Clinical value and potential pathways of miR-183-5p in bladder cancer: A study based on miRNA-seq data and bioinformatics analysis

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Abstract. The clinicopathological value and exploration of the potential molecular mechanism of microRNA-183-5p (miR-183-5p) have been investigated in various cancers; however, to the best of the author's knowledge, no similar research has been reported for bladder cancer. In the present study, it was revealed that the expression level of miR-183-5p was notably increased in bladder cancer tissues compared with adjacent non-cancerous tissues (P=0.001) and was markedly increased in the tissue samples of papillary, pathological T stage (T0-T2) and pathological stage (I-II) compared with tissue samples of their counterparts (P=0.05), according to data from The Cancer Genome Atlas. Receiver operating characteristic analysis revealed the robust diagnostic value of miR-183-5p for distinguishing bladder cancer from non-cancerous bladder tissues (area under curve=0.948; 95% confidence interval: 0.919-0.977). Amplification and deep deletion of miR-183-5p were indicated by cBioPortal, accounting for 1% (4/412) of bladder cancer cases. Data from YM500v3 demonstrated that compared with other cancers, bladder cancer exhibited high expression levels of miR-183-5p, and miR-183-5p expression in primary solid tumors was much higher compared with solid normal tissues. A meta-analysis indicated that miR-183-5p was more highly expressed in bladder cancer samples compared with normal counterparts. A total of 88 potential target genes of miR-183-5p were identified, 13 of which were discerned as hub genes by protein-protein interaction. The epithelial-to-mesenchymal transition pathway was the most significantly enriched pathway by FunRich (P=0.0001). In summary, miR-183-5p may participate in the tumorigenesis and development of bladder cancer via certain signaling pathways, particularly the epithelial-to-mesenchymal transition pathway. However, the exact molecular mechanism of miR-183-5p in bladder cancer must be validated by *in vitro* and *in vivo* experiments.

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Introduction

Due to the high mortality and recurrence, bladder cancer (BC) remains one of the most frequently appearing cancer of the urinary system (1). In America, ~79,030 new patients with BC will be diagnosed in 2017, including 60,490 males and 18,540 females (2). Although there has been huge progress in therapeutic methods, such as cystectomy and adjuvant treatments, BC occupies one of the most common cancers with a high mortality and recurrence rate worldwide (1). Among the patients with recurrent BC, more than one-tenth continue to develop into higher phases, such as muscle invasion and metastasis (3-5). The discovery of cancer at an advanced stage could lead to a poor prognosis. It is a prioritized event to explore the exact mechanism of BC to improve the sensitivity and specificity of early diagnosis. In recent years, evidence accumulation in the knowledge of molecular biology and application of bioinformatics has provided good opportunities to understand BC comprehensively via bioinformatic analysis, such as the application of microRNAs (miRNAs) (6-8).

miRNAs, a type of short non-coding RNA ~22 nucleotides in length, facilitate mRNA degradation by sequence-specific combination with mRNA, providing new strategies on diagnosis and treatment of cancers (9-12). miRNAs have been found to participate in the expression regulation of hub genes related to the development and progression of tumors, including BC (13-16). The abnormally expressed and genetically altered miRNAs have been reported to be involved in the

biological process of BC, including miR-199a-5p, miR-1-3p, miR-9, miR-182 and miR-200b (17-19).

miR-183-5p, located on chromosome 7q32.2, has been studied in various types of cancers, such as human breast cancer (20), esophageal squamous cell carcinoma (21), esophageal squamous cell carcinoma (22), gastric cancer (23), human pancreatic adenocarcinoma (24) and melanoma (25). The expression of miR-183 in BC patients was higher in tissues (26-28) and serum (29) and showed a moderate value of the BC diagnosis (27). However, no functional study of miR-183-5p in BC has been reported previously. Most of the published studies on miR-183-5p tended to focus on the higher expression of miR-183-5p in samples from patients with BC, including tissues, urine and serum, than in samples from normal individuals, or the diagnostic efficiency of miR-183-5p. However, the clinical significance, as well as the promising target genes of miR-183-5p in BC, needs to be explored (26-29). In addition, the studies mentioned above were based on a small scale of BC patient cohorts, and big data analysis was needed to uncover the real role of miR-183-5p in BC.

Therefore, in the present study, we first attempted to investigate the clinical significance of the expression level and genetic alteration of miR-183-5p in BC based on the data from The Cancer Genome Atlas (TCGA; https://cancergenome.nih.gov/), cBioPortal for Cancer Genomics (http://www.cbioportal.org/), Gene Expression Omnibus (GEO, https://www.ncbi.nlm.nih.gov/geo/), and YM500v3 (http://driverdb.tms.cmu.edu.tw/ym500v3/). In addition, we identified potential target genes of miR-183-5p via differential expressed genes calculated by RNA-seq data from TCGA, predicting platforms and gene profiling post miR-183-5p overexpression *in vitro*. Further bioinformatic analyses, including the enrichment of functional annotation and biological pathway analyses, were performed to explore the possible roles of miR-183-5p in the tumorigenesis and progression of BC.

Materials and methods

The work flow of the present study is shown in Fig. 1. Firstly, we evaluated the clinical significance of miR-183-5p in BC based on data from TCGA, cBioPortal, YM500v3 and PubMed. Secondly, the potential molecular mechanism of miR-183-5p in BC was explored via bioinformatic analysis with potential target genes overlapped with predicting target genes, low-expression genes based on RNA-seq data from TCGA and downregulated genes from Gene Expression Omnibus (GEO).

Data acquisition and analysis. The miRNA sequencing data of miR-183 and clinical information of patients with BC were obtained from TCGA and contained 412 cases and 19 para-carcinoma tissues of counterparts as controls (30,31). Only 409 cases possessed the miRNA sequencing data and clinical information. The clinical information and follow-up data of these cases, including sex, body mass index (BMI), primary therapy outcome, pack number of cigarettes smoked per year, primary therapy outcome, diagnosis subtype, lympho-vascular invasion, pathologic T stage, pathologic N stage, pathologic M stage, pathologic stage and new tumor events after initial treatment were also downloaded to analyze the correlation between miR-183 expression and clinical parameters (Table I). Receiver operator characteristic curve (ROC) and Kaplan-Meier (K-M) analyses were used to assess the diagnostic and prognostic roles of miR-183.

Furthermore, the expression data and prognostic analysis of miR-183-5p were provided from database of YM500v3 (http://driverdb.tms.cmu.edu.tw/ym500v3/). The genetic alteration of miR-183 was validated from the cBioPortal database (http://www.cbioportal.org/).

Meta-analysis of miR-183 expression based on the data from TCGA, GEO and the literature. A resourceful GEO database could provide strong support in mining the expression data of miRNAs in human cancers. Therefore, we also searched the GEO database to mine the miR-183-5p expression level in BC. The following terms were used for searching: (bladder OR urothelial OR urinary OR urogenital) AND (cancer OR carcinoma OR tumor OR neoplasm* OR malignant*). The miR-183-5p expression data were extracted from BC and relevant controls.

