Abstract. RNA‑binding protein 24 (RBM24) has been shown to play tumor‑suppressive functions in various types of cancer. The present study aimed to investigate the role of RBM24 in liver cancers and its downstream mechanisms. The present study demonstrated that RBM24 functioned as a tumor suppressor in liver cancer cells, and inhibited nuclear translocation of β‑catenin and tumor protein 63 expression by immunocytochemistry. In addition, RBM24 could suppress sphere formation in a multicellular tumor spheroid model of liver cancer cells. In conclusion, it is hypothesized that RBM24 is a tumor suppressor of liver cancer cells, which could be a potential novel therapeutic target for treatment of patients with liver cancer.

Introduction
Hepatocellular carcinoma is the most common primary liver cancer and the fourth leading cause of cancer‑related deaths worldwide, accounting for more than 782,000 deaths in 2018 (1‑3). Due to challenges associated with diagnosis, the majority of patients are diagnosed at later stages when surgical resection is not feasible (3). Therefore, the prognosis of liver cancer remains extremely poor (2). Clarifying the underlying molecular mechanisms may help develop more effective pharmacological therapies.

A recent study reported that RNA‑binding protein 24 (RBM24) has a tumor‑suppressive role in prostate cancer, suppressing cellular proliferation, migration, and invasion (4,5). RBM24 exhibits a tumor‑suppressive role, and RNA‑binding proteins (RBPs) are known to play a key role in post‑transcriptional regulation, including mRNA stabilization and translation (6‑8). Moreover, several oncogenes and tumor suppressor genes control RBPs in various cancer cell lines (9). RBM24, an RBP with a single conserved RNA recognition motif domain, is involved in post‑transcriptional regulation and has been shown to influence the proliferation and motility of various cancer cells (4,5,10). Previous studies have demonstrated that RBM24 may regulate the stability of p21 and p63 mRNA transcripts in different human cancer cell lines (11,12). Conversely, RBM24 has also been shown to destabilize tumor protein 63 (TP63) mRNA by binding to its 3'‑UTR (12).

Ruptier et al report that TP63 expression is regulated via the Wnt/β‑catenin pathway in human hepatocellular carcinoma and squamous cell carcinoma cell lines (13), suggesting that the activation of the β‑catenin (CTNNB1) pathway may contribute to TP63 overexpression during tumor progression in a cell type‑specific manner. It has also been reported that TP63 overexpression is related to oncogenesis, cell migration, and epithelial‑to‑mesenchymal transition (EMT)‑related features of cancer (14,15). However, the exact function of RBM24 in liver cancer tumorigenesis and progression remains largely unknown.

In the present study, we demonstrate that RBM24 acts as a tumor suppressor in liver cancer cells through regulation of CTNNB1 and TP63. We suggest that RBM24 plays a critical role in liver cancer progression and anticancer drug resistance.

Materials and methods
Cell culture and drug treatment. A total of 293 cells and human liver cells (Huh7, Hep3B and HepG2) were purchased from the Korean Cell Line Bank (KCLB, Seoul, Korea). LX‑2 cells were kindly provided by Dr Park (Yonsei University, Seoul, Korea). L‑O2 cells (an immortalized normal liver cell line) were provided by Dr Shin (Sung‑Kyung‑Kwan University, Gyeonggi, Korea). The cell lines were cultured in a growth medium consisting of Dulbecco's modified Eagle's medium (DMEM; HyClone; Cytiva) and MEM supplemented with 10% fetal bovine serum (FBS; Gibco; Thermo Fisher Scientific, Inc.), and 1% antibiotics (Gibco; Thermo Fisher Scientific, Inc.) in a 5% CO₂‑humidified incubator. The cell groups were treated with various concentrations of sorafenib (0, 0.1, 0.5, 1, 5, and 10 µM) in 10% FBS‑supplemented growth media for 4 days. Sorafenib concentration referred to Liang et al reports (16).
Cloning of RBM24 in an expression vector and siRNA knockdown. We constructed an RBM24 overexpressing DNA plasmid (6.7 kb) using pcDNA3.1 (Addgene, Inc.). The cDNA of RBM24 (720 bp fragment of RBM24 transcript variant 1 mRNA, GenBank accession no. NM_001143942.1) was ligated to the mammalian expression vector pcDNA3.1 (Addgene, Inc.), amplified in Escherichia coli (E. coli) DH5α, identified by restriction analysis (BamHI and EcoRI), and sequenced. RBM24-pcDNA contains CMV promoter/enhancer sequences that control the expression of the gene of interest in multiple cloning sites. This vector includes the Col E1 origin of replication and the E. coli Amp' gene for propagation and antibiotic selection in bacteria. The SV40 promoter controls the expression of the neomycin resistance gene (Neo') that allows antibiotic selection in eukaryotic cells. A total of 3 µg of RBM24 overexpression vector was transfected into three human liver cancer cell lines (Huh7, Hep3B and HepG2) using Lipofectamine 3000 transfection reagent (Invitrogen; Thermo Fisher Scientific, Inc.) at 37°C CO₂ incubator. After 72 h transfected liver cancer cells were G418-selected for two weeks. Scramble siRNA and the siRNAs against human CTNNB1 (On-TARGETplus human CTNNB1-SMART pool, L-003482-00-0005; GE Healthcare Dharmacon, Inc.) were purchased from GE Healthcare Dharmacon, Inc. Cells were transfected with each 100 nM siRNA using Lipofectamine RNAiMAX (Invitrogen; Thermo Fisher Scientific, Inc.) at 37°C CO₂ incubator for 72 h.

