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# The SUMO-specific protease SENP5 controls DNA damage response and promotes tumorigenesis in hepatocellular carcinoma

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**Abstract. – OBJECTIVE:** SUMOylation plays critical roles in a variety of physiological and pathological processes including tumorigenesis. SUMOylation is a reversible process which is mediated by the SENP (Sentrin/SUMO-specific protease) family to remove SUMO from conjugated substrates. SENP5 has been reported to play critical roles in the control of several cancers including breast cancer, osteosarcoma and oral squamous cell carcinoma. In this study, we uncovered a role of SENP5 in promoting tumorigenesis process in hepatocellular carcinoma (HCC) via regulating DNA damage response.

**MATERIALS AND METHODS:** The mRNA and protein levels of SENP5 in 10 pairs of HCC samples were determined by Realtime PCR and Western blot, respectively. SiRNAs were used to silence the expression of SENP5 in HepG2 cells. Male BALB/c nude mice were used to determine the roles of SENP5 on tumorigenesis. *In vivo* SUMOylation assay was used to detect the SUMOylation of ATRIP. Immunoprecipitation (IP) was used to detect the interaction between SENP5 and ATRIP.

**RESULTS:** We found that SENP5 was over-expressed in HCC samples and required for HCC cells proliferation both *in vitro* and *in vivo*. SENP5-depleted HepG2 cells exhibited hypersensitivity to IR and etoposide treatment with defective checkpoint activation including decreased activation of ATR and phosphorylation of ATR targets. At the molecular level, we found that SENP5 interacted with ATRIP and promoted ATRIP deSUMOylation.

**CONCLUSIONS:** Overall, our data suggest that SENP5 is required for HCC cell growth and might be a promising drug target for HCC.

*Key Words:*
SENP5, Tumorigenesis, Hepatocellular carcinoma, DNA damage response.

## Introduction

Liver cancer has become one of the most common malignancy in China and the third most lethal neoplasm worldwide[1]. Liver cancer is a malignant tumor that occurred in the liver, including primary liver cancer and metastatic liver cancer. According to cell type classification, primary liver cancer is divided into hepatocellular carcinoma (HCC), hepatic cholangiocarcinoma (CC) and combined hepatocellular-cholangiocarcinoma (cHCC-CC)[2]. Clinically, HCC accounted for more than 80% of total liver cancer. Although the roles of multiple oncogenes and (or) tumor suppressor in the development of HCC have been characterized, its molecular mechanisms remain to be elucidated[3]. Therefore, a better understanding of its molecular mechanisms may help to identify novel targets for its therapeutics.

The small ubiquitin-related modifier (SUMO) modifier regulates diverse cellular processes through their covalent attachment to a variety of proteins to modulate their activation, function and subcellular localization[4]. SUMOylation plays critical roles in a variety of physiological and pathological processes including tumorigenesis[5-7]. Four SUMO family members, SUMO-1 to SUMO-4,



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have been found. SUMO-1 shares 18% sequence identity with ubiquitin and have similar three-dimensional structures with Ubiquitin. SUMO-2 to SUMO-4 share greater amino acid sequence identity with each other than with SUMO-1[8]. SUMOylation is catalyzed by SUMO-specific activating (E1), conjugating (E2) and ligating (E3) enzymes[9]. SUMOylation is a dynamic process that is reversed by a family of SUMO-specific proteases (SENPs)[10]. In mammalian cells, six SENPs have been identified, including SENP1, SENP2, SENP3, SENP5, SENP6 and SENP7[10,11]. Each SENP member has different substrate specificities and subcellular localizations[11].

Appropriate DNA damage response (DDR) is required for the maintenance of genomic stability[12]. In mammal cells, DDR is primarily initiated by the ataxia telangiectasia-mutated (ATM) and the ATM and Rad3-related (ATR) kinases. ATM is primarily activated by DNA double-stranded breaks (DSBs), while ATR is activated by both DNA double-stranded breaks and DNA single-stranded breaks, and transmitted DNA damage signals through the ATR-Chk1 kinase cascade ATR-Chk1[12,13]. Recent studies[14,15] indicate that SUMOyation plays a key role in the activation of ATR pathway, and ATRIP has been found to be heavily SUMOylated by SUMO2 at K234 and K289. Importantly, ATRIP SUMOylation mutant fails to efficiently activate ATR signaling pathway[15]. However, how to regulate ATRIP SUMOylation remains largely unknown.