A comprehensive search in several main literary databases worldwide, including PubMed, Chinese VIP, CNKI, WanFang database, SinoMed, Embase, Web of science, Science Direct and Wiley Online Library, was performed for the validation of the miR-183 expression level, up to July 1, 2017. The following terms were used for searching: (bladder OR urothelial OR urinary OR urogenital) AND (cancer OR carcinoma OR tumor OR neoplasm* OR malignant*) AND (MicroRNA183 OR miRNA183 OR miR183 OR miR-183 OR miRNA-183 OR microRNA-183 OR 'microRNA183' OR 'miRNA1' OR 'miR183' OR miR-183-5p OR miRNA-183-5p OR microRNA-183-5p).

Prediction of the prospective target genes of miR-183-5p. The prediction of miR-183-5p target genes was conducted with different bioinformatics tools, including miRWalk, MicroT4, miRanda, miRBridge, miRDB, miRMap, miRNAMap, PICTAR2, PITA, RNA22, RNAhybrid, TargetScan. Only 7,421 genes appearing for over 4 times among 12 platforms were regarded as potential target genes of miR-183-5p.

Potentially related genes of miR-183-5p in BC cells as detected by microarray. According to the information provided by GSE24782 microarray, a few human cancer cell lines, including BOY, T24, A498, PC3, DU145, FaDu, SAS, HSC3 and IMC3, were transfected with different miRNAs (miR-183-5p, miR-218, miR-145, miR-1 and miR-874). Based on the functional mechanism of miRNA, low-expression genes with a fold change (FC) <0.85 after transfected with miR-183-5p in BOY and T24 cells were regarded as potential target genes of miR-183-5p. A total of 3,163 genes were selected for further analysis.

Selection of low-expression genes based on RNA-seq dataset from TCGA. The RNA-seq dataset from TCGA contained 60,483 mRNAs, which were then used for the analysis of the differential expression with the R package of edgeR (32,33). Differentially expressed genes with the expression data missing in >10% samples were excluded. Due to the high expression of miR-183 in tumor tissues, low-expression genes were selected as the candidates of target genes of miR-183-5p. Therefore, 2,918 low-expression genes with log2 FC<-1 were included.

Protein-protein interaction (PPI) analysis, Gene ontology (GO) and biological pathway. PPI was conducted to identify the hub

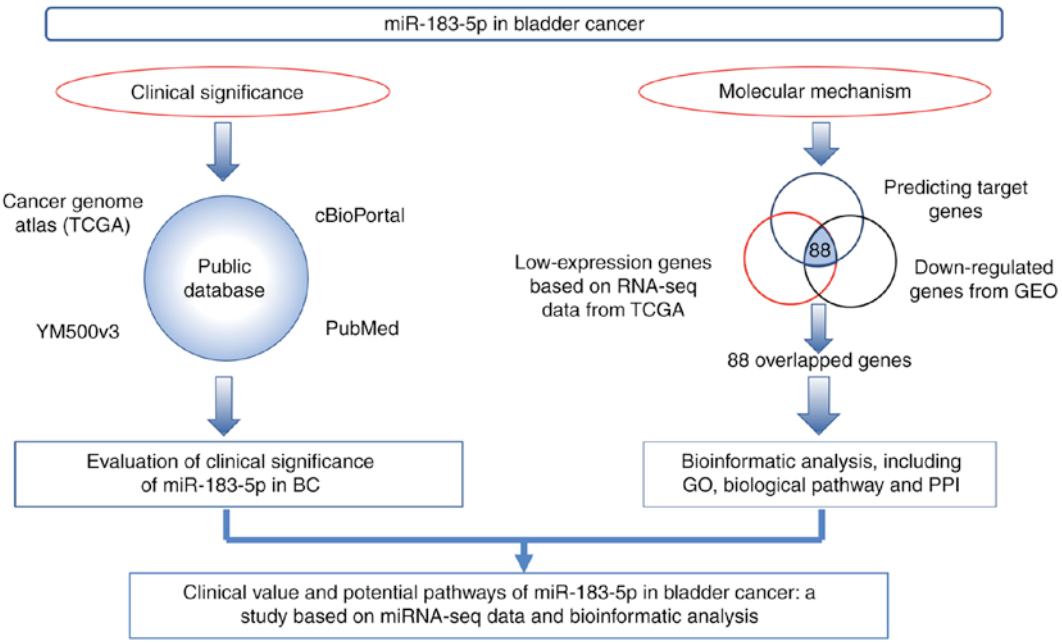

Figure 1. Work flow of the clinical value evaluation and bioinformatical analysis for miR-183-5p in bladder cancer.

genes by STRING: Functional protein association networks (https://string-db.org/). Furthermore, to study the prospective biological effects of miR-183-5p in BC, the potential target genes of miR-183-5p were sent for GO and biological pathway analyses, which was performed via FunRich: Functional Enrichment analysis tool (34,35) (http://www.funrich.org/).

Moreover, to validate the reliability of the potential target genes of miR-183-5p, correlation analysis between the mRNA expression data of the prospective target genes of miR-183-5p enriched in the first pathway of the biological pathway and miR-183-5p expression data were performed. The comparisons of potential target genes between BC and non-cancerous tissues were also carried out.

Statistical analysis. The miR-183-5p expression data are displayed as the means ± standard deviation (SD). Student's t-test for independent samples was performed to evaluate the relationship between miR-183 and clinical parameters. Pearson correlation analysis and Student's t-test were performed for the verification of genes significantly enriched in biological pathways. $P<0.05$ was considered to indicate a statistically significant difference.

Results

Clinical significance of miR-183. Due to the lack of expression data of mature miR-183-5p in the dataset of TCGA, the comparison of the stem-loop mir-183 expression level between BC and adjacent non-cancerous tissues was provided. The miR-183 expression level in BC tissues was notably higher than that in adjacent tissues (Fig. 2A; Table I). High expression of miR-183 was notably associated with the papillary subtype (t=-3.353, P=0.001), low pathologic T stage (t=2.106, P=0.036), and early pathologic stage (t=2.533, P=0.012). However, no remarkable differences were found between miR-183 expression and sex, BMI, primary therapy outcome, pack number of cigarettes smoked per year (mean), primary therapy outcome, lymphovascular invasion present, pathologic N stage, pathologic M stage or new tumor event after initial treatment (Table I).

ROC curve analysis showed that the area under the curve (AUC) was 0.948 (95% CI: 0.919-0.977) with 83.6% sensitivity and 100% specificity (Fig. 2B), indicating that a high expression level of miR-183 may be an ideal marker for BC diagnosis. Furthermore, the K-M curve uncovered that no significant difference in the survival time was noted between patients in the low and high miR-183 expression groups (P=0.861) (Fig. 2C).

The expression of miR-183-5p in primary solid tumors were much higher than that in solid normal tissues (Fig. 2D), which was consistent with the result from TCGA (Fig. 2A). The miR-183-5p expression data in various cancers were provided in YM500v3 (Fig. 2E). Compared with other cancers, BC exhibited higher expression levels of miR-183-5p. This finding again confirmed that there was no significant prognostic value of miR-183-5p in patients with BC (Fig. 2F).

