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Inhibition of miR-221 influences bladder cancer cell proliferation and apoptosis

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Abstract. – OBJECTIVE: Janus kinase (JAK) - signal transducer and activator of transcription (STAT) signaling pathway participate in cell proliferation and apoptosis. Suppressors of cytokine signaling 3 (SOCS3) are negative regulators of JAK-STAT3. SOCS3 was found significantly declined, while microRNA-221 (miR-221) obviously up-regulated in bladder cancer tissue. Bioinformatics analysis revealed the complementary binding site between miR-221 and 3'-UTR of SOCS3. This study investigated the [illegible]ole of miR-221 in regulating SOCS3/JAK-STA[illegible]naling pathway and bladder cancer cell [illegible]ation and apoptosis.

PATIENTS AND METHODS: Bladder canc[illegible]mor tissue and para-carcinoma tissue were [illegible]lected from patients to test miR-2[illegible] and SOC[illegible] expressions. Dual luciferase [illegible] used [illegible] test the targeting regulatory [illegible]ect o[illegible]-221 on SOCS3. MiR-221, SOCS3, [illegible]JAK1, p[illegible]K2, and survivin expressions we[illegible]pare[illegible] and HBEC cells. T24 cells were [illegible], miR-221 inhibitor, p[illegible]oR-blan[illegible]coR-SOCS3, and miR-221 inhi[illegible] + pSicoR-[illegible]3 groups. Flow cytometry [illegible]plied to dete[illegible]l apoptosis. EdU sta[illegible]ing [illegible]dopted to ev[illegible]uate cell proliferation.

RESULT[illegible]: MiR-221 si[illegible]antly increased, while S[illegible]3 obviously red[illegible] in bladder cancer ti[illegible]e compared with pa[illegible]a-carcinoma tissue[illegible]R-221 t[illegible]eted inhibited SOCS3 expressio[illegible]22[illegible] phosphorylated JAK1 (p-JAK1), phosp[illegible]ed JAK2 [illegible]-JAK2), phosphorylated STAT3 [illegible]TAT3) [illegible]nd survivin levels mark[illegible]up-reg[illegible]hereas SOCS3 expression ap[illegible]ntly de[illegible] in T24 cells compared with tha[illegible] HBEC cells. MiR-221 inhibitor and/or pSico[illegible] elevated SOCS3 expression, de[illegible]K1, p-JAK2, p-STAT3, and survivin [illegible]els, enhanced cell apoptosis, and attenuated [illegible]roliferation.

[illegible]CLUSIONS: MiR-221 elevated, while SO[illegible]3 reduced in bladder cancer tissue. Inhibition of miR-221 suppressed T24 cell proliferation and induced apoptosis by up-regulating SOCS3 ex[illegible] lowering JA[illegible]AT3 signaling path[illegible] act[illegible] and attenuating survivin expression.

Key[illegible]
[illegible]R-221, SOCS3, JAK-STAT[illegible], Bladder cancer, Prolif[illegible]ion, Apoptosis.

[illegible]ntroduction

Bladder cancer (BC) is a common malignancy [illegible] with the 9th morbidity among all types [illegible][1]. It accounts for the leading morbidity and mortality in urinary system malignancy in our country[2]. BC, especially muscle-invasive BC, is easy to occur pelvic lymph node metastasis or distant metastasis. Its 5-year survival may decrease lower than 30% once metastasis[3]. Following the development of detection and diagnostic technique, most BC patients were found in early stage. However, there are still about 30% patients appeared tissue infiltration and metastasis when diagnosed, leading to poor therapeutic effect and prognosis[4]. Janus kinase (JAK) - signal transducer and activator of transcription (STAT) signaling pathway widely exists in various tissues and cells. It participates in the regulation of cell proliferation[5], apoptosis[6], migration, and invasion[7]. Suppressors of cytokine signaling 3 (SOCS3) are members of SOCS family with the strongest activity. It suppresses JAK-STAT signaling pathway activation through direct inhibiting JAK[8]. SOCS3 was found down-regulated in breast cancer[9] and prostate cancer[10], and was closely associated with tumor progress and pathological classification. MicroRNA (miRNA) is a type of endogenous single stranded non-coding RNA at the length of 22-25 nt. It plays a degrading or inhibiting role on mRNA by binding with the 3'-UTR.

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miRNA expression and function in tumorigenesis receive more and more attention[11]. MiR-221 was showed significantly up-regulated in BC tissue, suggesting its potential oncogene role in BC occurrence[12]. Bioinformatics analysis revealed the complementary binding site between miR-221 and 3'-UTR of SOCS3. This study investigated the role of miR-221 in regulating SOCS3/JAK-STAT3 signaling pathway and bladder cancer cell proliferation and apoptosis.

