Functions of circular RNAs in bladder, prostate and renal cell cancer (Review)

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Abstract. Circular RNAs (circRNAs) are a class of non-coding RNAs formed by covalently closed loops through back-splicing and exon-skipping. circRNAs have been confirmed to play a vital role in various biological functions, acting as microRNA sponges and reservoirs, as well as combining with RNA-binding proteins during the progression of multiple cancer types. Therefore, the present review evaluated recent research articles in PubMed that were published between November 2017 and September 2020. Key word search strings included: 'Circular RNA (circRNA) AND bladder cancer (BC)', 'circular RNA (circRNA) AND prostate cancer (PCa)' and 'circular RNA (circRNA) AND renal cell cancer (RCC)'. In total, >58 circRNAs were found to be implicated in urological cancers, with several of the circRNAs targeting common carcinogenic pathways, such as the AKT, TGF-β, MAPK, VEGF and even metabolic pathways. circRNAs are important modulators of BC, PCa and RCC. circRNAs are functionally implicated in the pathogenesis of these cancer types, and have been found to act as biomarkers for the diagnosis and prognosis of urological cancer. However, to the best of our knowledge, the functions of circRNAs in tumors of the urinary system remain largely unknown and require further research.

Contents

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1. Introduction

Cancer is one of the leading cause of mortality worldwide; however, with incidences of cardiovascular disease decreasing in several countries, cancer is most likely to soon become the leading cause (1). According to estimates, there were 17.0 million new cases and 9.5 million cancer-related deaths worldwide in 2018, with bladder cancer (BC), prostate cancer (PCa) and renal cell cancer (RCC) ranking 12th, 3rd and 16th, respectively, in terms of global incidence (2). Surgical resection is the most common treatment method for these diseases, but its effect remains unsatisfactory. For example, the recurrence rates of BC and RCC are 50 and 40%, respectively (3,4). Furthermore, although 80% of newly diagnosed PCa cases are sensitive to androgen deprivation therapy, >50% of patients with PCa develop recurrence, infiltration or metastasis, or progress to hormone refractory PCa (5). Therefore, determining a new preventive and therapeutic target for these malignant tumors is an urgent requirement.

Circular RNAs (circRNAs), a class of non-coding RNAs ubiquitous in the cytoplasm of various eukaryotic cells, commonly originate from back-splicing events of exons or introns (6). 'Exon skipping' and 'direct back-splicing' are the two mechanisms that lead to the formation of exonic or exon-intron circRNAs, in which the 3' and 5' ends of circRNAs are covalently joined together to form single-stranded continuous loop structures, and can be regulated by certain splicing factors (Fig. 1). The outstanding characteristics of circRNAs include their marked stability, high abundance, evolutionary conservation and tissue-specific expression (7). In addition, circRNAs are different from microRNAs (miRNAs/miR) and long non-coding RNAs (lncRNAs), as they lack a 5'cap and a 3'polyadenylated tail, and they have the ability to encode regulatory peptides (8). To date, ~15,000 circRNAs have been identified in both humans and mice, representing 15 and 40% of the total circRNAs in humans and mice, respectively (9).

One of the main functions of circRNAs is to sponge miRNAs that regulate the function of target genes, with common features such as being derived from one or more exons of known protein-coding genes and being formed by a back-splice event. In addition, these circRNAs are predominantly localized in the cytoplasm, occupying the same space as miRNAs (10). circRNAs also act as a reservoir for miRNAs,

which means that they can increase the availability of miRNAs for binding to and inhibiting their target mRNAs (Fig. 1) (11). Another study confirmed that circRNAs play crucial roles in tumor growth, metastasis, epithelial-mesenchymal transition (EMT) and treatment resistance (12). However, the function of circRNAs in tumors of the urinary system remains unclear. The aim of the present review was to illustrate the roles of circRNAs in BC, PCa and RCC.