Cell viability, spheroid formation, and MCTS (multicellular tumor spheroid model) assay. Cell viability was assayed using the Cell Titer-Blue Cell Viability Assay kit (Promega Corporation) according to the manufacturer's protocol. The spheroids were trypsinized for 10 min and incubated with Cell Titer-Blue fluorescence for 2 h and an additional hour at ambient temperature. The fluorescence intensity (555-585 nm, gain: 57) was measured using Varioskan Flash Fluorescent Microplate Fluorometer. To generate spheroids, cells were suspended in a complete medium and seeded as a series of cell seeding/well density in a 94-well ultra-low attachment plate (Corning, Inc.). The plates were incubated for 4 days at 37°C in a humidified atmosphere supplied with 5% CO₂. MCTS assay was performed using the liver cancer cells and LX2 cells co-cultured in spheroids at a 7:3 ratio. Data were analyzed using SigmaPlot software (Systat Software, Inc.) to evaluate the logistic three parameters and determine the IC₅₀ of the chemotherapeutic agents.

Quantitative PCR analysis. For RT-qPCR analysis of the target genes, total RNA was isolated using the TRIzol reagent (Invitrogen; Thermo Fisher Scientific, Inc.). Reverse transcription was performed using TURiscript RT DryMIX (Enzymomics). RT-qPCR was performed using the iQ SYBR-Green supermix (Bio-Rad Laboratories, Inc.) and the CFX96™ Real-Time system [Bio-Rad Laboratories (Singapore)]. The amplification conditions consisted of an initial denaturation at 95°C for 2 min, then 40 cycles of denaturation at 95°C for 5 sec, and annealing at 58°C for 30 sec according to the manufacturer’s instructions. The relative amounts of target genes were normalized to those of GAPDH. The RT-qPCR primer sets were summarized in Table 1. The 2-ΔΔCq method was adopted to determine expression fold-changes (control vs. sample) (17).

Immunoprecipitation and immunoblotting assay. Cells were harvested and lysed with immunoprecipitation lysis buffer (REF87787; Thermo Fisher Scientific, Inc.). Transfer the lysate to a microcentrifuge tube and centrifuge at ~13,000 x g for 10 min to pellet the cell debris at 4°C. Protein concentrations were determined using a Bradford protein assay kit (#5000006; Bio-Rad Laboratories, Inc.). For immunoprecipitation, the isolated protein was transferred to a clean Falcon tube and incubated with anti-His-tag (1:100; sc-8036; Santa Cruz Biotechnology, Inc.), 2 µg of anti-Rbm24, or anti-rabbit IgG antibodies overnight at 4°C. A total of 5 µl (0.25 mg) of magnetic beads (Pierce™ Protein A/G Magnetic Beads, 88802; Thermo Fisher Scientific, Inc.) conjugated with pre-treated protein were incubated at room temperature for 1 h with continuous mixing. The target protein was eluted from the conjugated magnetic beads with elution buffer (0.1 M glycine, pH 2.0) and neutralization buffer (1 M Tris, pH 7.5-9). Equivalent amounts (30 µg) of protein from each lysate were separated using 10% sodium dodecyl sulfate (SDS)-polyacrylamide gel electrophoresis (PAGE) (Bio-Rad Laboratories, Inc.) and transferred to nitrocellulose membranes (#1620115; Bio-Rad Laboratories, Inc.) for immunoblotting. The membranes were washed three times with phosphate-buffered saline (PBS; Welgene, Inc.) containing 0.1% Tween-20 (PBST; Sigma-Aldrich; Merck KGaA). After blocking with PBST containing 1% BSA (BSAS0.1; Bovogen) for 1 h at room temperature, the membranes were incubated with the appropriate primary antibody in PBST containing 1% BSA at 4°C overnight. All primary antibodies were diluted to an appropriate concentration using PBST containing 1% BSA. After treatment with antibodies against RBM24 (diluted 1:1,000; ab94567; Abcam), CTNNB1 (diluted 1:1,000; 8480S; Cell Signaling Technology, Inc.), p63 (diluted 1:1,000; #7074S; Cell Signaling Technology, Inc.), or anti-mouse IgG-horseradish peroxidase-conjugated secondary antibodies (diluted 1:1,000; #7076S; Cell Signaling Technology, Inc.) for 2 h at room temperature, and washed three times with TBST for 30 min. The membranes were developed using ECL Buffer (REF34580; Thermo Fisher Scientific, Inc.).