Patients and Methods

Patients

A total of 42 BC patients were enrolled, including 32 males and 10 females with mean age at 62.9 (51-78) years old. Patients received treatment in Huaihe Hospital, Henan University between Apr and Nov 2016. Tumor tissue and para-carcinoma tissue were collected and stored at -80°C for RNA, protein, and immunofluorescence detection.

This study was approved by Ethics Committee in Huaihe Hospital, Henan University and [illegible] enrolled objects had signed informed con[illegible].

Main Reagents and Materials

Human BC cell T24 was purchased from [illegible] (Shanghai, China). Human norm[illegible]ladder e[illegible]thelial cell HBEC was boug[illegible]bo Bio[illegible]logical Technology Co., L[illegible] (Shang[illegible] China). Dulbecco's Modified Ea[illegible] Mediu[illegible]DMEM), fetal bovine serum (F[illegible]BS), [illegible]ill[illegible] tomycin were purch[illegible]d from [illegible]o BRL. Co. Ltd. (Grand Islan[illegible] NY, USA). [illegible]ure RNA Kit was obtain[illegible] TransGen [illegible]h (Beijing, China). [illegible]nsfe[illegible]eagent Lipofectamine 2000 was [illegible]urchased fro[illegible]vitrogen Life Technologies [illegible]arlsbad, CA, US[illegible]rimeScript™ RT reagen[illegible]it and SYBR Green were purchased fro[illegible]KaRa ([illegible]lian, China). miR-NC, miR-221 mim[illegible] inhibit[illegible] and EdU cell proliferation d[illegible]n kit w[illegible] purchased from Ribobio [illegible]ngzho[illegible]ina). [illegible]ouse anti-human p-JAK1, p-[illegible]2, and [illegible]3 primary antibodies were pur[illegible]sed from [illegible]bcam Biotechnology (Cambridg[illegible] USA). Rabbit anti-human p-STAT3 and [illegible]ary antibodies were obtained from [illegible]neTex Inc. (Irvine, CA, USA). Horseradish Pe[illegible]se (HRP) conjugated secondary antibody was [illegible]rived from Bio-Rad Laboratories (Hercules, CA, USA). Fluorescence secondary antibody was purchased from Molecular Probes (Eugene, OR, USA). pGRE-luc reporter gene plasmid, dual luciferase detection kit, apoptosis detection kit, and radio-immunoprecipitation assay (RIPA) were bought from Beyotime (Shangh[illegible] pSicoR-GFP was obtained from Ad[illegible]ne (London, UK).

Cell Culture

T24 and HBEC cells we[illegible]ultured [illegible]lbecco's Modified Eagle M[illegible]um (DMEM) [illegible]ning 10% FBS and 1[illegible] penicilli[illegible]-streptom[illegible]. Cells were passaged [illegible]

Dual-Lucifer[illegible] Report[illegible]ne [illegible]ay

The polym[illegible]e chain react[illegible]) products containing [illegible]ngth of SOC[illegible] gene 3'-UTR or mutan[illegible] segme[illegible]re cloned to pGRE-luc. Next, it was transform[illegible] DH5α competent cells and [illegible]iced to select [illegible]lasmid with correct s[illegible]uence, namely pGRE-SOCS3-wt and pGRE-[illegible]CS3-mut, res[illegible]ctively. Then, pGRE-SOCS3-[illegible] (or pGRE-SO[illegible]3-mut) was co-transfected to H[illegible]93T cells [illegible]using Lipofectamine 2000, toget[illegible]th mi[illegible]1 mimic (or miR-221 inhibitor, or miR-[illegible]he luciferase activity was detected [illegible]fter cultured for 48 h.

[illegible] Over-Expression Plasmid Construction

CDS segment of SOCS3 gene was amplified and connected to pSicoR-GFP plasmid after double digestion. After transformation, the positive bacterial strain was selected and amplified to extract the recombinant plasmid. The plasmid with correct sequence was named pSicoR-GFP-SOCS3. pSicoR-GFP-blank was treated as control.

Cell Transfection and Grouping

T24 cells were divided into miR-NC, miR-221 inhibitor, pSicoR-blank, pSicoR-SOCS3, and miR-221 inhibitor + pSicoR-SOCS3 groups. Cells were detected on 72 h after transfection.

qRT-PCR

Total RNA was extracted by using EasyPure RNA Kit and reverse transcribed to cDNA by using PrimeScript™ RT reagent Kit. The reverse transcription condition was 37°C for 15 min and 98°C for 5 min. The PCR reaction was composed of 95°C pre-denaturation for 5 min, followed by 40 cycles of 95°C denaturation for 15 s, 60°C annealing for 30 s, and 74°C elongation for 30 s. Real-time PCR was performed on CFX96 Touch™ to test the relative expression. The primers used were as follows. miR-221P_F:

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5′-GTTGGTGGGAGCTACATTGTCTGC-3′, miR-221P_R: 5′-GTGTCGTGGACTCGGCAATTC-3′; U6P_F: 5′-ATTGGAACGATACAGAGAAGATT-3′, U6P_R: 5′-GGAACGCTTCACGAATTTG-3′; SOCS3P_F: 5′-CCTGCGCCTCAAGACCTTC-3′, SOCS3P_R: 5′-GTCACTGCGCTCCAGTAGAA-3′; SurvivinP_F: 5′-AGGACCACCGCATCTCTACAT-3′, SurvivinP_R: 5′-AAGTCTGGCTCGTTCTCAGTG-3′; β-actinP_F: 5′-GAACCCTAAGGCCAAC-3′, β-actinP_R: 5′-TGTCACGCACGATTTCC-3′.

Western Blot

Total protein was extracted by RIPA from tissue and cells. A total of 50 µg protein was separated by 10% sodium-lauryl sulfate-polyacrylamide gel electrophoresis (SDS-PAGE) and transferred to membrane. Next, the membrane was blocked and incubated with primary antibody at 4°C overnight (SOCS3, p-JAK1, p-JAK2, p-STAT3, survivin, and β-actin at 1:300, 1:200, 1:200, 1:200, 1:200, and 1:800, respectively). Then the membrane was incubated with secondary antibody (1:10000) for 60 min after washed by phosphate buffer saline-tween 20 (PBST) for three times. At last, the protein expression was detect[illegible] enhanced chemiluminiscence (ECL).

Flow Cytometry

The cells were re-suspended in 500 µl bin[illegible] buffer and incubated with 5 µl A[illegible]in V-FI[illegible] avoid of light for 15 min. Ne[illegible] re adde[illegible] to 5 µl PI and tested on [illegible]CS XL[illegible]CL flow cytometry to evaluate ce[illegible]ptosis.

EdU Staining

Cells were add[illegible] to EdU so[illegible]in logarithmic phase an[illegible]ncubated fo[illegible]. Then, cells were di[illegible]ted b[illegible]25% trypsin and were collected; [illegible]fter, they we[illegible]ed in paraformaldehyde [illegible] neutralized in[illegible]ine. Next, cells were i[illegible]bated with 0.1% Trito[illegible]X-100 and re-suspe[illegible] in PBS[illegible]At last, the cells were stained by 500 [illegible]ll[illegible] room te[illegible]perature for 10 min and tested o[illegible]CS XL[illegible]CL flow cytometry (BD [illegible]ience[illegible]Jo[illegible]CA, USA).

Im[illegible]nofluore[illegible]cence Detection

[illegible] section was fixed in precooled ace[illegible] temperature for 10 min. After the [illegible]tion was washed by phosphate buffer sali[illegible]S) for three times, it was blocked in PBS co[illegible]ning 2% bovine serum albumin (BSA) and 0.1% Triton X-100 at room temperature for 60 min. Next, the section was incubated with mouse anti-human SOCS3 primary antibody at 4°C overnight. Then, the section was incubated with Alexa Fluor 594 labeled secondary antib[illegible] at room temperature for 60 min. At last, t[illegible] was stained by 0.1% 4′,6-diamidin[illegible]phenyli[illegible]dole (DAPI) for 1 min and obse[illegible] under the microscope.

Statistical Analysis

All data analyses were [illegible]formed by S[illegible] software (SPSS Inc., C[illegible]ago, IL, USA). The [illegible]asurement data were [illegible]ed a[illegible]ean ± standard deviation and co[illegible]pared [illegible]st or Ma[illegible]Whitney U test. p<[illegible] was co[illegible]ed a[illegible]atistical significance.

[illegible]lts

[illegible]-221 upregulated, while SOCS3 [illegible]duced in BC tissue

[illegible]RT-PCR de[illegible]ion revealed that miR-221 e[illegible]sion was s[illegible]ificantly higher in cancer tissue [illegible]in pa[illegible]carcinoma tissue (Mann-Whitney U [illegible].000, $p<0.001$) (Figure 1A). Immunofluorescence detection showed that SOCS3 [illegible]iously reduced in tumor tissue compared [illegible]cent normal control (Figure 1B).