The data from cBioPortal revealed that miR-183 contained two kinds of genetic alterations, including amplification and deep deletion, accounting for 1% (4/412) of patients with BC (Fig. 2G). In addition, no prominent correlation was found between miR-183 alteration and the outcome of BC patients, including overall survival or disease-free survival (Fig. 2H and I).

miR-183-5p expression level from GEO and literatures. A total of 16 microarrays were obtained from GEO, including GSE20414, GSE20418, GSE2564, GSE31616, GSE31617, GSE36121, GSE39067, GSE39093, GSE40355, GSE48008, GSE50894, GSE59483, GSE81201, GSE83586, GSE84525 and GSE86411. Eventually, only GSE39093 was eligible, and the data were used for recalculation. The expression level

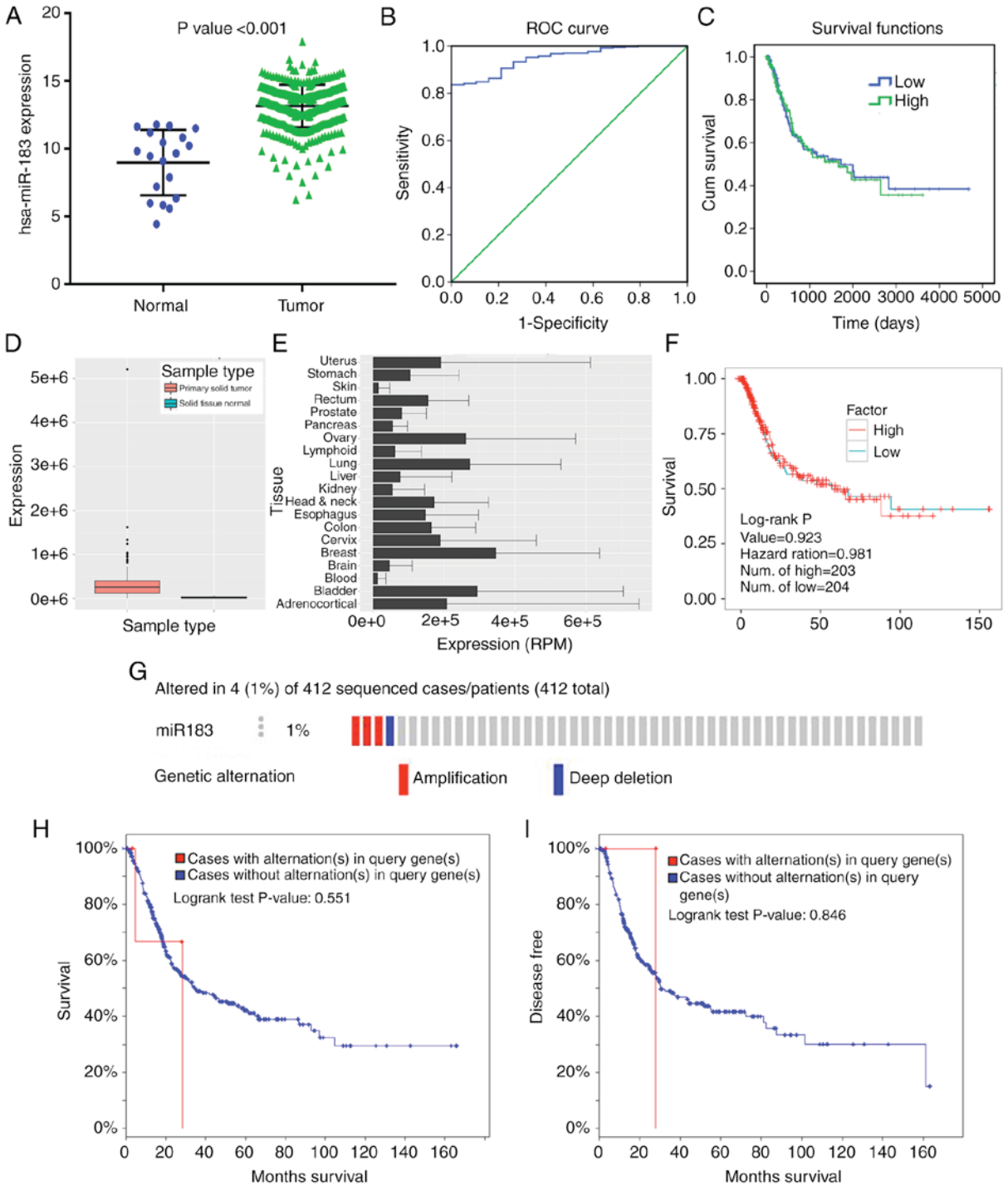

Figure 2. Clinical value of miR-183 in bladder cancer (BC) with different databases. (A) Expression data of miR-183-5p in normal and tumor tissues from TCGA (the y-axis represents log2 scaled). (B) Receiver operating characteristic (ROC) curve analysis of miR-183 to identify BC tissues from non-tumor bladder tissues based on TCGA dataset. (C) Kaplan-Meier survival curve of miR-183 for patients with BC. (D) Expression level of miR-183-5p in primary solid tumor and solid normal tissue from YM500v3 (http://driverdb.tms.cmu.edu.tw/ym500v3/). (E) Expression level of miR-183-5p in different cancers from YM500v3. (F) Relationship between miR-183-5p expression and overall survival by K-M curve analysis from YM500v3. (G) Genetic alterations of miR-183 in BC from cBioPortal (http://www.cbioportal.org). (H) Relationship between the alteration of miR-183 and overall survival from cBioPortal. (I) Disease-free survival from cBioPortal.

of miR-183-5p (4.216±0.485) in 10 BC tissue samples was moderately higher than that in the 10 normal counterparts (3.825±0.460, P>0.05) (Fig. 3A). A comprehensive search was performed in several literature databases; however, only one study provided normalized expression data. In detail, the expression of miR-183-5p in 104 urothelial carcinomas (4.225±0.414) was significantly higher than that in 31 normal bladder epitheliums (1.224±0.224, P<0.0001) (Fig. 3B) (27). All of the eligible expression data of miR-183-5p extracted from TCGA, one GEO microarray and one literature research provided an overall SMD of 3.76 (0.34-7.19) as analyzed by STATA software (Fig. 3C), suggesting that miR-183-5p was

Table I. Correlation between miR-183 expression and clinical parameters.

		miR-183 expression		
Clinical parameters	n	Mean ± SD	t	P-value
Tissue			-7.489	<0.001
Adjacent	19	8.975±2.409		
Tumor	403	13.155±1.562		
Sex			-0.151	0.880
Male	298	13.148±1.561		
Female	105	13.175±1.572		
BMI			0.591	0.555
≤25	146	13.188±1.381		
>25	209	13.088±1.683		
Primary therapy outcome			0.899	0.370
CR+PR+SD	187	13.175±1.533		
PD	42	12.938±1.613		
Pack number of cigarettes smoked per year			1.513	0.132
<39.003	132	13.225±1.486		
≥39.003	88	12.886±1.824		
Primary therapy outcome			0.899	0.370
CRR+PRR+SD	187	13.175±1.533		
PD	42	12.938±1.613		
Diagnosis subtype			-3.353	0.001
Non-papillary	270	12.993±1.700		
Papillary	129	13.486±1.186		
Lymphovascular invasion			-1.051	0.294
No	130	13.054±1.668		
Yes	147	13.253±1.488		
Pathologic T stage			2.106	0.036
T0-T2	123	13.333±1.502		
T3-T4	247	12.966±1.614		
Pathologic N stage			1.369	0.172
N0-N1	278	13.208±1.553		
N2-N3	84	12.948±1.430		
Pathologic M stage			-0.925	0.356
M0	193	13.515±1.317		
M1	10	13.921±1.975		
Pathologic stage			2.533	0.012
Stage I-II	132	13.420±1.445		
Stage III-IV	269	13.017±1.604		
New tumor event after initial treatment			0.864	0.388
No	224	13.168±1.488		
Yes	69	12.987±1.619		

BMI, body mass index; CRR, complete remission/response; PRR, partial remission/response; SD, stable disease; PD, progressive disease.

more highly expressed in samples from BC than in those from normal counterparts. The source of patients with BC and different detection methods may lead to strong heterogeneity.