In this study, we investigated the roles SENP5 in HCC development. Our data showed that SENP5 was required for HCC cell growth via regulating DNA damage response and might be a promising drug target for HCC.

## Materials and Methods

### Human Tissue Samples

Ten paired HCC tissues and adjacent non-tumor normal tissues were collected from routine therapeutic surgery at our department. All samples were obtained with informed consent and approved by the Hospital Institutional Review Board.

### Cell Culture and Drugs

HCC cell line HepG2 cells were obtained from The Cell Bank of Type Culture Collection of Chinese Academy of Sciences. Cells were grown in Dulbecco's modified Eagle's medium (DMEM, Shanghai, China) supplemented with 10% fetal bovine serum (Gibco, Shanghai, China) and maintained at 37°C in a humidified atmosphere with 5% $CO_2$. Etoposide and DMSO were purchased from Sigma (Saint Louis, MO, USA).

### BrdU Assays

A cell proliferation enzyme-linked immunosorbent assay (BrdU kit, Beyotime, Shanghai, China) was used to analyze the incorporation of BrdU during DNA synthesis following the manufacturer's protocols. Absorbance was measured at 450 nm in the Spectra Max 190 ELISA reader (Molecular Devices, Sunnyvale, CA, USA). All experiments were performed in triplicate.

### Colony Formation Assays

Cells were seeded in a 6-well plate 48 hours post-transfection and cultured for 8 to 10 days at 37°C in 5% $CO_2$. Cells were fixed with 4% paraformaldehyde in phosphate-buffered saline (PBS), washed twice with PBS, and stained with a crystal violet solution (1% crystal violet, 10% ethanol in water). Stained cells were washed thrice with water and counted by under an optical microscope.

### siRNA, RNA Extraction and Quantitative Real-time PCR

HepG2 cells were seeded on to 6-well plates then transfected with 20nM siGENOME non-targeting siRNA, human SENP5 (5'-GAACAUCGUUCUAAUACCAUGUUCA-3', Dharmacon, Lafayette, CO, USA). Total RNA from tissues and cells was extracted using the TRIzol Kit (Invitrogen, Carlsbad, CA, USA) according to the manufacturer's instructions. cDNA was transcribed from 1 $\mu$g of total RNA following the manufacturer's instructions (Promega, Madison, WI, USA). Quantitative real-time PCR was performed using SYBR Premix Ex Taq reagents (Takara, Dalin, China). Relative transcript quantities were calculated using the $2^{-\Delta\Delta Ct}$ method with beta-actin as the endogenous reference gene. The primers sequences are as follows: SENP5: F:5'TGCTAGATCACCTCGTCTTCA3' and R:5'AGTGCTTAGTGGTTTTCATGATA3'. Beta-actin: F:5'AGCGAGCATCCCCCAAAGTT3' and R:5'GGGCACGAAGGCTCATCATT3'.

### Western Blot

HepG2 cells were harvested and lysed with lysis buffer (50 mM Tris-HCl, pH 6.8, 100 mM 2-ME, 2% w/v SDS, 10% glycerol) at 4°C. After

centrifugation at 10000 × g for 15 min at 4 °C, proteins in the supernatants were separated by 12% sodium dodecyl sulphate-polyacrylamide gel electrophoresis (SDS-PAGE). Western blot assay was performed using anti-SENP5 (Santa Cruz Biotechnology, Santa Cruz, CA, USA), ATRIP, Chk1, p-CHK1, gamma-H2AX, p-gamma-H2AX antibodies (Abcam, Cambridge, USA), Flag M2, HA and His antibodies (Sigma-Aldrich, St. Louis, MO, USA). Protein levels were normalized to total beta-actin, using a rabbit anti-beta-actin antibody (Santa Cruz Biotechnology, Santa Cruz, CA, USA).

