European Review for Medical and Pharmacological Sciences 2019; 23: 5682-5690

MiR-155 affects proliferation and apoptosis of bladder cancer cells by regulating GSK-3β/β-catenin pathway

Z.-C. DONG, D. ZHANG, X.-X. ZHANG, Z.-Q. YAO, H. WU, C.-H. CHEN, Q. TIAN

Department of Urology, Key Laboratory of Gansu Province for Urological Disea, Depar of Urology of Lanzhou University Second Hospital, Urology institute of Lanzhou iversity Sec Hospital, Lanzhou, Gansu, P.R. China

RETRACTED

Abstract. – OBJECTIVE: GSK-3β negatively regulates Wnt/β-catenin signaling pathway. The abnormal miR-155 expression is associated with bladder cancer. Bioinformatics analysis revealed a complementary binding site between miR-155 and GSK-3β mRNA. This study investigated the role of miR-155 in the proliferation and apoptosis of bladder cancer cells.

PATIENTS AND METHODS: The dual luciferase reporter gene assay validated the t ed regulation between miR-155 and GSK- mor tissues and adjacent tissues were coll d from bladder cancer patients and the expres of miR-155 and GSK-3β mRNA was detected RT-PCR. Bladder cancer cell li U-87 ce were cultured in vitro and di miR-N group and miR-155 inhibito oup. expressions of miR-155, GSK- nd β-c in were compared, cell apopto is det cytometry, and cell p erat detecte by EdU staining.

RESULTS: Co d with ad t tissues, miR-155 expr on significant creased in bladder ca cer ti , and GSK-3β mRNA exp on was s cantly decreased. There a targeted reg ory relationship betw miR-15 and GSK- . Compared with SV -1 ce iR-155 expression in bladder canc and 56 cells was significantly increas d GSK expression was significa y de ed nsfection of miR-155 inhibitor gnific creased GSK-3β expression in -87 and 37 cells, decreased β-catenin e increased cell apoptosis, and de- ase proliferation.

CONCLUSIONS: The increased expression miR-155 plays a role in reducing the expres- of GSK-3β and in promoting the pathogenes of bladder cancer. Inhibition of miR-155 can up-regulate the expression of GSK-3β, inhibit the activity of Wnt/β-catenin pathway, attenuate proliferation and promote apoptosis of bladder cancer cells.

Key Words:
MiR-155, GSK-3β, W atenin, Bladder cancer.

roduction

er can BC) is one of the common malignan in the genitourinary system. It is one of the top ten malignant tumors in the world, incidence rate ranks 9th in systemic ma- umors[1].

Glycogen synthase kinase-3β (GSK-3β) is an important negative regulator in Wnt/β-catenin signaling pathway. GSK-3β can phosphorylate β-catenin protein and degrade it, leading to its decreased expression in the cytoplasm, thereby blocking the activation of the Wnt/β-catenin pathway and playing an important role in tumor suppression in the development and progression of various tumors[2-4]. Studies have shown that the decrease in GSK-3β expression is associated with the occurrence and progression of various tumors such as colorectal cancer[5] and breast cancer[6], but there are few studies on its role in bladder cancer.

MicroRNAs are a class of endogenous non-coding single-stranded small RNAs with a length of approximately 22-25 nucleotides. They are important epigenetic regulatory molecules that can bind to the 3'-untranslated region (3'-UTR) region of target gene mRNA, leading to degradation of mRNA or inhibition of its translation, and is involved in the regulation of various biological effects such as cell proliferation, differentiation, cycle, and apoptosis[7]. The abnormal expression of miR-155 plays an important role in the occurrence, progression, drug resistance and drug resistance of various tumors such as gastric cancer, breast cancer,

Corresponding Author: Junqiang Tian, MD; email: tianjunqiang1@163.com

colon cancer and cervical cancer[8-11]. Multiple studies have shown that abnormal changes in miR-155 expression are associated with the development, progression, and metastasis of bladder cancer[8,12,13]. Bioinformatics analysis revealed a complementary binding site between miR-155 and the 3'-UTR of GSK-3β mRNA. This study compared the expression of miR-155 and GSK-3β in tumor tissues and adjacent tissues of bladder cancer patients, and intervened miR-155 expression in bladder cancer cells cultured *in vitro* to explore whether miR-155 regulates GSK-3β expression, Wnt/β-catenin pathway activity, affects proliferation and apoptosis of bladder cancer cells.

Patients and Methods

Patients

Forty patients with bladder cancer who were treated in our hospital from April 2018 to November 2018 were enrolled. The specimens of the tumor tissue removed during the operation were collected, and the adjacent tissues at least 2 cm away from the bladder cancer tissue were collected as controls. The collection of clinical specimens was reviewed and approved by the Hospital Ethics Committee and informed consent was obtained from the patients.