Identification of the potential target genes of miR-183-5p. In the present study, the overlapped genes from 3 subsets of genes, including predicted target genes, related potential target genes of miR-183-5p from GEO and low-expression genes from

Table II. A total of 88 potential target genes of miR-183-5p.

Ensemble ID	Gene name	Ensemble ID	Gene name	Ensemble ID	Gene name
ENSG00000163431	LMOD1	ENSG00000138685	FGF2	ENSG00000140450	ARRDC4
ENSG00000118496	FBXO30	ENSG00000136842	TMOD1	ENSG00000135269	TES
ENSG00000102271	KLHL4	ENSG00000184985	SORCS2	ENSG00000163661	PTX3
ENSG00000113196	HAND1	ENSG00000169554	ZEB2	ENSG00000108797	CNTNAP1
ENSG00000100784	RPS6KA5	ENSG00000144655	CSRNP1	ENSG00000163083	INHBB
ENSG00000104447	TRPS1	ENSG00000167483	FAM129C	ENSG00000105835	NAMPT
ENSG00000140090	SLC24A4	ENSG00000064309	CDON	ENSG00000083067	TRPM3
ENSG00000017427	IGF1	ENSG00000159167	STC1	ENSG00000152217	SETBP1
ENSG00000183454	GRIN2A	ENSG00000152102	FAM168B	ENSG00000104313	EYA1
ENSG00000143878	RHOB	ENSG00000134531	EMP1	ENSG00000151929	BAG3
ENSG00000105974	CAV1	ENSG00000166974	MAPRE2	ENSG00000007312	CD79B
ENSG00000173334	TRIB1	ENSG00000105784	RUNDC3B	ENSG00000138944	KIAA1644
ENSG00000188385	JAKMIP3	ENSG00000173068	BNC2	ENSG00000182168	UNC5C
ENSG00000095794	CREM	ENSG00000188803	SHISA6	ENSG00000169083	AR
ENSG00000106829	TLE4	ENSG00000169504	CLIC4	ENSG00000163788	SNRK
ENSG00000187098	MITF	ENSG00000058272	PPP1R12A	ENSG00000004799	PDK4
ENSG00000113448	PDE4D	ENSG00000172399	MYOZ2	ENSG00000145861	C1QTNF2
ENSG00000126351	THRA	ENSG00000115252	PDE1A	ENSG00000151892	GFRA1
ENSG00000163328	GPR155	ENSG00000164741	DLC1	ENSG00000169946	ZFPM2
ENSG00000178662	CSRNP3	ENSG00000066382	MPPED2	ENSG00000101333	PLCB4
ENSG00000198961	PJA2	ENSG00000181773	GPR3	ENSG00000163171	CDC42EP3
ENSG00000018408	WWTR1	ENSG00000140416	TPM1	ENSG00000107968	MAP3K8
ENSG00000058668	ATP2B4	ENSG00000073910	FRY	ENSG00000136267	DGKB
ENSG00000018625	ATP1A2	ENSG00000107562	CXCL12	ENSG00000126524	SBDS
ENSG00000136158	SPRY2	ENSG00000112320	SOBP	ENSG00000091831	ESR1
ENSG00000134201	GSTM5	ENSG00000142627	EPHA2	ENSG00000079308	TNS1
ENSG00000118922	KLF12	ENSG00000058866	DGKG	ENSG00000131016	AKAP12
ENSG00000186354	C9orf47	ENSG00000162616	DNAJB4	ENSG00000131018	SYNE1
ENSG00000078687	TNRC6C	ENSG00000157368	IL34	ENSG00000146151	HMGCLL1
ENSG00000067900	ROCK1				

TCGA, were regarded as the potential target genes of miR-183-5p. Finally, 88 overlapped genes were obtained (Table II).

Bioinformatic analyses of the target genes of miR-183-5p. As shown in Fig. 4, hub genes, which contained >3 connected lines, were identified, including estrogen receptor 1 (ESR1), melanogenesis-associated transcription factor (MITF), androgen receptor (AR), C-X-C motif chemokine ligand 12 (CXCL12), insulin-like growth factor 1 (IGF1), caveolin 1 (CAV1), DLC1 Rho GTPase activating protein (DLC1), fibroblast growth factor 2 (FGF2), EPH receptor A2 (EPHA2), Rho associated coiled-coil containing protein kinase 1 (ROCK1), Ras homolog family member B (RHOB), phospholipase C beta 4 (PLCB4) and tropomyosin 1 (TPM1) (single genes without connections are not shown) (Fig. 4).

The overlapped genes were also categorized in GO and biological pathway analyses using the software of FunRich: Functional Enrichment analysis tool. The top 5 pathways in molecular functions (MFs), such as cytoskeletal protein binding, protein threonine/tyrosine kinase activity, were displayed in Fig. 5A and Table III. In addition, the top 5 pathways of biological processes (BPs) (Fig. 5B) and cellular component (CC) were also noted (P-value <0.05) (Fig. 5C; Table III). Via the biological pathway analysis, we discovered that the epithelial-to-mesenchymal transition pathway was the most significantly enriched (P-value <0.00001) (Fig. 5D; Table III).

Validation of potential target genes enriched in the epithelial-to-mesenchymal transition pathway by mRNA expression data from TCGA. The mRNA expression data of potential target genes enriched in epithelial-to-mesenchymal transition pathway in BC and non-carcinomatous tissues, including zinc finger protein, FOG family member 2 (ZFPM2), A-kinase anchoring protein 12 (AKAP12), chloride intracellular channel 4 (CLIC4), zinc finger E-box binding homeobox 2 (ZEB2), basonuclin 2 (BNC2), caveolin 1 (CAV1), C-X-C motif chemokine ligand 12 (CXCL12), sine oculis binding protein homolog (SOBP), tensin 1 (TNS1), insulin-like growth factor 1 (IGF1), spectrin repeat containing nuclear envelope protein 1 (SYNE1), pentraxin 3 (PTX3), WW domain containing transcription regulator 1 (WWTR1), were extracted from TCGA. The correlation of the expression level between miR-183