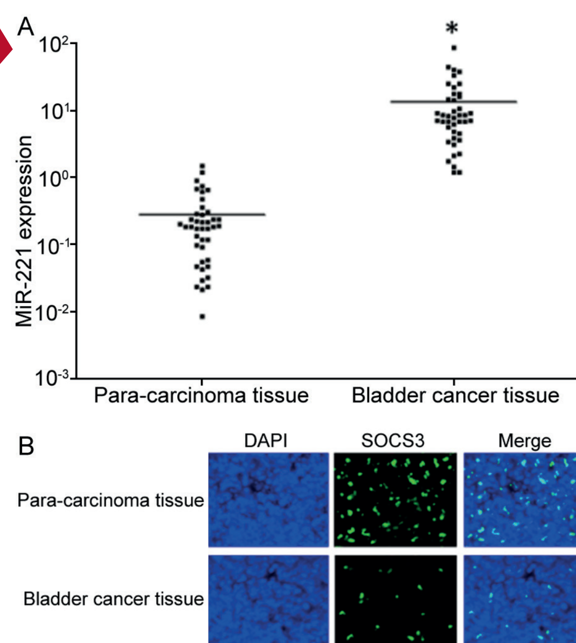

Figure 1. MiR-221 upregulated, while SOCS3 reduced in BC tissue. ***(A)*** qRT-PCR detection of miR-221 expression; ***(B)*** immunofluorescence detection of SOCS3 expression. *$p<0.05$, compared with para-carcinoma tissue.

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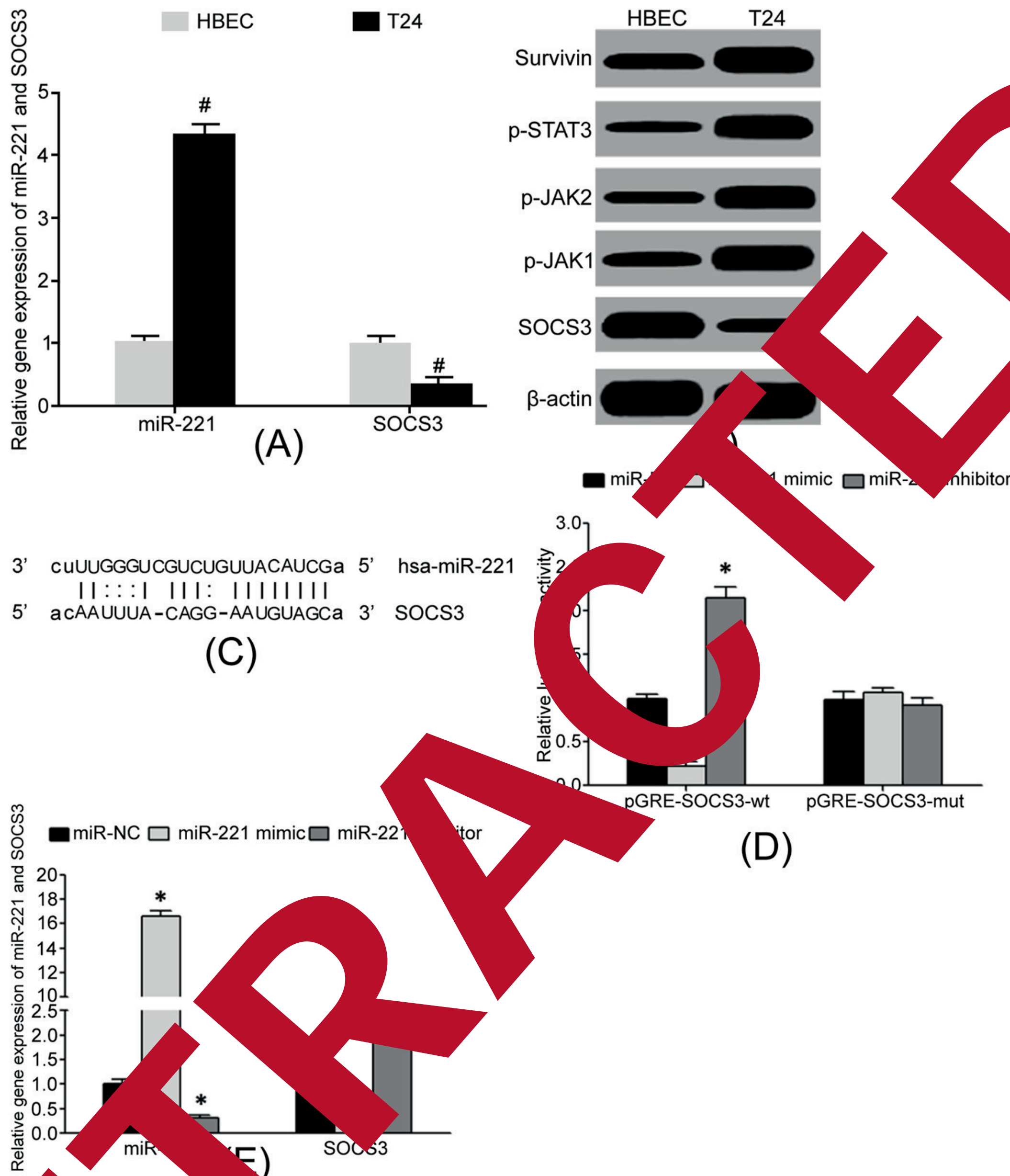

Figure 2. [illegible]R-221 targeted regu[illegible]OCS3 expression in T24 cells. ***(A)*** qRT-PCR detection of miR-221 and SOCS3 expressions; ***(*** [illegible] estern blot detection of p[illegible]ein expressions; ***(C)*** the binding site between miR-221 the 3'-UTR of SOCS3 mRNA; ***(D)*** d[illegible]uciferase [illegible]say; ***(E)*** qRT-PCR detection of miR-221 and SOCS3 expressions. $^{\#}p<0.05$, compared with HBEC; $^{*}p<0.05$, com[illegible]ith [illegible]NC.