### *Immunoprecipitation (IP)*

Cells were lysed in 2 ml of cell lysis buffer (50 mM Tris-HCl pH 7.4, 150 mM NaCl, 0.5% Nonidet P40) for 30 min at 4°C. Lysates were cleared using centrifugation (13,000 rpm, 20 min), the supernatant was then subjected to IP with 15 μl anti-ATRIP antibodies with 50 μl protein G beads (Sigma-Aldrich, St. Louis, MO, USA) overnight at 4°C with gentle rotation. Beads containing immune complexes were washed with lysis buffer 3 times. Precipitates were denatured in 2X SDS buffer at 99°C for 5 min.

### *Tumor Growth Assay*

Male BALB/c nude mice aged 4 weeks were purchased from Shanghai Laboratory Animal Company (SLAC, Shanghai, China). $1.5 \times 10^5$ HepG2 cells were injected into subcutaneously to the skin under the front legs of the nude mice. At around 2 weeks after tumor cell injection, the mice with tumor burden were randomly grouped (n=5 for each group) and treated weekly by intratumoral injection over 4 weeks with indicated siRNA (10 μg/kg/week). Tumor size was measured weekly before each administration. The treated mice were sacrificed at day 40 post tumor cell injection and the tumor samples were collected; then, the wet weights of each tumor were determined.

### *Statistical Analysis*

The data shown represent the mean ± standard error (SE) values of three independent experiments. Significance was analyzed using Student's *t*-test (*$p < 0.05$, **$p < 0.01$, ***$p < 0.001$).

## Results

### *SENP5 was Over-expressed in Human Hepatocellular Carcinoma*

In order to explore the impact of SENP5 on tumorigenesis, we detected SENP5 expression from 10 pairs of HCC samples, each consisting of a sample of HCC tissue and a corresponding sample of adjacent normal tissue. The results of Real-time PCR showed that the average SENP5 mRNA levels were about 3.3-fold higher in HCC tissues than in adjacent normal tissues ($p < 0.01$) (Figure 1A). SENP5 expression was also assessed by Western blot and the results further confirmed that the protein levels of SENP5 in HCC tissues were higher than that in adjacent normal tissues (Figure 1B). Taken together, these data suggested that SENP5 was abnormally highly expressed in HCC tissues.

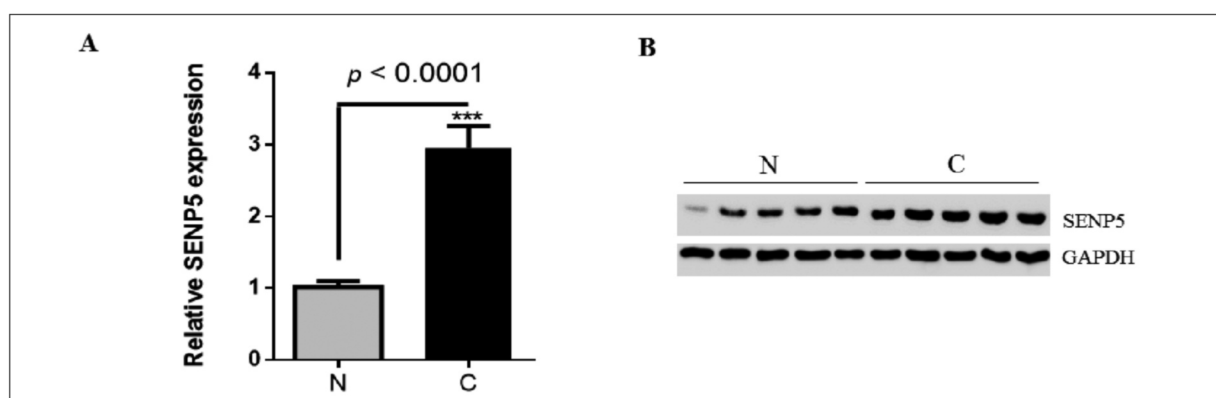


**Figure 1.** SENP5 was over-expressed in human hepatocellular carcinoma. ***A-B,*** mRNA ***(A)*** and representative protein ***(B)*** levels of SENP5 were analyzed by Real-time PCR and Western blot in human hepatocellular carcinoma tissues or adjacent normal tissues. C: Human hepatocellular carcinoma; N: normal tissues.