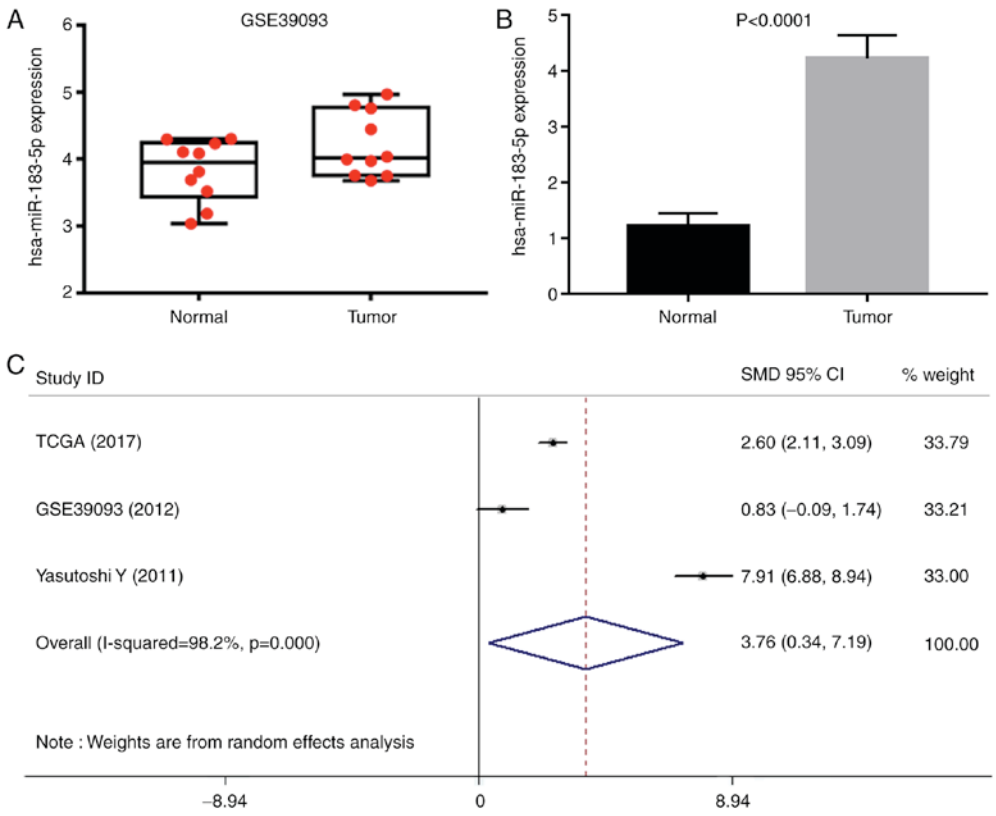

Figure 3. Meta-analysis of miR-183-5p. (A) Expression level of miR-183-5p from GSE39093. (B) miR-183-5p expression reported by Yamada *et al* (27). (C) Forest plot of the meta-analysis.

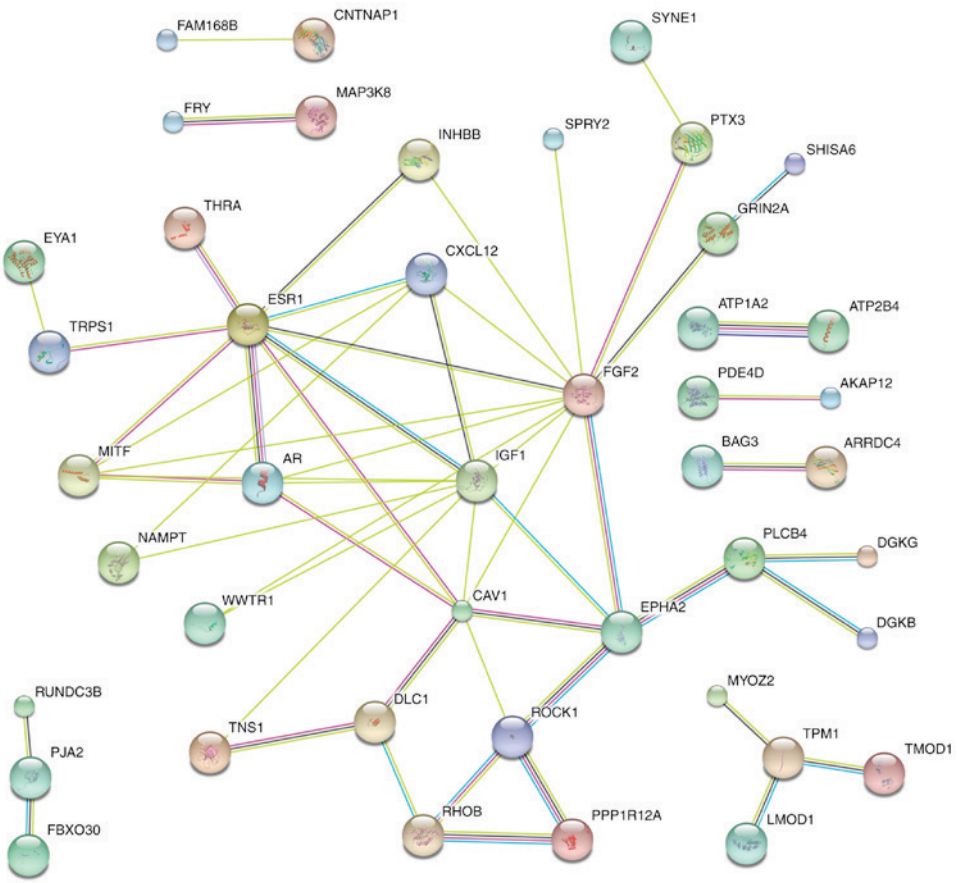

Figure 4. Protein-protein interaction (PPI) of the probable target genes of miR-183-5p in bladder cancer. The PPI network is pictured with the candidates target genes of miR-183-5p by STRING (http://string-db.org). Small nodes represent protein of unknown 3D structure; large nodes represent some 3D structure is known or predicted; colored nodes represent query proteins and first shell of interactors; white nodes represent second shell of interactors.