M[illegible]21 Ta[illegible]d regulated SOCS3 Ex[illegible]ssion in [illegible]24 Cells

[illegible]221 expression was obviously higher, [illegible] level was markedly lower in T24 [illegible]ls compared with HBEC cells, suggesting the p[illegible]ial regulatory relationship between miR-221 [illegible]d SOCS3 (Figure 2A and B). Western blot demonstrated that p-JAK1, p-JAK2, p-STAT3, and survivin levels markedly up-regulated in T24 cells compared with that in HBEC cells (Figure 2B). microRNA.org online prediction showed the complementary binding site between miR-221 and the 3'-UTR of SOCS3 mRNA (Figure 2C). Dual luciferase assay revealed that miR-221 mimic and miR-221 inhibitor significantly declined and enhanced relative luciferase activity in HEK293 cells (Figure 2D), indicating the regulatory relationship between miR-221 and SOCS3

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mRNA. MiR-221 mimic or inhibitor transfection apparently reduced or elevated SOCS3 mRNA expression in T24 cells, confirming that miR-221 targeted regulated SOCS3 expression (Figure 2E).

Inhibition of miR-221 Upregulated SOCS3 expression, Suppressed T24 cell Proliferation, and Promoted Apoptosis

MiR-221 inhibitor and/or pSicoR-SOCS3 elevated SOCS3 expression, decreased p-JAK1, p-JAK2, p-STAT3, and survivin levels (Figure 3A and B), enhanced cell apoptosis (Figure 3C), and attenuated cell proliferation (Figure 3D).

Discussion

JAK-STAT signaling pathway could be activated by various extra-cellular cytokin[illegible] factors, and mitogen, leading to recep[illegible] dimerization, which phosphorylated JAK ki[illegible]e. Activated JAK phosphorylates membrane [illegible]or, leading to conformation, changes to promot[illegible]T, covering the tyrosine phosphory[illegible]on loci o[illegible]brane receptor complex. At t[illegible]ime, JAK kin[illegible]sphorylates STAT to le[illegible]orm di[illegible]er with an[illegible]r STAT, thus entering [illegible]cleu[illegible] regulate gene transcription and [illegible]press[illegible]AT tran[illegible]ption