2. circRNAs in BC

circRNAs act as oncogenes in BC. circRNA-miRNA-mRNA interaction networks, as a major function of circRNAs, have been associated with cell signaling transduction in BC. For instance, the expression levels of TGF-β2, Smad3 and phosphorylated (p)-Smad3 could be increased by circ_0005777 (circRIP2), which reverses the miR-1305-induced suppression of BC progression (Fig. 2) (13). AKT signaling is another regulator of cancer metastasis. The expression of p-AKT/PI3K was increased by circKIF4A (circ_0007255), which promoted BC growth and metastasis *in vitro* and *in vivo*. circKIF4A could act as a sponge for miR-375 and miR-1231 to enhance the level of Notch2, which has been found to play an oncogenic role in BC (14). Likewise, Notch1, NICD-1 and HES1, all downstream genes of the Notch signaling pathway, have been shown to be highly expressed in BCa and repressed by circ_0008532 and MTGR1. In addition, circ_0008532 was shown to increase the progression of BC by regulating MTGR1 expression, an effect that could be reversed by miR-155-5p/miR-330-5p. circ_0008532 is derived from the MTGR1 gene (15). circ_0068871 produced at the fibroblast growth factor receptor 3 gene (FGFR3) was highly expressed in BC, activated p-STAT3 and facilitated tumor development; however, its effects could be reversed by miR-181a-5p (16). The incidence and metastasis of BCa is 4-fold higher in men compared with that in women, indicating that sex steroid pathways play a vital role in BC progression (2). Indeed, estrogen receptor α (ERα) exhibits low expression in BC, decreases the expression of epidermal growth factor receptor, and is mediated by circ_0023642 and miR-490-5p. Moreover, circ_0023642 was found to promote the metastasis of BC, but its effect could be inhibited by ERα (17).

Unlike healthy cells, tumor cells do not undergo apoptosis when mitosis arrests, thus the dysfunction of mitosis and apoptosis participates in tumor progression (18). For instance, kinesin family member 2C (KIF2C), a mitotic centromere-associated kinesin, is highly expressed in BC, is upregulated by circRGNEF (circ_0072995) and is downregulated by miR-548; it also enhances tumor progression following circRGNEF upregulation or miR-548 downregulation, and circ_0072995 is derived from the RGNEF gene (Table I) (19). Another study demonstrated that insulin-like growth factor binding protein 2 (IGFBP2), a key anti-apoptotic regulator, is upregulated by circVANGL1 or inhibited by miR-1184 in BC. In addition, circVANGL1 facilitates tumor progression by upregulating IGFBP2, while its effect could be reversed by miR-1184; circVANGL1 is derived from the VANGL1 gene (20). Notably, BC stem cells (BCSCs), which have self-renewal and differentiation capacities, may contribute to the tumor initiation, metastasis, recurrence and drug resistance of BC (21). For example, circ_103809, which is derived from the zinc finger RNA-binding protein gene, is highly expressed in BCSCs and has been shown to increase the cell oncosphere formation and aggressiveness of BC, and decrease the expression of miR-511 (22).

circRNAs can bind to numerous RNA-binding proteins (RBPs), acting as protein sponges or decoys to regulate protein functions. Hypoxia-inducible factor-1α enhances the expression of circ_403658, and promotes BC growth *in vitro* and *in vivo*. In addition, circ_403658 improves the expression of L-lactate dehydrogenase A chain (LDHA), vascular endothelial growth factor and VEGF receptor in BC, and increases lactate production, LDH activity, ATP production and glucose uptake in tumor cells. LDHA serves as a key checkpoint of glycolysis (Fig. 2) (10). In addition, as a member of the zinc finger protein (ZNF) family, circZNF139 (circ_0001727) is derived from the ZNF139 gene, which is highly expressed in BC, and promotes tumor cell development by improving the level of p-AKT and PI3K (23).