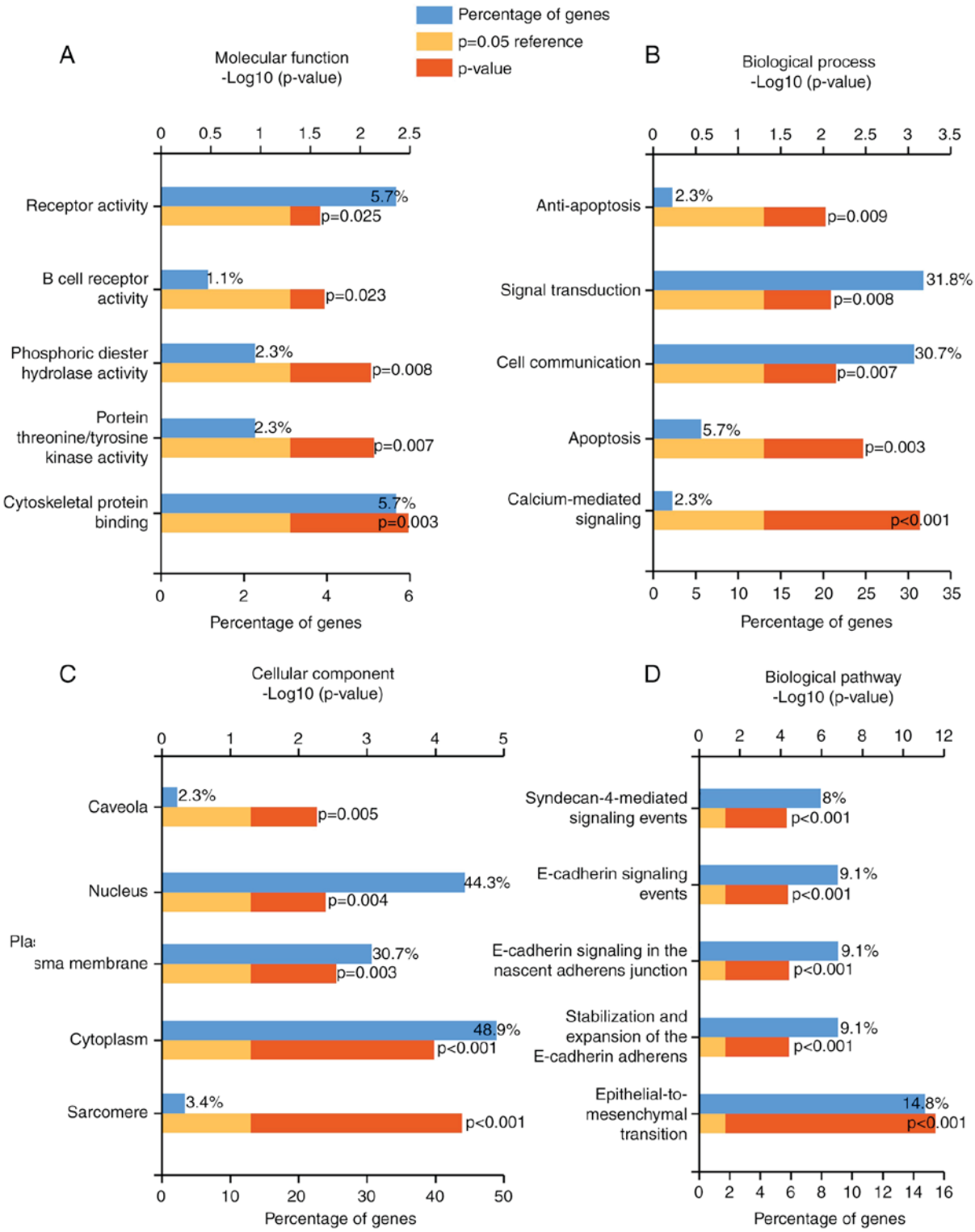

Figure 5. The top 5 enriched (A) molecular function (MF) pathways, (B) biological process (BP) pathways, (C) cellular component (CC) pathways and (D) biological pathways of candidate target genes of miR-183-5p in bladder cancer from GO analysis.

and potential target genes in BC tissues was evaluated by Pearson correlation analysis. The results showed that miR-183 expression in BC tissues were all notably correlated with the expression levels of prospective target genes, respectively (P-value <0.001) (Fig. 6). Furthermore, Student' t test was executed to compare the expression levels of candidate genes between the BC and non-carcinomatous tissues. Consequently, candidate gene expression data were all remarkably higher in BC than in non-carcinomatous tissues (Fig. 6; Table IV).

Discussion

In the present study, the clinical role of miR-183-5p in BC was first evaluated according to the data from miRNA sequencing

Table III. Pathways of potential target genes of miR-183-5p in bladder cancer.

Pathway	No. of genes in the dataset	Percentage of genes	Fold enrichment	P-value (Hypergeometric test)	Gene
MF: Cytoskeletal protein binding	5	5.682	5.021	0.003	TPM1; KLHL4; LMOD1; TMOD1; MAPRE2
MF: Protein threonine/ tyrosine kinase activity	2	2.273	15.679	0.007	MAP3K8; TRIB1
MF: Phosphoric diester hydrolase activity	2	2.273	15.139	0.008	PDE1A; PDE4D
MF: B cell receptor activity	1	1.136	44.049	0.023	CD79B
MF: Receptor activity	5	5.682	3.032	0.025	CDON; GFRA1; UNC5C; CNTNAP1; SORCS2
BP: Calcium-mediated signaling	2	2.273	48.744	0.001	PLCB4; TRPM3
BP: Apoptosis	5	5.682	4.976	0.003	CSRNP1; CSRNP3; BAG3; SNRK; DLC1
BP: Cell communication	27	30.682	1.589	0.007	STC1; CDC42EP3; GPR3; PLCB4; SPRY2; EPHA2; MAP3K8; RHOB; AR; CDON; CXCL12; DGKB; GRIN2A; PDE1A; PDE4D; TNS1; UNC5C; CNTNAP1; GPR155; IGF1; ROCK1; SORCS2; FGF2; INHBB; TRIB1; MYOZ2; RUNDC3B
BP: Signal transduction	28	31.818	1.556	0.008	STC1; CDC42EP3; GPR3; PLCB4; SPRY2; EPHA2; MAP3K8; RHOB; AR; CDON; CXCL12; DGKB; GFRA1; GRIN2A; PDE1A; PDE4D; TNS1; UNC5C; CNTNAP1; GPR155; IGF1; ROCK1; SORCS2; FGF2; INHBB; TRIB1; MYOZ2; RUNDC3B
BP: Anti-apoptosis	2	2.273	13.720	0.009	NAMPT; IGF1
CC: Sarcomere	3	3.409	43.816	<0.001	TPM1; SYNE1; MYOZ2
CC: Cytoplasm	43	48.864	1.653	<0.001	STC1; ATP2B4; CDC42EP3; SPRY2; THRA; AKAP12; ATP1A2; CLIC4; FBXO30; MAP3K8; TLE4; TPM1; AR; DGKB; DGKG; GFRA1; GRIN2A; KLHL4; LMOD1; MITF; NAMPT; PDE1A; PDE4D; PPP1R12A; SBDS; SETBP1; TMOD1; BAG3; HAND1; IGF1; MAPRE2; ROCK1; SYNE1; TRPM3; ESR1; EYA1; TRIB1; WWTR1; MYOZ2; CD79B; GSTM5; RPS6KA5; DLC1

Table III. Continued.

Pathway	No. of genes in the dataset	Percentage of genes	Fold enrichment	P-value (Hypergeometric test)	Gene
CC: Plasma membrane	27	30.682	1.696	0.003	ATP2B4; GPR3; SPRY2; AKAP12; ATP1A2; CLIC4; EPHA2; RHOB; AR; CAV1; CDON; DGKB; DGKG; GFRA1; GRIN2A; PPP1R12A; TNS1; UNC5C; CNTNAP1; GPR155; SORCS2; TRPM3; ESR1; FGF2; TES; SLC24A4; CD79B
CC: Nucleus	39	44.318	1.458	0.004	STC1; ZFPM2; ATP2B4; PLCB4; THRA; TRPS1; AKAP12; ATP1A2; CLIC4; CSRNP1; CSRNP3; TLE4; TPM1; ZEB2; AR; BNC2; CREM; GFRA1; MITF; NAMPT; PDE4D; PPP1R12A; SBDS; SETBP1; TMOD1; CNTNAP1; HAND1; MAPRE2; SYNE1; TRPM3; ESR1; EYA1; FGF2; TRIB1; KLF12; WWTR1; SNRK; RPS6KA5; DLC1
CC: Caveola	2	2.273	18.292	0.005	CAV1; DLC1
Biological pathway: Epithelial-to-mesenchymal transition	13	14.773	15.365	<0.001	ZFPM2; AKAP12; CLIC4; ZEB2; BNC2; CAV1; CXCL12; SOBP; TNS1; IGF1; SYNE1; PTX3; WWTR1
Biological pathway: Stabilization and expansion of the E-cadherin adherens junction	8	9.091	6.364	<0.001	SPRY2; EPHA2; TLE4; AR; GFRA1; MITF; IGF1; ROCK1
Biological pathway: E-cadherin signaling in the nascent adherens junction	8	9.091	6.364	<0.001	SPRY2; EPHA2; TLE4; AR; GFRA1; MITF; IGF1; ROCK1
Biological pathway: E-cadherin signaling events	8	9.091	6.250	<0.001	SPRY2; EPHA2; TLE4; AR; GFRA1; MITF; IGF1; ROCK1
Biological pathway: Syndecan-4-mediated signaling events	7	7.955	7.328	<0.001	TLE4; AR; CAV1; CXCL12; MITF; ROCK1; FGF2