Main Reagents and Materials

Normal human bladder epithelial cell line SV-HUC-1 was purchased from Shanghai Sixth People's Hospital; bladder cancer cell lines BIU-87 and 5637 were purchased from Shanghai Fuheng Biological; DMEM, Opti-MEM, FBS, and streptomycin culture medium were purchased from Gibco (Rockville, MD, USA); Fluorescence Quantitative PCR Kit TransScript Green One-Step qRT-PCR SuperMix was purchased from Beijing Quanshijin gold bio; TR[illegible] transfection reagent Lip 2000 purchased from Invitrogen (Carlsbad, CA, USA); miR-NC, miR-155 mimic, miR-155 inhibitor purchase In[illegible]gzhou Ribobio; EdU cell proliferation assay kit agent was purchased from Sigma-Aldrich (St. Louis, MO, USA); rabbit anti-human GSK-3β, β-catenin, β-actin antibody was purchased from Abcam (Cambridge, MA, USA); HRP-conjugated secondary antibody was purchased from Wuhan Boster Bio; pMIR plasmid Purchased in Changsha Youbao Bio; Dual-Luciferase Reporter Assay System purchased from Promega (Madison, WI, USA); BCA protein quantification kit was purchased from Jiangsu Biyuntian; FITC Annexin V/PI apoptosis detection reagent was purchased from Beijing Suo Labao Bio.

Cell Culture

SV-HUC-1, BIU-87, and 5637 cells were cultured in Dulbecco's Modified Eagle's Medium (DMEM) medium containing 10% fetal bovine serum (FBS) and 1% streptomycin in a cell culture incubator containing 5% CO_2 at 37°C until cells reached a confluence of 80%. After 24 h, cells were collected using 0.25% trypsin digestion and sub-cultured at a ratio of 1:3. The experiment was performed when the cells were in the logarithmic growth phase.

Dual Luciferase Reporter Gene Assay

HEK293 cells were inoculated with 24-well plates, and after 24 h of adherence, pMIR-GSK-3β-WT (or pMIR-GSK-3β-MUT) and miR-155 mimic (or miR-NC) were co-transfected with Lipofectamine 2000. In HEK293 cells, after 6 h, DMEM was replaced with DMEM medium containing 10% fetal bovine serum (FBS), and culture was continued for 48 h. The activity of double luciferase was detected according to the kit instructions.

Cell Transfection and Grouping

BIU-87 cells were cultured *in vitro* and divided into two transfection groups: miR-NC transfection group and miR-155 inhibitor transfection group. The transfection step was as follows: 100 μL of Opti-MEM, 10 μL of Lip 2000 and 10 μL of the plasmid were gently mixed, and then incubated at room temperature for 20 min. When the density of the cells was close to 60%, the original culture solution was discarded, and the PBS was washed twice and added. The mixture was transfected. After 6 hours, the original medium was discarded and replaced with DMEM medium containing 10% FBS and 1% streptomycin. After 72 hours, the cells were collected for various tests.

qRT-PCR Detection of Gene Expression

Total RNA was extracted using TRIzol reagent, and the relative expression of the gene was detected by one-step qRT-PCR using TransScript Green One-Step qRT-PCR SuperMix in the 20 μL reaction system including: 1 μg of template RNA, 0.2 μM of pre-primer, 0.2 μM of post-primer, 10 μL of 2×TransStart Tip Green qPCR SuperMix, 0.4 μL of One-Step RT Enzyme Mix, 0.4 μL of Passive Reference Dye II, RNase-free water. The qRT-PCR reaction conditions were: 45°C, 5 min; 94°C, 30 s; (94°C,

RETRACTED

5 s; 60°C, 30 s) × 40 cycles, and gene expression was detected on an ABI 7500 Real-time PCR instrument. Primer information was GSK-3β-F: 5'-GGCAGCATGAAAGTTAGCAGA-3', GSK-3β-R: 5'-GGCGACCAGTTCTCCTGAATC-3'; β-actin-F: 5'-CATGTACGTTGCTATCCAGGC-3', β-actin-R: 5'-CTCCTTAATGTCACGCACGAT-3'.

Western Blot

The cells of each transfection group were collected by trypsinization, centrifuged at 300 g for 5 min, the supernatant was collect followed by addition of 100 μL RIPA lysate, and the protein supernatant was transferred to a new pre-cooled Eppendorf (EP) tube after 15 min lysis on ice. After quantification of the concentration by BCA method, 40 μg was separated by electrophoresis on 10% sodium dodecyl sulphate-polyacrylamide gel electrophoresis (SDS-PAGE), transferred to a polyvinylidene difluoride (PVDF) membrane, blocked with 5% skim milk powder in PBST for 60 min at room temperature, and incubated with the primary antibodies (GSK-3β, β-catenin and β-actin with a dilution of 1:2000, 1:1000, 1:8000, respectively) overnight at 4°C. After washing the membr[illegible] times with PBST, the membrane was inc[illegible] with HRP-conjugated secondary antibody (1:[illegible], 60 min) at room temperature followed by w[illegible]ing with PBST 3 times and subsequent addition[illegible] ECL chemiluminescence soluti[illegible] min i[illegible] cubation at room temperature[illegible]er th[illegible]e mem[illegible] brane was exposed and de[illegible]ed.

