol Biol 8: 1-22.

Tsai WW, Wang Z, Yiu TT, Akdemir KC, Xia W, Winter S, Tsai CY, Shi X, Schwarzer D, Plunkett W (2010) TRIM24 links a non-canonical histone signature to breast cancer. Nature 468, 927-932.

Valiyeva F, Jiang F, Elmaadawi A, Moussa M, Yee SP, Raptis L, Izawa JI, Yang BB, Greenberg NM, Wang F, Xuan JW (2011) Characterization of the oncogenic activity of the novel TRIM59 gene in mouse cancer models. Mol Cancer Ther 10: 1229-1240.

van Zijl F, Zulehner G, Petz M, Schneller D, Kornauth C, Hau M, Machat G, Grubinger M, Huber H, Mikulits W (2009) Epithelial-mesenchymal transition in hepatocellular carcinoma. Future Oncol 5: 1169-1179.

Wang Y, He D, Yang L, Wen B, Dai J, Zhang Q, Kang J, He W, Ding Q, He D (2015) TRIM26 functions as a novel tumor suppressor of hepatocellular carcinoma and its downregulation contributes to worse prognosis. Biochem Biophys Res Commun 463: 458-465.

Zhan W, Han T, Zhang C, Xie C, Gan M, Deng K, Fu M, Wang JB (2015) TRIM59 promotes the proliferation and migration of non-small cell lung cancer cells by upregulating cell cycle related proteins. PLoS One 10: e0142596.

Zhou Z, Ji Z, Wang Y, Li J, Cao H, Zhu HH, Gao WQ (2014) TRIM59 is up-regulated in gastric tumors, promoting ubiquitination and degradation of p53. Gastroenterology 147: 1043-1054.

Zhu RX, Seto WK, Lai CL, Yuen MF (2016a) Epidemiology of hepatocellular carcinoma in the Asia-Pacific region. Gut Liver 10: 332-339.

Zhu Z, Wang Y, Zhang C, Yu S, Zhu Q, Hou K, Yan B (2016b) TRIM25 blockade by RNA interference inhibited migration and invasion of gastric cancer cells through TGF-β signaling. Scientific Reports 6: 19070.