Immunocytochemistry. To examine CTNNB1 translocation, cells were incubated with 25 mM LiCl (Sigma-Aldrich; Merck KGaA) for 24 h. After fixing with 4% paraformaldehyde for 5 min, the cells were incubated for 10 min with PBS containing 0.25% Triton X-100 (Sigma-Aldrich; Merck KGaA) at room temperature. The cells were then washed three times with PBS, incubated with blocking solution (1% PBS containing 1% BSA and 0.1% Tween-20) followed by primary antibodies against CTNNB1 (1:100; 8480S; Cell Signaling...
Table I. Reverse transcription-quantitative PCR primers.

| Gene      | 5' primer sequence                     | 3' primer sequence                     |
|-----------|----------------------------------------|----------------------------------------|
| RBM24     | 5'-GTGAACCTGGCATATTAGGAGC-3'            | 5'-GCACAAAGCCCTGCGGATAGAC-3'          |
| CTNNB1    | 5'-CACAAAGCAAGTGCTGAAAGGTG-3'          | 5'-GATCCCTGAGAGTCCAAAGACAG-3'         |
| TP63      | 5'-CAGGAAGACAGATGTGCTGTT-3'            | 5'-AAATGGACGGGGGTTCCATCCCT-3'         |
| GAPDH     | 5'-GTCTCCCTCTGACTTCAACACG-3'           | 5'-ACCACCTTGTTGCTGTAACCA-3'           |

RBM24, RNA-binding protein 24; CTNNB1, β-catenin; TP63, tumor protein 63.

Technology, Inc.) and p63 (diluted 1:1,000; sc-25268; Santa Cruz Biotechnology, Inc.) at 4°C for 24 h. Before incubation with primary antibodies, the membranes were blocked with a blocking solution at room temperature for 1 h. The cells were incubated with donkey anti-mouse IgG conjugated with Alexa Fluor 594 (1:200; A21203; Thermo Fisher Scientific, Inc.) and donkey anti-rabbit IgG Alexa Fluor 488 (1:200; A21206; Thermo Fisher Scientific, Inc.) at room temperature for 2 h. All secondary antibodies were diluted in an appropriate concentration of the blocking solution. Nuclei were stained with DAPI containing mounting solution (H-1200; Vector Laboratories, Inc.). The cells were then visualized using an Axiovert 200 fluorescence microscope (Carl Zeiss AG).

Statistical analysis. Statistical significance was analyzed using SigmaPlot v12.5 software (Systat Software, Inc.). The densitometry value was normalized to β-actin value using ImageJ v1.45s software. All experiments were performed in triplicate, and the data are presented as the mean ± standard deviation. Unpaired Student’s t-test was used to compare differences between two groups. A one-way ANOVA test followed by a post hoc test using the Holm-Sidak method was used to compare multiple groups. P<0.05 was considered to indicate a statistically significant difference.