### *SENP5 is Required for the Proliferation HCC Cells*

To knockdown endogenous SENP5 in HepG2 cells, non-target siRNA and siRNA against SENP5 were transfected into HepG2 cells, and the knockdown efficiency was verified by both Real-time PCR and Western blot, respectively (Figure 2A and 2B). The result of the BrdU assay showed that the proliferation of HepG2 cells was significantly inhibited by transfection of siRNA that targeted SENP5 (Figure 2C). Moreover, we found that the colony-forming efficiency of HepG2 cells was suppressed when SENP5 was silenced (Figure 2D). Taken together, these data indicated that SENP5 played a key role in the regulation of HCC cells proliferation.

### *SENP5 is Required for Tumor Growth in vivo*

To further determine the roles of SENP5 in tumorigenesis, the HepG2 cells were injected into subcutaneously to the skin under the front legs of the nude mice. At around 2 weeks after tumor cell injection, the mice with tumor burden were randomly grouped (n=5 for each group) and treated weekly by intratumoral injection over 4 weeks with indicated siRNA. Tumor size was measured weekly before each administration. The treated mice were sacrificed at day 40 post tumor cell injection and tumor samples were collected. As a result, the tumor size and weight was markedly reduced in SENP5-depleted tumors compared to control tumors (Figure 3A and 3B), suggesting that SENP5 could promote HCC growth *in vivo*.

### *SENP5 Regulated DNA Damage Response*

To further investigate the potential mechanism of SENP5 on tumorigenesis, we tested whether SENP5 could be involved in DNA damage response controlling. Because deregulated DNA damage response usually leads to tumorigenesis[12]. To this end, we evaluated the cell viability on