Flow Cytometry D[illegible]ctio[illegible] of Cell Apopto[illegible]

Follow the in[illegible]s, cells we[illegible]uspended in 100 μL An[illegible]n V [illegible]ng Buffer, [illegible]llowed by addition o[illegible]μL FITC A[illegible]xin V and 10 μL PI for 15 m[illegible]ncubation at ro[illegible]mperature. After that, [illegible] μL of [illegible]nnexin V [illegible]nding Buffer was ad[illegible]d cel[illegible]optosis was measured by EPICS XL-M[illegible] cytom[illegible]

[illegible] Cyt[illegible]etection of Cell Pr[illegible]eratio[illegible]

[illegible]ove, miR-NC and miR-155 inhibitor [illegible]sfec[illegible]cells were collected by trypsinization [illegible]d incubated in medium containing 10 μM EdU [illegible]2 h at 37°C, re-inoculated into 60 mm culture d[illegible]s, and returned to the incubator for 72 h. After collecting cells by trypsin digestion, the cells were fixed at room temperature by paraformaldehyde, and saponin was permeabilized. 500 μL of the test solution was added, incubated at room temperature for 30 min in the dark, centrifuged once at 300 g, and resuspended in 500 μL of wash reagent followed by analysis of cell proliferation by FC500 MCL flow cytometry.

Statistical Analysis

Statistical analysis was performed[illegible]g SPSS 18.0 software (SPSS Inc., Chicago[illegible]USA). The measurement data were expressed as[illegible]± standard deviation (SD). The com[illegible]ison b[illegible]n the measurement data of the [illegible]ps was pe[illegible] by Student *t*-test or Man[illegible]nitney [illegible]test. p was considered statist[illegible] sign[illegible]nt.

Results

Abnormal Expre[illegible]n of MiR-155 and GSK-[illegible] Bladder [illegible]er

[illegible]esults of qRT-PC[illegible]howed that the expr[illegible]ion of miR-155 was significantly increased i[illegible]mor tissues [illegible] bladder cancer patients compa[illegible] with adjac[illegible] tissues (Figure 1A). The expre[illegible] of GSK[illegible] mRNA in bladder cancer tissues w[illegible]antly lower than that in adjacent tissues (Figure 1B).

[illegible]ed Regulatory Relationship Between MiR-155 and GSK-3β mRNA

Bioinformatics analysis revealed a complementary binding site between miR-155 and the 3'-UTR of GSK-3β mRNA (Figure 2A). Dual luciferase gene reporter assays showed that transfection of miR-155 mimic significantly reduced the relative luciferase activity in pMIR-GSK-3β-WT transfected HEK293T cells, but miR-NC or miR-155 mimic did not affect the relative luciferase activity in the HEK293T cells transfected with pMIR-GSK-3β-MUT (Figure 2B), indicating that miR-155 has a targeted regulatory relationship with the 3'-UTR region of GSK-3β mRNA.

Increased MiR-155 and Decreased GSK-3β Expression in Bladder Cancer Cells

The results of qRT-PCR showed that the expression of miR-155 was significantly increased in bladder cancer BIU-87 and 5637 cells compared with that in normal bladder epithelial SV-HUC-1 cells (Figure 3A), while GSK-3β mRNA expression was significantly reduced (Figure 3B). Western blot analysis showed that the expression of GSK-3β protein in bladder cancer BIU-87 and 5637 cells was significantly lower than that in SV-

RETRACTED

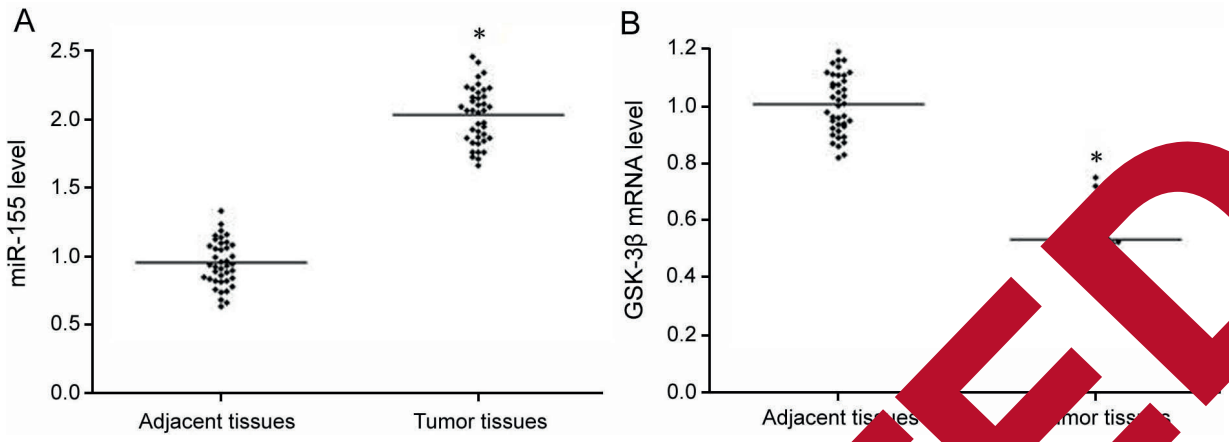


Figure 1. Abnormal expression of miR-155 and GSK-3β in bladder cancer. ***(A)*** qRT- detection R-155 ession in bladder cancer tissues; ***(B)*** qRT-PCR detection of GSK-3β mRNA expression in l cancer tissu nts $p<0.05$ compared with adjacent tissues.