(TCGA, cBioPortal and YM5003v). miR-183-5p in BC contained two types of genetic alteration, gene amplification and deep deletion. Furthermore, pathway analyses uncovered that miR-183-5p could deeply affect multiple pathways and

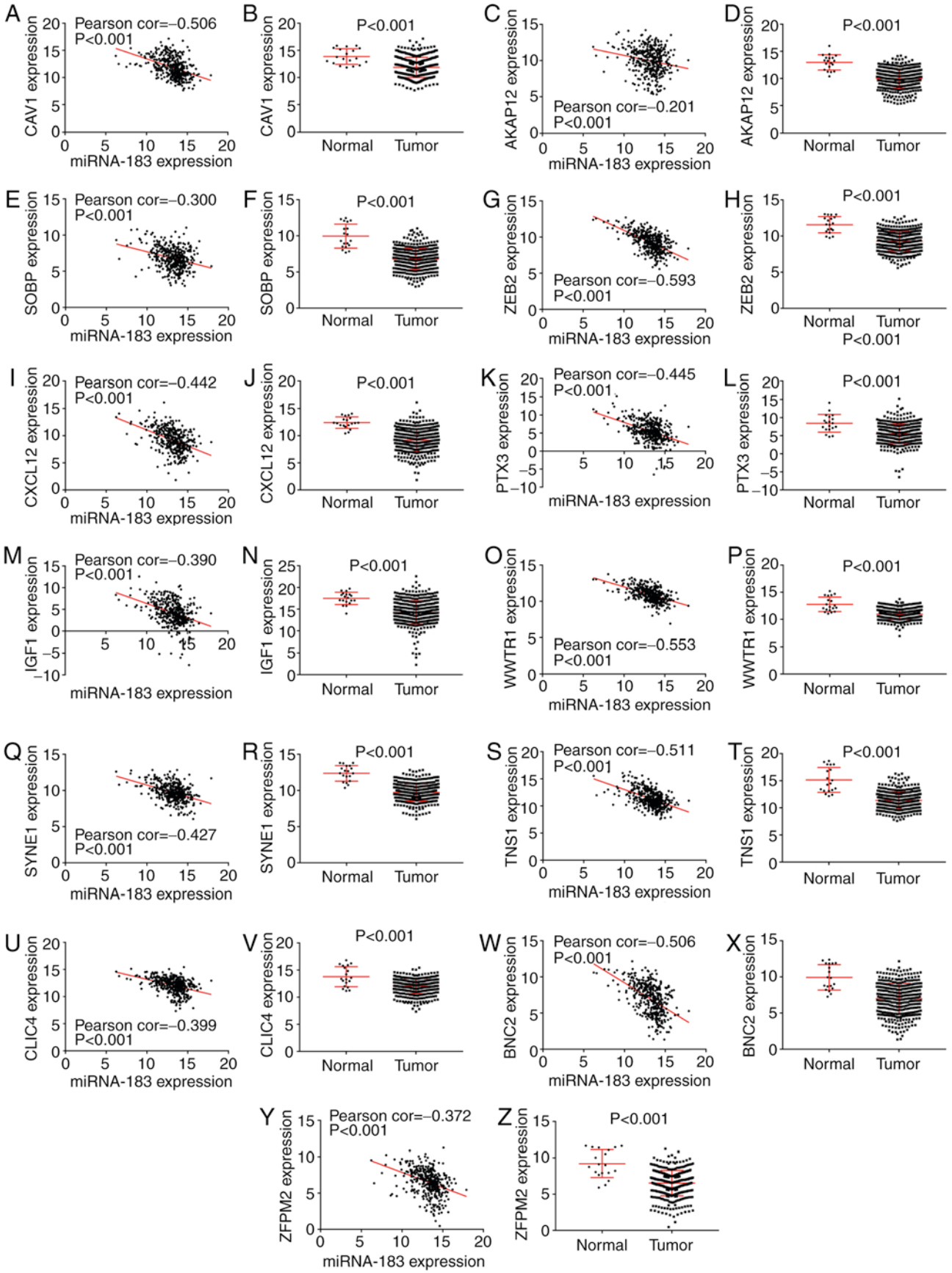

Figure 6. Validation of the potential target genes enriched in the epithelial-to-mesenchymal transition pathway by mRNA expression data from The Cancer Genome Atlas (TCGA), including (A and B) caveolin 1 (CAV1), (C and D) A-kinase anchoring protein 12 (AKAP12), (E and F) sine oculis binding protein homolog (SOBP), (G and H) zinc finger E-box binding homeobox 2 (ZEB2), (I and J) C-X-C motif chemokine ligand 12 (CXCL12), (K and L) pentraxin 3 (PTX3), (M and N) insulin-like growth factor 1 (IGF1), (O and P) WW domain containing transcription regulator 1 (WWTR1), (Q and R) spectrin repeat containing nuclear envelope protein 1 (SYNE1), (S and T) tensin 1 (TNS1), (U and V) chloride intracellular channel 4 (CLIC4), (W and X) basonuclin 2 (BNC2) and (Y and Z) zinc finger protein, FOG family member 2 (ZFPM2).

Table IV. Comparison of the expression levels of potential target genes between normal bladder tissues and bladder cancer (BC) tissues.