Results

RBM24 inhibits liver cancer cell growth. To assess whether RBM24 exhibits a tumor-suppressive function, we compared RBM24 expression in three liver cancer cells and generated RBM24 overexpression liver cancer cells. As shown in Fig. 1A, RBM24 expression was significantly downregulated in all three liver cancer cell lines compared to those of the normal human fibroblast 293 cells. However, normal liver cells (L-02) showed higher expression of RBM24. To address the function of RBM24 in liver cancer cells, we established RBM24 overexpression systems using a pcDNA expression vector in the liver cancer cell lines of HepG2, Hep3B, and Huh7 cells. Then, we evaluated the effect of the overexpression of RBM24 in the spheroid culture models. We demonstrated that RBM24 overexpression could significantly reduce the efficiency of sphere formation in all the three liver cancer cell lines, from an average of 100% to 72% (HepG2), 58% (Hep3B), and 55% (Huh7), respectively, under 8000 seeding conditions (Fig. 1B). These results confirm that RBM24 has a tumor-suppressive function, suppressing sphere formation of liver cancers.

RBM24 inhibits liver cancer cell progression and induces sorafenib sensitivity. Recently, a MCTS model has emerged as a powerful tool for simulating tumor complexity and enhancing heterogeneity in anticancer research, recapitulating the interplay between cancer cells and their microenvironments (18). Hence, we investigated the tumor-suppressive function of RBM24 in the MCTS for liver cancer cells. We developed liver cancer MCTS by co-culturing the liver cancer cells with a liver stellate cell lines LX-2. Using this system, we could demonstrate that overexpression of RBM24 could inhibit the viability of liver cancer cells of Hep3B (100% to 70%) and Huh7 (100% to 72%), although the viability of HepG2 cells was not inhibited by RBM24 overexpression (100% to 92%) (Fig. 2A).

In addition, liver cancer MCTS have shown strong resistance against sorafenib treatment (19). When we evaluated the effect of the RBM24 expression and sorafenib treatment in the spheroid growths of liver cancer cells, we could observe that the RBM24 overexpression could significantly reduce the spheroid progression of cancer cells (Fig. 2B). Moreover, we could demonstrate that the RBM24 expressing HepG2-MCTS cells exhibited decreased sorafenib resistance (IC50: 8.2 vs. 99 µM). Unfortunately, Hep3B-MCTS and Huh7-MCTS cells did not alter the sorafenib sensitivity by RBM24 overexpression (data not shown). Taken together, we suggest that RBM24 expression can increase the sorafenib sensitivity, at least in HepG2 cells.

TP63 expression is suppressed by interaction of RBM24 and CTNNB1. To investigate whether RBM24 interacts with CTNNB1 and impacts TP63 expression in the signaling pathway, we performed protein expression analysis in the three liver cancer cell lines overexpressing RBM24 using immunoblotting and RT-qPCR. The results indicated that RBM24 overexpression in liver cancer cells specifically decreased TP63 expression and induced a slight reduction in CTNNB1 expression at the protein level (Fig. 3A and B). Additionally, RBM24 overexpression in the liver cancer cells could increase the cleaved-caspase3 levels, thereby inhibiting cell proliferation and promoting apoptosis. To further confirm that the altered TP63 expression is associated with the interaction between RBM24 and CTNNB1, we demonstrated that TP63 mRNA expression was inhibited by RBM24 overexpression or by knockdown of CTNNB1 using RT-qPCR (Fig. 3C) and immunoblotting (Fig. 3D), respectively. These results suggest that TP63 expression is regulated by RBM24 and CTNNB1.
RBM24 inhibits nuclear translocation of CTNNB1 in liver cancer cells. Next, to further evaluate the subcellular localization of CTNNB1 upon RBM24 overexpression, we performed immunoblot analysis of CTNNB1 on both nuclear and cytoplasmic subcellular fractions. Notably, RBM24 overexpression marginally inhibited the CTNNB1 expression in HepG2 and Hep3B cells but suppressed the TP63 expression (Fig. 4A and B). In addition, we could observe that the treatment of LiCl induced CTNNB1 translocation and increased TP63 expression in liver cancer cells. Moreover, overexpression of RBM24 could suppress the LiCl-induced CTNNB1 translocation and the nuclear TP63 expression. This finding the interaction between RBM24 and CTNNB1 could be further confirmed by immunoprecipitation (IP) analyses using an anti-RBM24 antibody (Fig. 4C).

Next, we further validated the effect of RBM24 on the nuclear localization of CTNNB1 using immunocytochemistry. As previously described previously (20), we could demonstrate that the LiCl-treated liver cancer cells strongly induce the CTNNB1 translocation and TP63 expression, however,
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the RBM24 overexpressing cells showed suppressed nuclear translocation of CTNNB1 and expression of TP63 (Fig. 5). In addition, we demonstrated that knockdown of CTNNB1 significantly suppressed TP63 expression in the LiCl-treated cells. Taken together, we suggest that RBM24 interacts with CTNNB1 and inhibits its nuclear translocation and suppress TP63 expression.