RETRACTED

HUC-1 cells (Figure 3C).

Inhibition of MiR-155 Expression Inhibits Bladder Cancer Cell Proliferation and Promotes Apoptosis

The results of qRT-PCR showed that the expression of miR-155 in BIU-87 cells was signific decreased in miR-155 inhibitor transfected compared with miR-NC transfected group ure 4A), while the expression of GSK-3β m was increased (Figure 4B). Western blot analy showed that compared with mi nsfecti group, the expression of GS pro in BIU-87 cells was significantly reased miR-155 inhibitor transfection g ile of β-catenin protein sig y decreased (Figure 4C). Flow metry ana showed that transfection of inhibitor s antly increased apopt (Fig D) and inh ted proliferation (Fi 4E) of in 87 cells.

Discussion

Bladd ncer i aracterized by easy inva- easy and high recurrence rate. It is cult to and its prognosis is very poor[14]. T to study the pathogenesis of bladder ca xplore the abnormal changes in the athogenesis of bladder cancer signal molecules f great significance to improve the diagnosis, t ent effect, as well as prognosis.

Wnt/β-catenin is a widely existing signaling pathway in mammals involved in the regulation of embryonic development[15,16], tissue and organogenesis[17,18], cell proliferation, apoptosis, migration and invasion[19,20]. Ele d level of β-catenin p in and accumulation in the cytoplasm of the n us can lea abnormal activation of the W -catenin si ling pathway, which is closely l to th currence, progression and me-

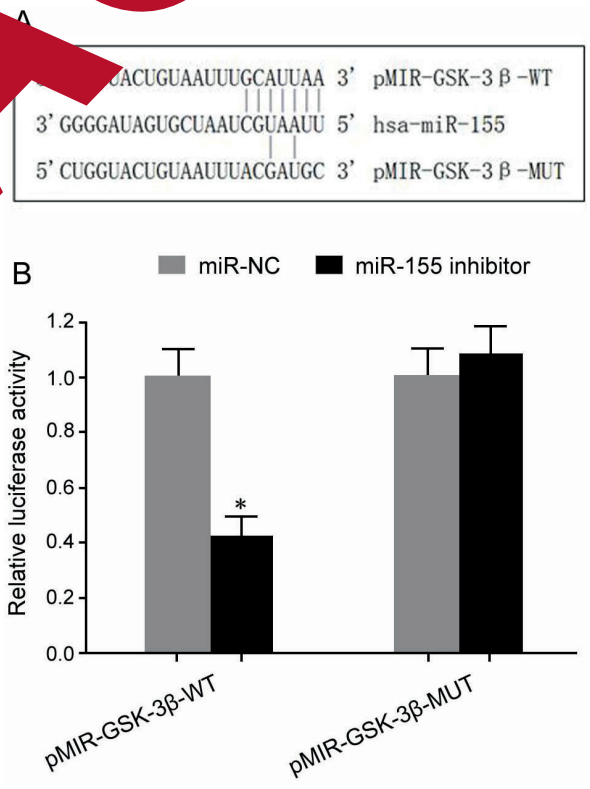
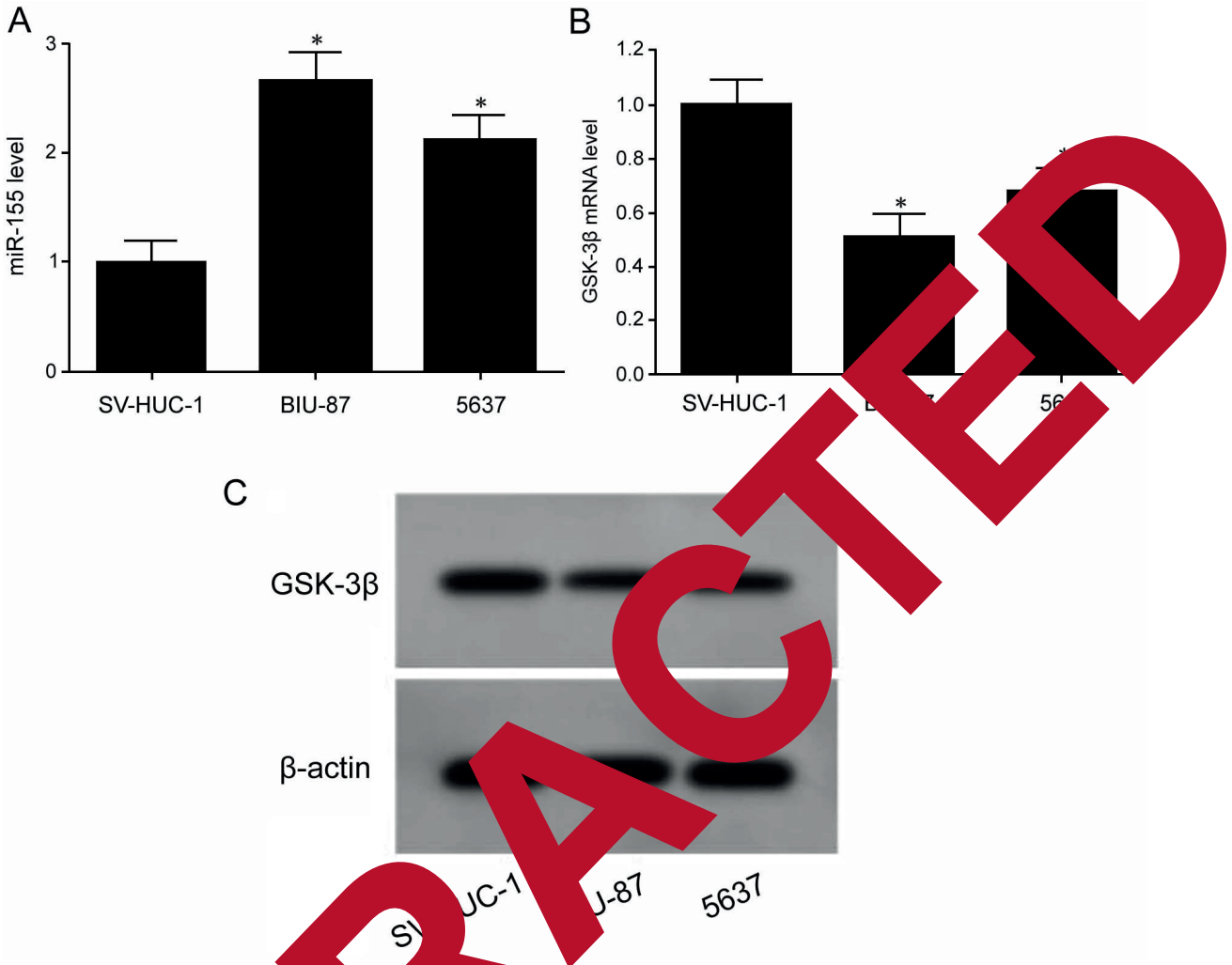