Gene	Group	N	Mean	Std. Deviation	P-value	Featurea
CAV1					<0.001	Down
	Normal	19	13.87475	1.427754		
	Tumor	399	11.86889	1.857218		
AKAP12					<0.001	Down
	Normal	19	12.96746	1.407823		
	Tumor	399	9.992088	1.793414		
SOBP					<0.001	Down
	Normal	19	9.964385	1.65852		
	Tumor	399	6.790578	1.474642		
ZEB2					<0.001	Down
	Normal	19	11.57411	1.129419		
	Tumor	399	9.299417	1.35383		
CXCL12					<0.001	Down
	Normal	19	12.41901	1.059525		
	Tumor	399	9.179279	2.088323		
PTX3					<0.001	Down
	Normal	19	8.439694	2.440688		
	Tumor	399	5.515195	2.690033		
IGF1					<0.001	Down
	Normal	19	7.488964	1.422601		
	Tumor	399	4.200803	2.727906		
WWTR1					<0.001	Down
	Normal	19	12.77304	1.334257		
	Tumor	399	10.95718	0.966398		
SYNE1					<0.001	Down
	Normal	19	12.37864	1.079004		
	Tumor	399	9.730599	1.186041		
TNS1					<0.001	Down
	Normal	19	15.15798	2.307397		
	Tumor	399	11.36795	1.597026		
CLIC4					<0.001	Down
	Normal	19	13.79678	1.851609		
	Tumor	399	12.06632	1.372628		
BNC2					<0.001	Down
	Normal	19	9.935324	1.7555		
	Tumor	399	6.986046	2.130077		
ZFPM2					<0.001	Down
	Normal	19	9.218381	1.91825		
	Tumor	399	6.539535	1.752474		

'epithelial-to-mesenchymal transition' was the most remarkable one as defined by the FunRich: Functional Enrichment analysis tool, containing several genes ZFPM2, AKAP12, CLIC4, ZEB2, BNC2, CAV1, CXCL12, SOBP, TNS1, IGF1, SYNE1, PTX3 and WWTR1; among these genes, CAV1, CXCL12 and IGF1 were also identified as hub genes of miR-183-5p in BC by STRING: Functional protein association networks.

It has been fully demonstrated that miRNA expression levels could become reliable markers for the diagnosis and prognosis of cancers (36). miR-183-5p is one of the attractive cancer-relative miRNAs that has been reported to play important roles in various cancers with remarkably high or low expression levels compared with normal tissues. A remarkably high expression of miR-183-5p that could

promote the proliferation and restrain apoptosis in cells through targeting PDCD4 was reported in human breast cancer tissues compared with that in the adjacent non-cancerous tissues (20). A similar phenomenon and function of miR-183-5p was also reported in esophageal squamous cell carcinoma and glioblastoma multiforme (21-23). Upregulation of oncogenic miR-183-5p was reported to enhance the ability of proliferation and metastasis in human pancreatic adenocarcinoma cells probably via targeting the SOCS-6 gene (24). A notable lower expression of miR-183-5p was found in nasopharyngeal carcinoma and cervical cancer tissues, where miR-183-5p could act as the tumor suppressor by targeting MTA1 and MMP-9, respectively (37,38). Reduced expression of miR-183-5p was discovered in pancreatic ductal adenocarcinoma tissues; and significantly associated with tumor grade, metastasis and TNM stage. Patients with low expression of miR-183-5p tended to have notably worse overall survival than those with high expression of miR-183-5p expression (38). Patients with low-expression of miR-183-5p tended to have a poor overall survival. miR-183-5p was involved in cell proliferation by regulating the expression of Bmi-1 (39). Low-expression miR-183-5p was found in melanoma tissues and cells and was correlated with poor overall survival, while high-expression of miR-183-5p caused remarkable inhibition of cell growth *in vitro* and *in vivo* (25). Thus, miR-183-5p could play different roles in various cancers.

To date, only several studies were reported concerning the research of miR-183-5p in BC. It was validated that miR-183-5p expression in samples from patients with BC, including tissues (26,40-42), urine (27,43) and serum (29), were all prominently higher than that those in normal counterparts. In the present study, we revealed the consistent results in tissue samples.

Eissa *et al* performed ROC analysis of miR-183-5p expression in urine samples. However, only the sensitivity (71.3%) and specificity (88.9%) were provided (43). Yamada *et al* showed the result of ROC analysis (AUC=0.817; 95% CI: 0.752-0.872) with 74.0% sensitivity and 77.3% specificity, indicating a moderate diagnostic efficiency of miR-183-5p expression in urine, and they also found a significant correlation between miR-183-5p expression and clinical parameters, including tumor grade and pathological stage (P-value <0.05) (27). In our study, ROC curve analysis showed a robust diagnostic efficiency of miR-183-5p in BC tissues (AUC=0.948; 95% CI: 0.919-0.977). The expression of miR-183-5p was markedly related to the diagnosis subtype, pathologic T stage and pathologic stage (P-value <0.05). However, K-M curve analysis showed no prognostic efficiency of miR-183-5p, based on the data from TCGA, YM500v3 and cBioPortal.

miR-183-5p was conformed to affect the biological behavior of cells by targeting different kind of proteins in various types of cancers, such as regulating cell proliferation by targeting PDCD4 in breast (44) and esophageal cancer (21), and esophageal squamous cell carcinoma (22), inhibiting tumorigenesis by targeting MTA1 in nasopharyngeal carcinoma (37), promoting cell proliferation by targeting NEFL in glioblastoma multiforme (45), and suppressing retinoblastoma cell growth by targeting LRP6 (46). However, no study has reported the possible molecular mechanisms of miR-183-5p in BC. In the present, the potential target genes of miR-183-5p were obtained by the overlap of genes from 3 datasets, including the available predicting online tools, low-expression genes from TCGA and low-expression genes from microarray data after miR-183-5p mimic transfection.

The potential molecular mechanism of miR-183-5p in BC was explored. In total, 7,421 genes were predicted using the online predicting tool of miRwalk2.0. The low-expression genes from the RNA-seq data of TCGA with log2 FC <-1 were regarded as potential target genes of miR-183-5p, and 2,918 genes were involved. The GSE24782 microarray, which contained the data of differential-expressed genes after the overexpression of miR-183-5p in BOY and T24 cells, was reassessed to identify the downregulated genes with a fold change <0.85; 3,163 eligible genes were included. Consequently, 88 overlapped genes were identified and were more prone to be the target genes of miR-183-5p in BC. Next, bioinformatics analyses discovered that these potential target genes were enriched in several pathways involved in the tumorigenesis and development of BC. Forty-three genes were enriched in the pathway of cytoplasm, which ranked the 2nd most significant pathways in the cellular component (CC). The most significant pathway indicated in molecular function (MF) was the pathway of cytoskeletal protein binding. Several significant pathways relative to signal transduction or cell communication were involved in biological process (BP), such as calcium-mediated signaling, cell communication and signal transduction. The pathway of epithelial-to-mesenchymal transition was the most enriched pathway in the biological pathway, playing a crucial role in tumor progression with genes of ZFPM2, AKAP12, CLIC4, ZEB2, BNC2, CAV1, CXCL12, SOBP, TNS1, IGF1, SYNE1, PTX3 and WWTR1. The expression of these 13 target genes was negatively correlated with the expression of miR-183-5p in BC tissues. miR-183-5p was conformed to target the tumor suppressor AKAP12 and plays an important role in human hepatocarcinogenesis (47). CAV1, CXCL12 and IGF1 were also identified as hub genes of miR-183-5p in BC which may deeply affect the generation and development of BC. However, rigorous experiments *in vitro* and *in vivo* are needed to confirm the potential molecular mechanism.

In summary, miR-183-5p may play critical roles in the tumorigenesis and development of BC; however, the clinical function of miR-183-5p in BC urgently requires exploration. Furthermore, several crucial pathways for miR-183-5p in BC were predicted by bioinformatics analysis. However, validation of the real molecular mechanisms of miR-183-5p in BC by well-designed and rigorous functional experiments is still needed.

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Competing interests

The authors declare that they have no competing interests.

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