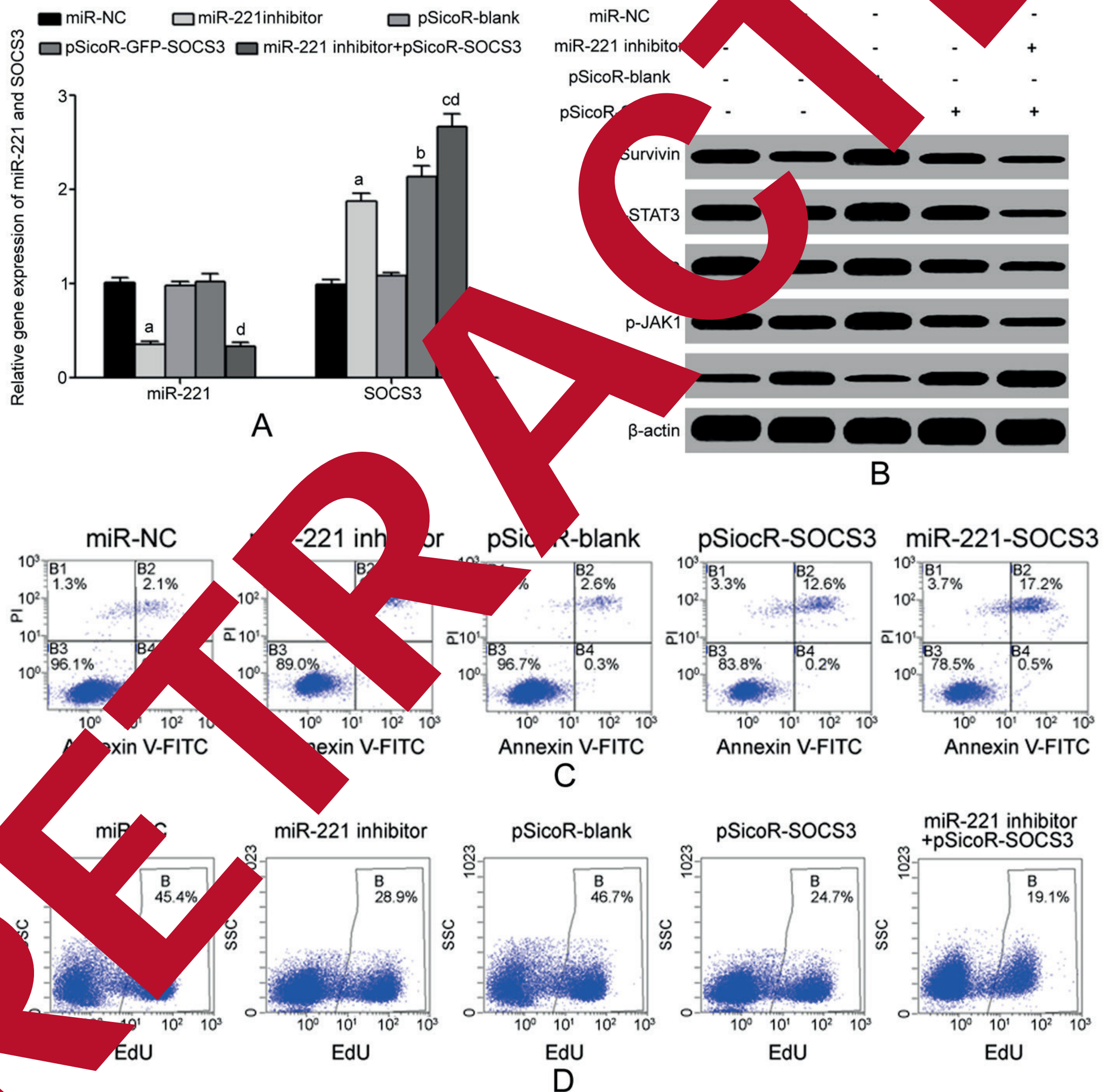

Figure 3. Inhibition of miR-221 up-regulated SOCS3 expression, suppressed T24 cell proliferation, and promoted apoptosis. ***(A)*** q[illegible]-PCR detection of miR-221 and SOCS3 expressions; ***(B)*** Western blot detection of protein expressions; ***(C)*** flow cytometry detection of cell apoptosis; ***(D)*** EdU staining detection of cell proliferation. [a]$p<0.05$, compared with miR-NC; [b]$p<0.05$, compared with pSicoR-blank; [c]$p<0.05$, compared with miR-221 inhibitor; [d]$p<0.05$, compared with pSicoR-SOCS3.

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factor family contains seven members, including STAT1, STAT2, STAT3, STAT4, STAT5a, STAT5b, and STAT6. STAT3 is most widely investigated and exhibits the closest relationship with tumor occurrence and development. Inhibitor of apoptosis protein (IAPs) is a protein family with homological structure and anti-apoptosis function[14]. Survivin is the most important member of IAPs family with the strongest function in apoptosis inhibition. Survivin blocks cell apoptosis by inhibiting caspase-3 and caspase-7[15]. Moreover, survivin also plays a crucial role in regulating cell cycle and facilitating cell proliferation[16]. It was showed that JAK-STAT3 signaling pathway activation mediated survivin enhancement plays an important role in promoting malignancy[17,18]. SOCS3 is the strongest member to SOCS family[8]. It restrains JAK1 and JAK2 phosphorylation and kinase activity by binding to receptor, thus blocking STAT3 phosphorylation and playing a negative regulatory role in JAK-STAT3 signaling pathway[19]. SOCS3 down-regulation is closely associated with multiple tumor occurrence and development, including colorectal cancer[20], lung cancer[21], and breast cancer[22]. Recently it was found that SOCS3 expression reduced in bladder cancer tissue, suggesting its potential anti-tumor effect[23]. MiR-221 level was reported to be elevated in bladder cancer tissue, indicating its promoting effect on bladder cancer[12]. Bioinformatics analysis revealed the complementary binding site between miR-221 and 3'-UTR of SOCS3. This study investigated the role of miR-221 in regulating SOCS3/JAK-STAT3 signaling pathway and bladder cancer cell proliferation and apoptosis. qRT-PCR revealed that miR-221 expression was significantly higher in cancer tissue than in para-carcinoma tissue. Immunofluorescence detection showed that SOCS3 level obviously reduced in tumor tissue compared with adjacent normal control. It suggested that miR-221 up-regulation may play a role in decreasing SOCS3 expression and promoting bladder cancer tumorigenesis. Gottardo et al[12] demonstrated that