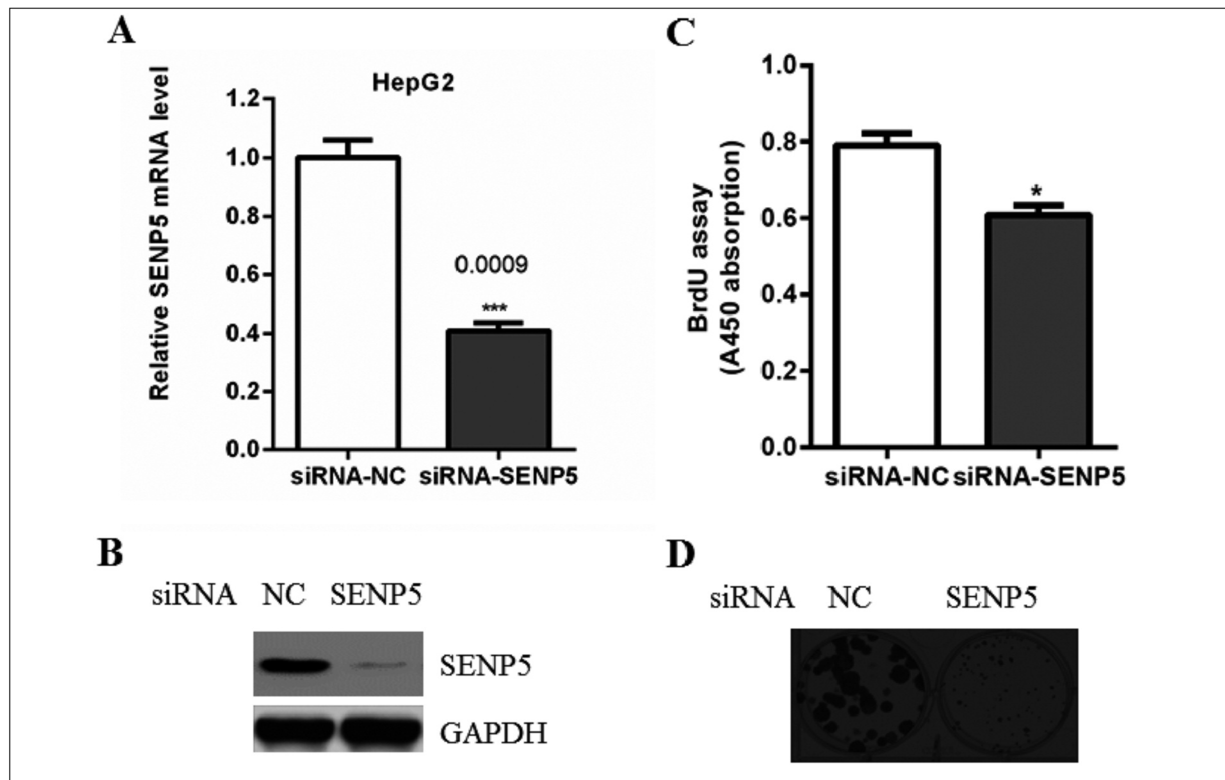


**Figure 2.** SENP5 is required for the proliferation HCC cells. ***A,*** SENP5 mRNA level was determined by real-time PCR in HepG2 cells. Cells were transfected with siRNA oligos targeting SENP5 or scramble siRNA (NC) for 48 hr before harvest. ***B,*** Protein level of SENP5 was determined by Western blot in HepG2 cells. Cells were transfected with siRNA oligos targeting SENP5 or scramble siRNA (NC) for 48 hr before harvest. ***C,*** The cell proliferative potential (BrdU) was determined in HepG2 cells transfected with siRNA oligos targeting SENP5 or scramble siRNA (NC). ***D,*** The tumor formation activity of HepG2 cells transfected with siRNA oligos targeting SENP5 or scramble siRNA (NC) were determined.

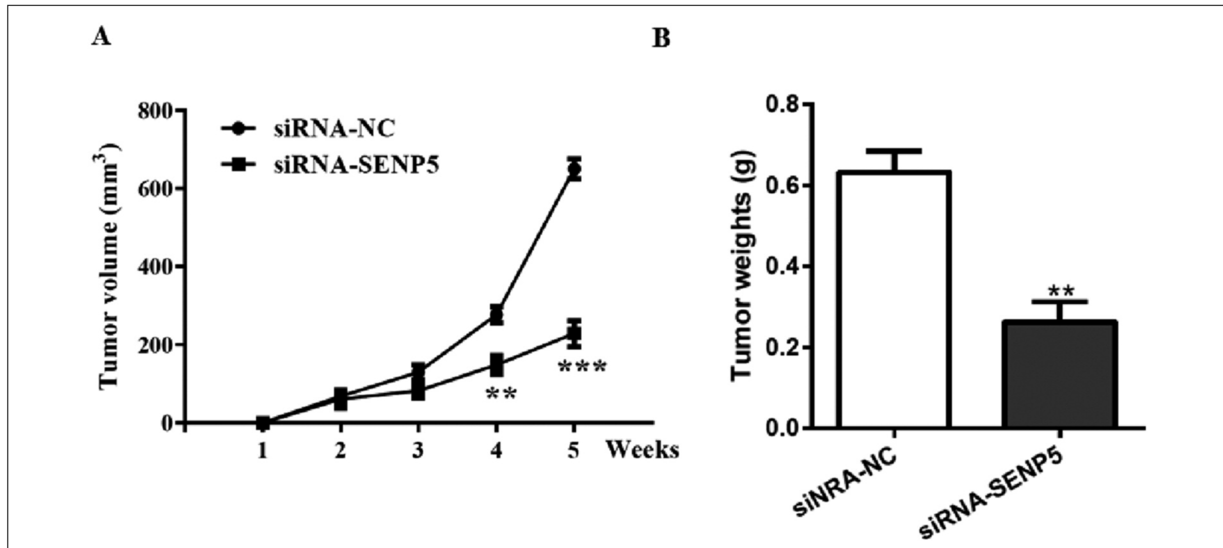


**Figure 3.** SENP5 is required for tumor growth *in vivo*. ***A,*** The HepG2 cells were injected into subcutaneously to the skin under the front legs of the nude mice. At around 2 weeks after tumor cell injection, the mice with tumor burden were randomly grouped (n = 5 for each group) and treated weekly by intratumoral injection over 4 weeks with indicated siRNA (10 $\mu$g/kg). Tumor size was measured weekly before each administration. The treated mice were sacrificed at day 40 post tumor cell injection and tumor samples were collected. ***B,*** The tumor weights were determined at day 40 post tumor cell injection.