Figure 2. Targeted regulatory relationship between miR-155 and GSK-3β mRNA. ***(A)*** Schematic diagram of the interaction site between miR-155 and the 3'-UTR of GSK-3β mRNA; ***(B)*** Dual luciferase gene reporter assay. *Represents $p<0.05$ compared to miR-NC.



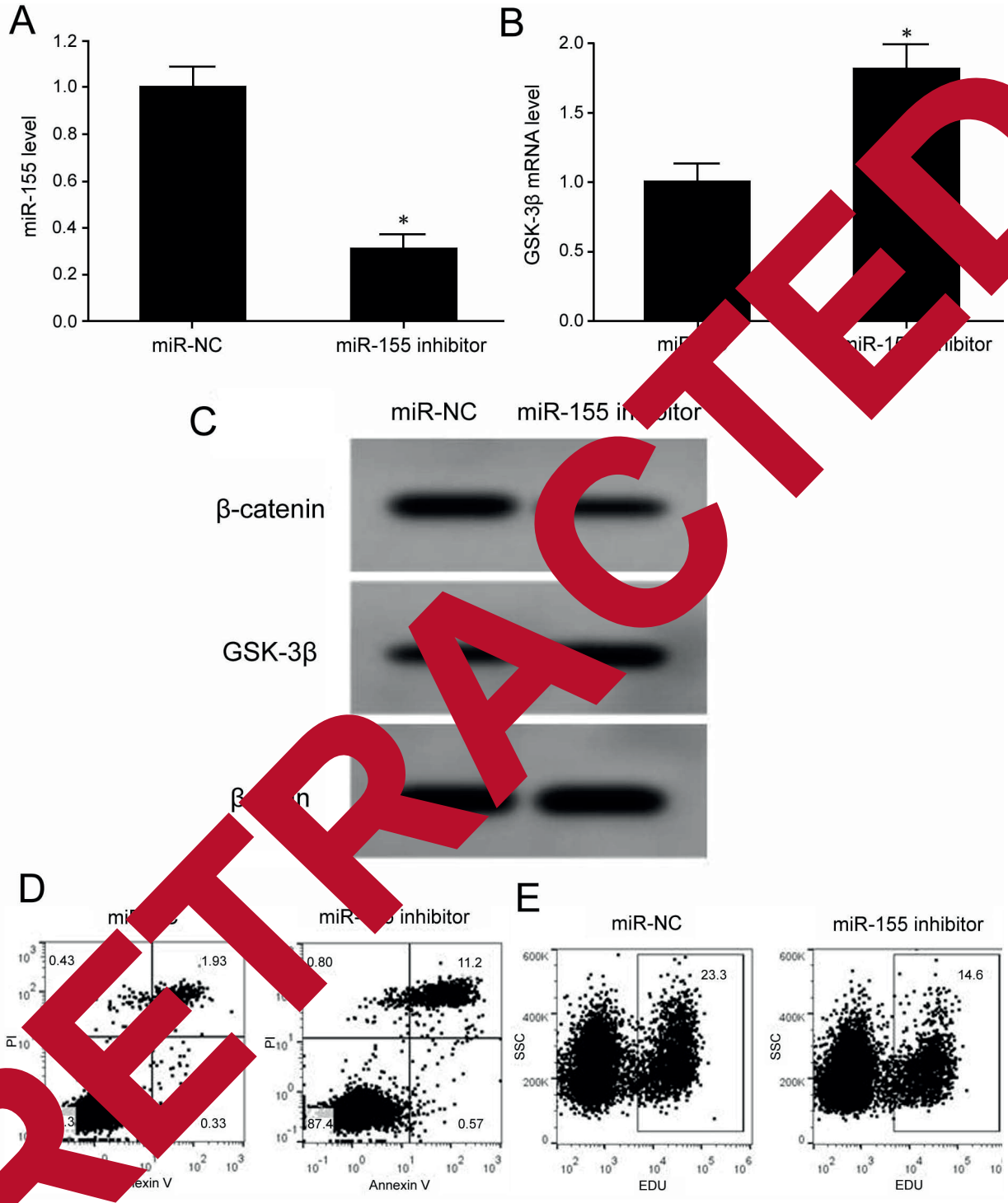
RETRACTED

Figure 3. Increased expr[illegible]on [illegible]ncer cells and decreased expression of GSK-3β. (A) qRT-PCR was used to detect the expre[illegible] of mi[illegible] bladder cancer cells; (B) qRT-PCR was used to detect the expression of GSK-3β mRNA in bladder ca[illegible]ells; (C) We[illegible]lot was used to detect the expression of GSK-3β protein in bladder cancer cells. * Represents p <0.[illegible]ed to SV-HU[illegible]lls.

tasta[illegible] vari[illegible] tumors[21,22]. Unlike β-catenin, a p[illegible]e re[illegible]or in the Wnt/β-catenin signaling p[illegible]SK-3β [illegible]negative regulator, and [illegible]K-3β p[illegible]horyl[illegible] the serine/threonine at the a[illegible] term[illegible]-catenin. The residue forms a c[illegible]plex wi[illegible]in and adenomatous polyposis c[illegible]), which degrade the β-catenin protein, [illegible]reby[illegible]cing the expression of β-catenin in [illegible]e cytoplasm, thereby blocking the activation of [illegible] Wnt/β-catenin pathway and attenuating the i[illegible]ition of apoptosis by the Wnt/β-catenin pathway and promoting cell proliferation[2-4].

Multiple studies[8,12,13] have shown that abnormal changes in miR-155 expression are associated with the development, progression, and metastasis of bladder cancer. Bioinformatics analysis revealed a complementary binding site between miR-155 and the 3'-UTR of GSK-3β mRNA. This study compared the expression of miR-155 and GSK-3β in tumor tissues and adjacent tissues of bladder cancer patients, and intervened miR-155 expression in bladder cancer cells cultured *in vitro* to explore whether miR-155 regulates GSK-3β expression, Wnt/β-catenin pathway activity, play a role in the proliferation and apoptosis of bladder cancer cells.

The results of clinical samples showed that the expression of miR-155 was abnormally increased in tumor tissues of patients with bladder cancer compared with adjacent tissues, and the expres-



RETRACTED

Figure 4. Inhibition of miR-155 expression can significantly inhibit bladder cancer cell proliferation and promote apoptosis. ***(A)*** qRT-PCR detection of intracellular miR-155 expression; ***(B)*** qRT-PCR detection of intracellular GSK-3β mRNA expression; ***(C)*** Western blot detection of intracellular protein expression; ***(D)*** Flow detection of apoptosis; ***(E)*** EdU staining for cell proliferation. * Represents $p < 0.05$ compared to miR-NC.