Discussion

Several recent studies have conducted in vitro and in vivo assays and have demonstrated that RBPs exhibit strong tumor suppression potential in various cancer patients (4,5,21‑23). Additionally, RBM24 overexpression decreased prostate cancer cell growth, indicating a tumor-suppressive role in prostate cancer in association with the long non-coding RNA HAND2-AS1 (4). Mechanistically, RBM24 binds to AAU/U-rich elements in target mRNAs and regulates oncogene TP63 gene expression via regulating mRNA stability (11,12,24). In the present study, we first validated that RBM24 exhibited strong tumor-suppressive potential in liver cancer. These results consistent with the tumor-suppressive role of RBM24 in other cancer types, including lung, prostate, and nasopharyngeal carcinomas (4,5,10). In fact, we observed that HepG2 cells did not show the suppression of sphere formation by RBM24 expression, which may indicate the cell type-specific regulation of RBM24.

TP63 expression has been shown to be regulated by TP53 and CTNNB1 (13). In particular, TP63 expression may be

Figure 2. RBM24-overexpression decreases tumor progression in three liver cancer MCTS, and increases sensitivity to sorafenib. All values were calculated based on cell viability analyses and are depicted in the chart. (A) Using ultra-low attachment plate analysis, three liver cancer cells and RBM24oe liver cancer cells were analyzed for tumor suppression in liver cancer-MCTS co-cultured with LX-2. (B) Sorafenib sensitivity was assessed using RBM24-overexpression in HepG2-MCTS at 0, 0.1, 0.5, 1, 5 and 10 µM sorafenib. The values indicate the mean and standard deviation of three independent experiments. *P<0.01, **P<0.001 vs. pcDNA. MCTS, multicellular tumor spheroids; RBM24, RNA-binding protein 24; RBM24oe, RBM24-overexpressing; pcDNA, control plasmid; LX-2, stellate cells.
upregulated in the tumor cells containing a non-functional TP53 and an activated β-catenin pathway, thereby favoring tumor progression (25). Moreover, p53 regulates RBM24, facilitating cell cycle arrest, and CTNNB1 and TP63 have been implicated in the maintenance of stemness of cancer stem cells in tumor cells (11,26-28). We observed that RBM24 decreased TP63 expression but increased caspase3 expression in tumor cells, as described previously (12,29); however, we failed to detect any significant change in CTNNB1 expression related to that of TP63. This suggests a novel mechanism that, in addition to controlling CTNNB1 expression, RBM24 interacts with CTNNB1 affecting its binding to TP63 promoter (13). Accordingly, in our experiments, we detected a decrease in CTNNB1 nuclear

Figure 3. RBM24 reduces TP63 expression by downregulating CTNNB1 expression. (A) Immunoblot analysis of RBM24, CTNNB1, TP63, c-Casp3 and Casp-3 expression in HepG2, Hep3B and Huh7 cells transfected with the RBM24oe or pcDNA. (B) Quantified immunoblotting results indicate the densitometry value, normalized to β-actin value. (C) Reverse transcription-quantitative PCR analysis of TP63 and CTNNB1 expression in three liver cancer cell lines transfected with RBM24oe, siCTNNB1, pcDNA or scrambled siRNAs. (D) Immunoblotting assay of TP63 and CTNNB1 expression in three liver cancer cell lines transfected with siCTNNB1 or scrambled siRNAs. The values indicate the mean and standard deviation of three independent experiments. *P<0.05, **P<0.01 vs. pcDNA or Scramble. RBM24, RNA-binding protein 24; RBM24oe, RBM24-overexpressing; pcDNA, control plasmid; TP63, tumor protein 63; CTNNB1, β-catenin; c-Casp3, cleaved-caspase 3; Casp-3, pro-caspase-3; si-, small interfering.
translocation after RBM24 overexpression; this could affect the interaction between CTNNB1 and the TP63 promoter, leading to a change in TP63 expression through interaction with RBM24.
Collectively, we suggest that RBM24 functions as a tumor suppressor in liver cancer cells, which is related to the interaction between TP63 and CTNNB1. RBM24 could be a potential therapeutic target for treating the patients with liver cancer.

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Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Authors' contributions

SUM and HGW conceived, designed and performed all experiments and wrote the manuscript. SUM and JHK analyzed the data. All authors have read and approved the manuscript. SUM and HGW confirm the authenticity of all the raw data.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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