HepG2 cells with silencing of SENP5 or non-specific gene and treated with or without several DNA damaging agents. SENP5-depleted HepG2 cells exhibited hypersensitivity to IR (Figure 4A). Moreover, when compared with control cells, SENP5-depleted HepG2 cells showed increased apoptosis treated with etoposide (Figure 4B) and defective checkpoint activation (Figure 4C), when compared with mock transfected cells, including decreased activation of ATR and phosphorylation of ATR targets after etoposide treatment, suggesting that silencing of SENP5 could sensitize HepG2 cells to genotoxic stress via decreased cellular DNA damage response.

### SENP5 Mediated ATRIP deSUMOylation

ATRIP has been identified to be a potential substrate of SUMO2 in a proteomic study[16]. A recent study[15] further showed that ATRIP was heavily SUMOylated by SUMO2 at K234 and

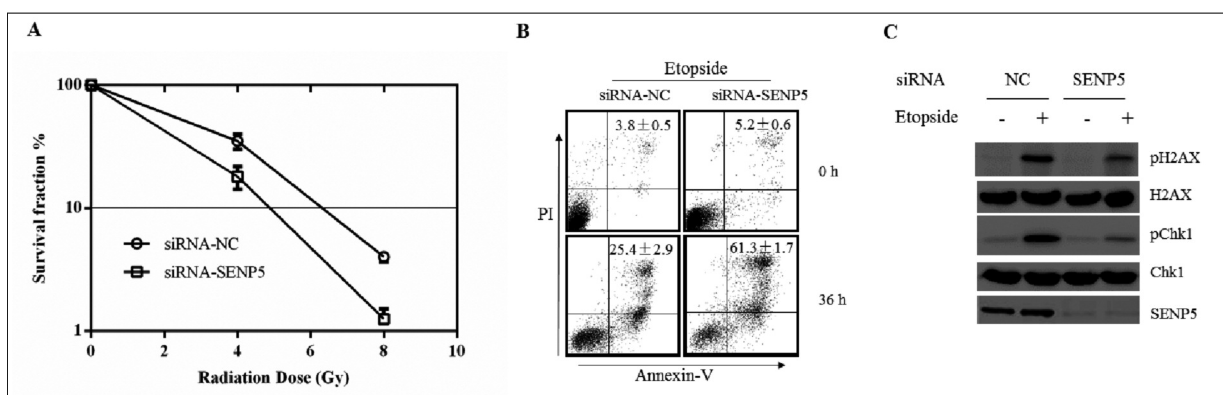


**Figure 4.** SENP5 regulated DNA damage response. ***A,*** HepG2 cells transfected with siRNA oligos targeting SENP5 or scramble siRNA (NC) were irradiated as indicated and clonogenic cell survival assays carried out. Data shown are the mean and SE from three independent experiments. ***B,*** HepG2 cells transfected with siRNA oligos targeting SENP5 or scramble siRNA (NC) were treated with or without 10 μM Etoposide for 24h and annexin-V+ cells % was determined by flow cytometry. C, HepG2 cells transfected with siRNA oligos targeting SENP5 or scramble siRNA (NC) were treated with or without 10 μM Etoposide for 24h. Western blot was used to determine the expression of indicated proteins.