sion of GSK-3β was significantly decreased, suggesting that the increased expression of miR-155 may play a role in reducing the expression of GSK-3β and promoting the pathogenesis of bladder cancer. Dual luciferase activity assay showed that transfection of miR-155 mimic significantly reduced relative luciferase activity in pMIR-GSK-3β-WT transfected HEK293T cells, but miR-NC or miR-155 mimic did not affect the relative luciferase activity of HEK293T cells transfected with pMIR-GSK-3β-MUT, confirming the targeted regulation relationship between miR-155 and GSK-3β mRNA. The results of cell culture *in vitro* showed that compared with normal bladder epithelial SV-HUC-1 cells, the expression of miR-155 in bladder cancer BIU-87 and 5637 cells was significantly increased, while the expression of GSK-3β was significantly increased, further suggesting that miR-155 and GSK-3β abnormalities are associated with bladder cancer. In the study of the relationship between miR-155 and bladder cancer, Peng et al[12] showed that the expression of miR-155 was significantly increased in tumor tissues of bladder cancer patients compared with adjacent tissues. The expression level of its targeted tumor suppressor gene DMTF1 was significantly reduced. Wang et al[23] indicated that the expression of miR-155 in urine of patients with bladder cancer was abnormally higher than that of the control group, suggesting that miR-155 may play a role in promoting cancer. Wang et al[13] detected that the expression of miR-155 was significantly increased in tissues of bladder cancer patients compared with adjacent tissues. Compared with patients with lower miR-155 expression, survival and prognosis of patients with higher expression of miR-155 were significantly worse. Xie et al[24] observed that the expression of miR-155 was abnormally elevated in tumor tissues of bladder cancer patients, and the increased expression of miR-155 was an indicator of poor prognosis. Zhang et al[25] and others showed that compared with healthy controls and cystitis, the expression of miR-155 in urine of patients with bladder cancer was significantly increased, and the expression of miR-155 was related to the bladder cancer stage, indicating that detection of miR-155 expression can be used as a predictor of prognosis in patients with bladder cancer. In this study, the expression of miR-155 in bladder cancer tumor tissues and bladder cancer cell lines was abnormally elevated, and miR-155 may be a cancer-promoting factor in the pathogenesis of bladder cancer, which was consistent with Peng et al[12] and Wang et al[23]. The further results of this study showed that transfection of miR-155 inhibitor significantly increased the expression of GSK-3β in BIU-87 cells, decreased the expression of β-catenin, increased apoptosis and decreased cell proliferation. The results that miR-155 can promote the cancer-promoting effect of bladder cancer by inhibiting GSK-3β, while down-regulating the expression of miR-155 can increase the expression of tumor suppressor GSK-3β and inhibit Wnt/β-catenin. The activity of the pathway plays a role in weakening the proliferation ability of bladder cancer cells and inducing cell apoptosis. In the study of the relationship between miR-155 and the biological effects of bladder cancer, Xie et al[26] found that the bladder cancer cell line expression of miR-155 was increased, which can promote cancer, and administration of several active drugs. The active components of *Hedyotis diffusa* and *Scutellaria barbata L.