miR-221 level significantly increased in bladder cancer tissue compared with normal bladder mucosa tissue[12]. In this study, miR-221 expression was obviously higher in tumor tissue compared with para-carcinoma tissue, which was similar with Gottardo et al[12] findings. Gaballah et al [illegible] showed that SOCS3 expression markedly declined in bladder cancer tissue compared with normal control. Its expression was related to pathological grading, as it declined in patients with higher pathological grade. This study observed that SOCS3 expression abnormally reduced in tumor tissue, which was in accordance with Gaballah et al[23]. MiR-221 expression was obviously higher, while SOCS3 level was markedly lower in T24 cells compared with HBEC cells. Furthermore, p-JAK1, p-JAK2, p-STAT3, and survivin levels were markedly up-regulated in T24 cells compared with that in HBEC cells. It indicated that miR-221 elevation, SOCS3 down-regulation, and JAK-STAT3 signaling pathway enhancement may be related to the malignancy of bladder cancer. Liu et al[13] showed that miR-221 up-regulation plays a key role in T24 cell epithelial-mesenchymal transition (EMT) induced by TGF-β and cell invasion and migration enhancement, revealing that miR-221 abnormal elevation was a regulator in malignancy enhancement in bladder cancer. Dual luciferase assay revealed that miR-221 mimic and miR-221 inhibitor significantly declined and enhanced relative luciferase activity in HEK293 cells, and apparently reduced or elevated SOCS3 mRNA expression in T24 cells, confirming that miR-221 targeted regulated SOCS3 expression. Moreover, miR-221 inhibitor and/or [illegible]coR-SOCS3 elevated SOCS3 expression, decreased p-JAK1, p-JAK2, p-STAT3, and survivin levels, enhanced cell apoptosis, and attenuated cell proliferation. Liu et al[24] reported [illegible]pression of miR-221 markedly declined [illegible] expression, enhanced E-cadherin level, and attenuated EMT, migration, and invasion in T24 cells induced by TGF-β. Fu et al[25] revealed that miR-221 inhibitor transfection obviously increased Bax expression, declined Bcl-2 level, and accelerated cell apoptosis in bladder cancer cell 5637, J82, and T24. Fu et al[25] also reported that inhibition of miR-221 apparently decreased MMP-2, MMP-9, and VEGF-C expression, and weakened cell migration and invasion in bladder cancer cells[25]. In this study, down-regulation of miR-221 weakened bladder cancer malignancy, which was in accordance with Liu et al[24] and Fu et al[25]. This study demonstrated that miR-221 elevation plays a role in reducing SOCS3 expression, enhancing JAK-STAT3 signaling pathway activity, and promoting bladder cancer tumorigenesis.