K289. Interestingly, ATRIP SUMOylation mutant fails to fully activate ATR signaling during DDR[15]. As a dynamic process, the SUMOylation of ATRIP is certain to be regulated by SENPs to remove the SUMO protein. Given the critical role of SENP5 in the regulation of ATR signaling, we then ask whether SENP5 regulates the deSUMOylation of ATRIP. To this end, we tested whether the SUMOylation of ATRIP could be increased in when SENP5 was silenced. As depicted in Figure 5A, the endogenous SUMOylation of ATRIP was increased in SENP5 knockdown HepG2 cells. To further determine whether SENP5 is the deSUMOylation enzyme for ATRIP, 293T cells were co-transfected HA-ATRIP, Flag-SENP5WT or Flag-SENP5Mut (catalyze inactive form) and his-SUMO2 plasmids. We observed that the SUMOylated ATRIP was largely diminished in the present of SENP5WT but not SENP5Mut (Figure 5B). These results indicated that SENP5 could specifically de-SUMOylate ATRIP.

### *SENP5 Physically Interacted with ATRIP*

To determine whether the regulation of ATRIP by SENP5 is direct, we examined if SENP5 physically interacts with ATRIP by immunoprecipitation. 293T cells were co-transfected with HA-ATRIP and Flag-SENP5 for 48h, and we found that ATRIP was immunoprecipitated in SENP5 precipitates, indicating a physical interaction between ATRIP and SENP5 (Figure 6A). Moreover, we also observed endogenous SENP5 was present in ATRIP precipitates from HepG2 cells (Figure 6B). Taken together, our data suggested that SENP5 physically interacted with ATRIP and mediated-ATRIP deSUMOylation.

## Discussion

Loss of balance between SUMOylation and deSUMOylation has been reported in a number of studies in a variety of disease types including cancer[17]. Several SENP family members have been found to play an important role in diverse cancers[17]. For example, SENP1 has been reported to be over-expressed in many human cancers, including prostate cancer, colon cancer and lung cancers[18-20]. SENP3 has been shown to promote the epithelial-mesenchymal transition in gastric cancer cells[21]. The expression of SENP6 was also increased in HCC[22].

SENP5 has been reported to be overexpressed in breast cancer, osteosarcoma and oral squamous cell carcinoma[23-25]. The SENP5 expression has been showed to be negatively correlated with survival in breast cancer. SENP5 promotes the tumorigenesis in breast cancer induces TGF□RI post translation modification and regulates TGF□RI downstream genes[25]. In the present study, we found that SENP5 was over-expressed in HCC samples. Silencing the expression of SENP5 affected HCC cells proliferation both *in vitro* and *in vivo*.

Dysregulation of DNA damage repair is associated with a predisposition to cancer and affects responses to DNA-damaging anticancer therapy[26,27].

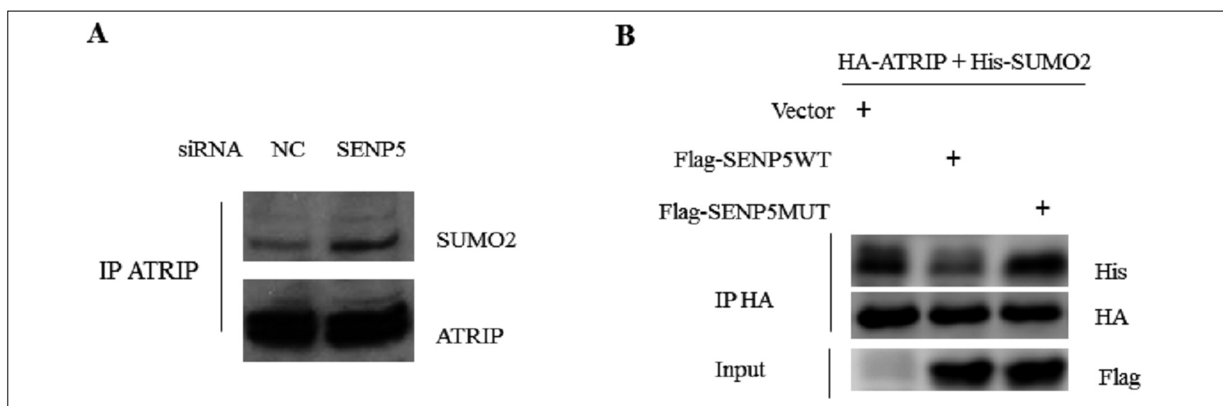


**Figure 5.** SENP5 mediated ATRIP deSUMOylation. ***A,*** HepG2 cells transfected with siRNA oligos targeting SENP5 or scramble siRNA (NC) were harvested and subjected to IP with ATRIP antibody. The endogenous SUMOylation of ATRIP was determined by Western blot with the SUMO2 antibody. ***B,*** 293T cells were co-transfected HA-ATRIP, Flag-SENP5WT or Flag-SENP5Mut (catalyze inactive form) and his-SUMO2 plasmids for 48h. Cells were collected and subjected to IP with HA antibody. Western blot was used to determine the expression of indicated proteins.