* can significantly down-regulate the expression of miR-155 and promote the apoptosis of bladder cancer cells. Overexpression of miR-155 can significantly activate the activity of Akt pathway and regulate the expression of anti-apoptotic factor Bcl-2 and Mcl-1, which antagonizes the apoptosis-inducing effect of *Hedyotis diffusa* and *Scutellaria barbata L.* on bladder cancer cells and plays a role as a cancer-promoting gene. Peng et al[12] showed that overexpression of miR-155 in bladder cancer um-uc-3 and T24 cells down-regulated the expression of DMTF1, promoted cell proliferation, and enhanced cell growth and tumor formation in nude mice. Similar to overexpression of miR-155, siRNA interferes with the expression of DMTF1 can promote the cancer-promoting effect, promote the proliferation and cycle progression of bladder cancer cells, and enhance the ability of cell cloning. This study links miR-155 and GSK-3β and reveals that elevated expression of miR-155 plays a role in down-regulating GSK-3β expression and promoting bladder cancer, while inhibition of miR-155 expression increases GSK -3β expression, attenuating the malignant characteristics of bladder cancer cells. However, whether miR-155 regulates GSK-3β affects the biological effects of bladder cancer cells *in vivo* is unclear, and requires further research in animal studies.

Conclusions

The increased expression of miR-155 plays a role in reducing the expression of GSK-3β and

RETRACTED

promoting the pathogenesis of bladder cancer. Inhibition of miR-155 can up-regulate the expression of GSK-3β, inhibit the activity of Wnt/β-catenin pathway, attenuate proliferation and promote apoptosis of bladder cancer cells.

Conflict of interest

The authors declare no conflicts of interest.

Acknowledgments

This work was supported by the Fundamental Research Funds for the Central Universities (No. 561219007); Supported by Doctoral Research Foundation of Lanzhou University Second Hospital (No. Ynbskyjj2015-2-7); Supported by Cuiying Scientific and Technological Innovation Program of Lanzhou University Second Hospital (No. CY2017-BJ16, Doctoral Supervisor Training Program); Supported by Industry Planning Project of Health Department of Gansu Province (No. GWGL2013-30). Science and Technology Project of Chengguan District, Lanzhou City, Gansu Province Science and Technology Bureau (No. 2017KJGG0052).

References

1) Latini DM, Lerner SP, Wade SW, Lee DW, Quale... Bladder cancer detection, treatment and ... comes: opportunities and ch... Urolog... 2010; 75: 334-339.

2) Martelli AM, Buontempo ... Angelisti ... GSK-3beta: a key regulator of ... t canc... sistance. Cell Cycle 20... 1... 6...

3) Hsieh CH, Hsu ... Shibu M... CH, Bau DT, Ho CC, Lin Y... en MC, Wa... Huang CY. Down-regul... ta-catenin a... associated migrati... bility ... iwanin C in a ecoline and 4-NQO ... duced oral ... r cells via GSK-3beta acti... . Mol Carcinog ... 56: 1055-1067.

4) C... enuto M, De Antonelli..., Liguori L, Benvenu... G, Magg... D, Alonzi A, Turino C, Attanasio C, ... ni ... llo AM, Vitiello F, Pasquinelli R, Terra... Federic... usco A, Freeman J, Dale TC, Decr... Chi... A G, Piantedosi F, Calabrese C, ... llo M... through GSK-3beta interaction ... stains ... ical WNT/beta-catenin signaling ... hancing c...ncer progression in NSCLC. Onco... , 5: 5736-5749.

5) Jain S, Ghanghas P, Rana C, Sanyal SN. Role of GSK-3beta in regulation of canonical Wnt/beta-catenin signaling and PI3-K/Akt oncogenic pathway in colon cancer. Cancer Invest 2017; 35: 473-483.

6) Sokolosky M, Chappell WH, Stadelman K, Abrams SL, Davis NM, Steelman LS, McCubrey JA. Inhibition of GSK-3beta activity can result in drug and hormonal resistance and alter sensitivity to targeted therapy in MCF-7 breast cancer cells. Cell Cycle 2014; 13: 820-833.