Conclusions

MiR-221 elevated, while SOCS3 reduced in bladder cancer tissue. Inhibition of miR-221 suppressed T24 cell proliferation and induced apoptosis by up-regulating SOCS3 expression, lowering JAK-STAT3 signaling pathway activity, and attenuating survivin expression.

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Conflict of Interest

The Authors declare that they have no conflict of interests.

References

1) Meng FM, Meng FM, Song XL. MiR-576-3p is a novel marker correlated with poor clinical outcome in bladder cancer. Eur Rev Med Pharmacol Sci 2017; 21: 973-977.
2) Chen W, Zheng R, Baade PD, Zhang S, Zeng H, Bray F, Jemal A, Yu XQ, He J. Cancer statistics in China, 2015. CA Cancer J Clin 2016; 66: 115-132.
3) Rose TL, Deal AM, Nielsen ME, Smith AB, Milowsky MI. Sex disparities in use of chemotherapy and survival in patients with advanced bladder cancer. Cancer 2016; 122: 2012-2020.
4) Masson-Lecomte A, Rava M, Real FX, Hartmann A, Allory Y, Malats N. Inflammatory biomarkers and bladder cancer prognosis: a systematic review. Eur Urol 2014; 66: 1078-1091.
5) Yu RX, Hu XM, Xu SQ, Jiang ZJ, Yang W. Effects of fucoxanthin on proliferation and apoptosis in human gastric adenocarcinoma MGC-803 cells via JAK/STAT signal pathway. Eur J Pharmacol 2011; 657: 10-19.
6) Li HX, Zhao W, Shi Y, Li YN, Zhang LS, Zha[...] Wang D. Retinoic acid amide inhibits J[...] pathway in lung cancer which leads to ap[...]sis. Tumour Biol 2015; 36: 8671-8678.
7) Kowshik J, Baba AB, Giri H, Deepak Reddy G, [...] M, Nagini S. Astaxanthin inhibits JAK/STAT-3 [...]gnaling to abrogate cell prolife[...]vasion a[...] angiogenesis in a hamster [...]l cance[...] PLoS One 2014; 9: e1091[...]
8) Tamiya T, Kashiwagi I, Ta[...]R, Yasu[...]H, Yoshimura A. Suppressors of c[...]si[...] proteins and JAK[...]AT pa[...] regulation of T-cell inflamma[...] by SOCS1[...]OCS3. Arterioscler Thro[...]c Biol 2011; [...]985.
9) Muhammad [...]ya S, Steele R, [...]y RB. Anti-miR-203 suppress[...]-positive breast cancer growth[...]d stemness b[...]eting SOCS3. Oncotarg[...]16; 7: 58595-586[...]
10) P[...]nti F, Martini M, Pinto F, Cenci T, Capodimon-[...] Calarc[...], Bassi PF, Larocca LM. Epigenetic [...]ing [...]OCS3 identifies a subset of prostate[...] with an a[...]essive behavior. Prostate 2011[...]8-325.
11) [...]e C, W[...]W, Liu Z, Zhang J, Wang Z, Li R, [...]ang Z, Li[...]ng S, Wang Y, Xue Y, Yang J, Tan [...] Song X. m[...]R-942 promotes cancer stem cell-[...]its in esophageal squamous cell carcinoma [...]tivation of Wnt/beta-catenin signalling pathway. Oncotarget 2015; 6: 10964-10977.
12) [...]ottardo F, Liu CG, Ferracin M, Calin GA, Fassan [...] Bassi P, Sevignani C, Byrne D, Negrini M, Pagano [...], Gomella LG, Croce CM, Baffa R. Micro-RNA profiling in kidney and bladder cancers. Urol Oncol 2007; 25: 387-392.
13) Chen W, Hong YQ, Meng ZL. Bioinformatics analysis of molecular mechanisms of chronic obstructive pulmonary disease. Eur Rev Med Pharmacol Sci 2014; 18: 3557-3563.
14) Rodriguez-Berriguete G, Torrealba N, [...]tega [...], Martinez-Onsurbe P, Olmedilla G, P[...]agua R, Guil-Cid M, Fraile B, Royuela M. Pr[...]stic value of inhibitors of apoptosis protei[...]s) and caspases in prostate cancer: caspa[...]rms and XIAP predict biochemica[...]ogressio[...] radical prostatectomy. BMC [...]ncer 2015; [...]
15) Wang C, Zheng X, S[...] C, Shi Y. MicroRN[...] suppresses cell pr[...]tion a[...]igration by targeting BIRC5 and [...] in [...]man triple-negative breast ca[...]r ce[...] Clin C[...]r Res 2012; 31: 58[...]
16) Zhao X, Y[...], Zhang Z, Fen[...]g J, Yuan X, Li J. Ef[...]s [...]RNA-silenced [...] and survivin on lu[...] cance[...] proliferation and apoptosis. J BUON 2014; 19: [...]2.
17) [...] Qiu W, Zhan[...] S, Gao Q, Yang Z. Micro[...]A-204 targets JAK2 [...] breast cancer and induces cell apoptosis through the STAT3/BCl-2/survivin pathway. Int J [...] Exp Pathol 2015; 8: 5017-5025.
18) Glienke W, Ma[...]L, Wicht J, Bergmann L. Curcumin [...]ibits const[...]ve STAT3 phosphorylation in hu[...]ancre[...] cancer cell lines and downregula[...]tio[...]in/BIRC5 gene expression. Cancer Invest 2010; 28: 166-171.
19) [...]ins AS, McCoy CE, Lloyd AT, O'Farrelly C, [...]son NJ. miR-19a: an effective regulator of SOCS3 and enhancer of JAK-STAT signalling. PLoS One 2013; 8: e69090.
20) Igci M, Cakmak EA, Oztuzcu S, Bayram A, Arslan A, Gogebakan B, Igci YZ, Cengiz B, Ozkara E, Camci C, Demiryurek AT. Mutational screening of the SOCS3 gene promoter in metastatic colorectal cancer patients. Genet Test Mol Biomarkers 2012; 16: 1395-1400.
21) Zhang S, Wang W, Wang E, Qiu X. SOCS3 expression is inversely correlated with Pyk2 in non-small cell lung cancer and exogenous SOCS3 inhibits proliferation and invasion of A549 cells. Pathology 2012; 44: 434-440.
22) Barclay JL, Anderson ST, Waters MJ, Curlewis JD. SOCS3 as a tumor suppressor in breast cancer cells, and its regulation by PRL. Int J Cancer 2009; 124: 1756-1766.
23) Gaballah HH, Shafik NM, Wasfy RE, Abou Farha MO. Significance of suppressor of cytokine signaling-3 expression in bladder urothelial carcinoma in relation to proinflammatory cytokines and tumor histopathological grading. Asian Pac J Cancer Prev 2015; 16: 307-314.
24) Liu J, Cao J, Zhao X. miR-221 facilitates the TGF-beta1-induced epithelial-mesenchymal transition in human bladder cancer cells by targeting STMN1. BMC Urol 2015; 15: 36.
25) Fu B, Wang Y, Zhang X, Lang B, Zhou X, Xu X, Zeng T, Liu W, Guo J, Wang G. MiR-221-induced PUMA silencing mediates immune evasion of bladder cancer cells. Int J Oncol 2015; 46: 1169-1180.