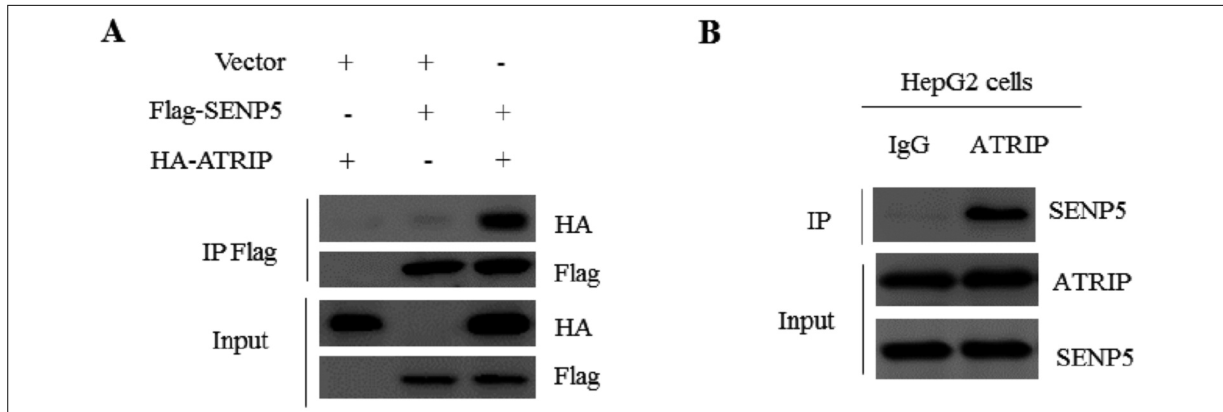


***Figure 6.*** SENP5 physically interacted with ATRIP. ***A,*** 293T cells were co-transfected HA-ATRIP with or without Flag-SENP5 plasmid for 48h. Cells were collected and subjected to IP with Flag antibody. Western blot was used to determine the expression of indicated proteins. ***B,*** HepG2 cells were harvested and subjected to IP with ATRIP antibody. The endogenous interaction between ATRIP and SENP5 was determined by Western blot.

Our studies provide new insights into mechanisms of DNA-damage signal transduction and reveal that SENP5 regulates cellular DNA damage response, including activation of ATR and phosphorylation of ATR targets. ATR kinase is a master regulator of the response to multiple DNA damage insults and replication stress, phosphorylating multiple targets to institute cell cycle arrest and coordinate the repair of DNA damage[28]. Our data showed that SENP5-depleted HepG2 cells exhibited hypersensitivity to IR and etoposide treatment with defective checkpoint activation. Moreover, we demonstrated that SENP5 physically interacted with ATRIP and mediated its deSUMOylation reaction. Indeed, SUMOylated ATRIP was ready to be detected in SENP5-depleted HepG2 cells. Given the critical role of ATRIP SUMOylation in the regulation of ATR signaling pathway and the DNA damage response, our data suggested that SENP5-mediated ATRIP deSUMOylation played an important role in ATR signaling in response to DNA damage.

## Conclusions

Our data not only revealed SENP5 played key roles in HCC cell growth and DNA damage response control, but also identified its SUMOylated target in HCC. It is possible that the overexpression of SENP5 would affect the pathogenesis through the ATRIP-ATR pathway. Thus, our data suggested SENP5 was required for DNA damage response and tumorigenesis, which might be a promising drug target for HCC.

### Conflict of Interest

The Authors declare that there are no conflicts of interest.

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