7) Gomase VS, Parundekar AN. microRNA: human disease and development. Int J Bioinform Res Appl 2009; 5: 479-500.

8) Zhang W, Chen CJ, Guo GL. MiR-155 pro... proliferation and migration of breast ... via targeting SOCS1 and MMP16 ... Rev Med Pharmacol Sci 2018; 22: 7323-73...

9) Li S, Zhang T, Zhou X, Du Z, Chen F, ... Liu Q. The tumor suppressor role ... iR-155 ... gastric cancer. Oncol Lett 20... 6: 2709-27...

10) Cao H, Huang S, Liu ... hen Z. U... egulate... pression of miR-15... human ... nic cancer. J Cancer Res The... 201... 6... 07.

11) Wang F, Shan... o Y, Xie... g Y, O... hen F, Li Y, Sun B. M... 5-5p inhibi... 1... promotes autopha... mTOR path... ervical cancer. In... och... ell Biol 2018; ...: 91-99.

12) Peng Y, Dong W, Li... Zhong GZ, Liao B, Wang B, ... ang L, Xie Y, ... Chen X, Xie WB, He W, ... SX, Huang J. Micror... 155 promotes bladder cancer growth by repressing the tumor suppressor DMTF1. ... otarget 2015; 6: 16043-16058.

13) ... Yang H, Me... P. Correlation of increased expression of ... oRNA-155 in bladder cancer and ... Med 2015; 46: 118-122.

14) Izumi K, ... aguri M, Miyamoto H, Hara Y, Kishida T, Chiba K, Murai T, Hirai K, Suzuki K, Fujinami K, Ueki T, ... gawa K, Kitami K, Moriyama M, Miyoshi Y, Tsuchiya ... eda I, Kobayashi K, Sato M, Morita S, Noguchi K, Uemura H. Androgen deprivation therapy prevents bladder cancer recurrence. Oncotarget 2014; 5: 12665-12674.

15) Caronia-Brown G, Anderegg A, Awatramani R. Expression and functional analysis of the Wnt/beta-catenin induced mir-135a-2 locus in embryonic forebrain development. Neural Dev 2016; 11: 9.

16) Hussain M, Xu C, Lu M, Wu X, Tang L. Wnt/beta-catenin signaling links embryonic lung development and asthmatic airway remodeling. Biochim Biophys Acta Mol Basis Dis 2017; 1863: 3226-3242.

17) Brafman D, Willert K. Wnt/beta-catenin signaling during early vertebrate neural development. Dev Neurobiol 2017; 77: 1239-1259.

18) Fujimura N. WNT/beta-catenin signaling in vertebrate eye development. Front Cell Dev Biol 2016; 4: 138.

19) Ishiguro H, Okubo T, Kuwabara Y, Kimura M, Mitsui A, Sugito N, Ogawa R, Katada T, Tanaka T, Shiozaki M, Mizoguchi K, Samoto Y, Matsuo Y, Takahashi H, Takiguchi S. NOTCH1 activates the Wnt/beta-catenin signaling pathway in colon cancer. Oncotarget 2017; 8: 60378-60389.

20) Song Y, Li ZX, Liu X, Wang R, Li LW, Zhang Q. The Wnt/beta-catenin and PI3K/Akt signaling pathways promote EMT in gastric cancer by epigenetic regulation via H3 lysine 27 acetylation. Tumour Biol 2017; 39: 1010428317712617.

RETRACTED

21) Deitrick J, Pruitt WM. Wnt/beta catenin-mediated signaling commonly altered in colorectal cancer. Prog Mol Biol Transl Sci 2016; 144: 49-68.

22) Li B, Cai S, Zhao Y, He Q, Yu X, Cheng L, Zhang Y, Hu X, Ke M, Chen S, Zou M. Nerve growth factor modulates the tumor cells migration in ovarian cancer through the WNT/beta-catenin pathway. Oncotarget 2016; 7: 81026-81048.

23) Wang G, Chan ES, Kwan BC, Li PK, Yip SK, Szeto CC, Ng CF. Expression of microRNAs in the urine of patients with bladder cancer. Clin Genitourin Cancer 2012; 10: 106-113.

24) Xie Y, Ma X, Chen L, Li H, Gu L, Gao Y, Zhang Y, Li X, Fan Y, Chen J, Zhang X. MicroRNAs with prognostic significance in bladder cancer: a systematic review and meta-analysis. Sci Rep 2017; 7: 5619.

25) Zhang X, Zhang Y, Liu X, Fang A, Wang J, Yang Y, Wang L, Du L, Wang C. Direct quantitative detection for cell-free miR-155 in urine: a potential role in diagnosis and prognosis for non-muscle invasive bladder cancer. Oncotarget 2016 3266.

26) Pan LT, Sheung Y, Guo WP, Rong ZP M. Hedyotis diffusa plus Scutellaria barbata bladder cancer cell apoptosis by inhiting A maling pathway through downreg ng miR-15 es-sion. Evid Based Comp nt Alternat Me 2016: 9174903.

RETRACTED