circRNAs act as tumor suppressors in BC. The abnormal activation of transcription factors promotes the proliferation and differentiation of tumor cells (24). For instance, ΔNP63, a transcription factor of the p53 family, is upregulated by circ family with sequence similarity 114 member A2 (FAM114A2), thus suppressing the miR-762-induced growth of urothelial carcinoma of the bladder. circFAM114A2 (circ_0001546) is derived from the FAM114A2 gene (25). circ activin A receptor type 2A attenuates tumor growth and aggressiveness *in vitro* and *in vivo* by improving the expression of eye absent 4 (EYA4), and reduces miR-626-induced BC progression. EYA4 is a transcription factor (26). A different study illustrated that Krüppel-like factor (KLF)9 and KLF10, which are zinc finger transcription factors, repress the progress of miR-636- and miR-570-3p-induced BC through the upregulation of circ protein tyrosine phosphatase receptor type A and circFUT8 (circ_0003028), respectively (27,28). c-Myc is a famous oncogene and transcription factor, that has been reported to participate in the progression of bladder cancer. For example, c-Myc promotes the growth and mobility of BCSCs, an effect that could be improved by miR-147 or repressed by circ_0068307; circ_0068307 is derived from the ALG3 α-1,3-mannosyltransferase gene (29). In addition, c-Myc sabotages the G_0/G_1 phase of circ chromodomain Y-like (CDYL)-induced cell cycle arrest, consequently facilitating the progression of BC; circCDYL is generated from the CDYL gene (Table II) (7).

Abnormal cell signal transduction is closely associated with the occurrence of BC. For example, circ_0071662 abolishes the activation of AKT by increasing the expression of 15-hydroxyprostaglandin dehydrogenase, and inhibits BC development; however, its effect could be reversed by miR-146-3p (30). Furthermore, the expression of PETN is upregulated by circ solute carrier family 8 member A1 (SLC8A1) or downregulated by miR-130b/miR-494 in BC. circSLC8A1 blocks BC progression by sponging miR-130b/miR-494, and impairs the expression of p-AKT; circSLC8A1 (circ_0000994) is derived from the SLC8A1 gene (Fig. 2) (31). Another study showed

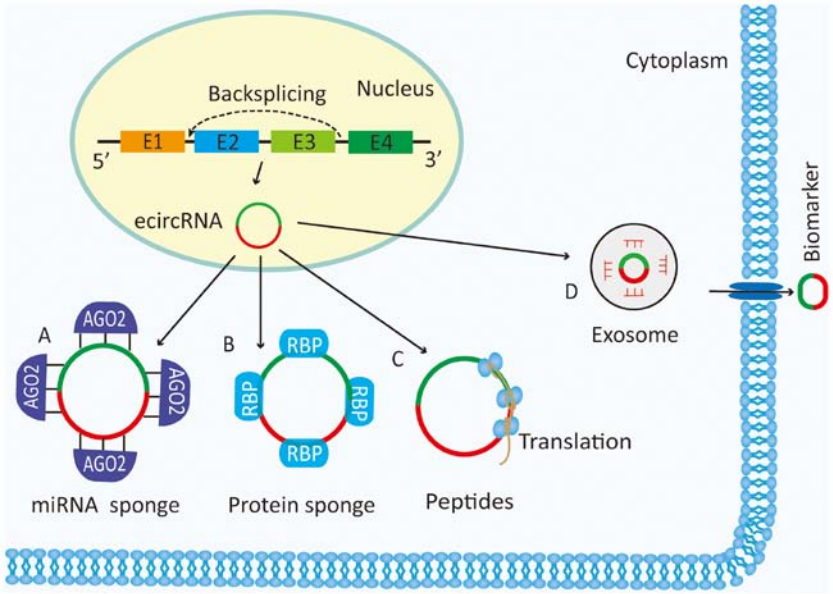

Figure 1. Functions of circRNAs. (A) circRNAs can act as miRNA sponges and subsequently regulate the expression of relevant target genes. (B) circRNAs can bind to several proteins and mediate their actions. (C) circRNAs can be translated into peptides or proteins. (D) circRNAs exist in the serum and other bodily fluids, and can function as molecular biomarkers for the diagnosis and treatment of cancer. ecircRNA, exonic circRNA; circRNA, circular RNA; AGO2, Argonaute-2; RBP, RNA-binding protein.

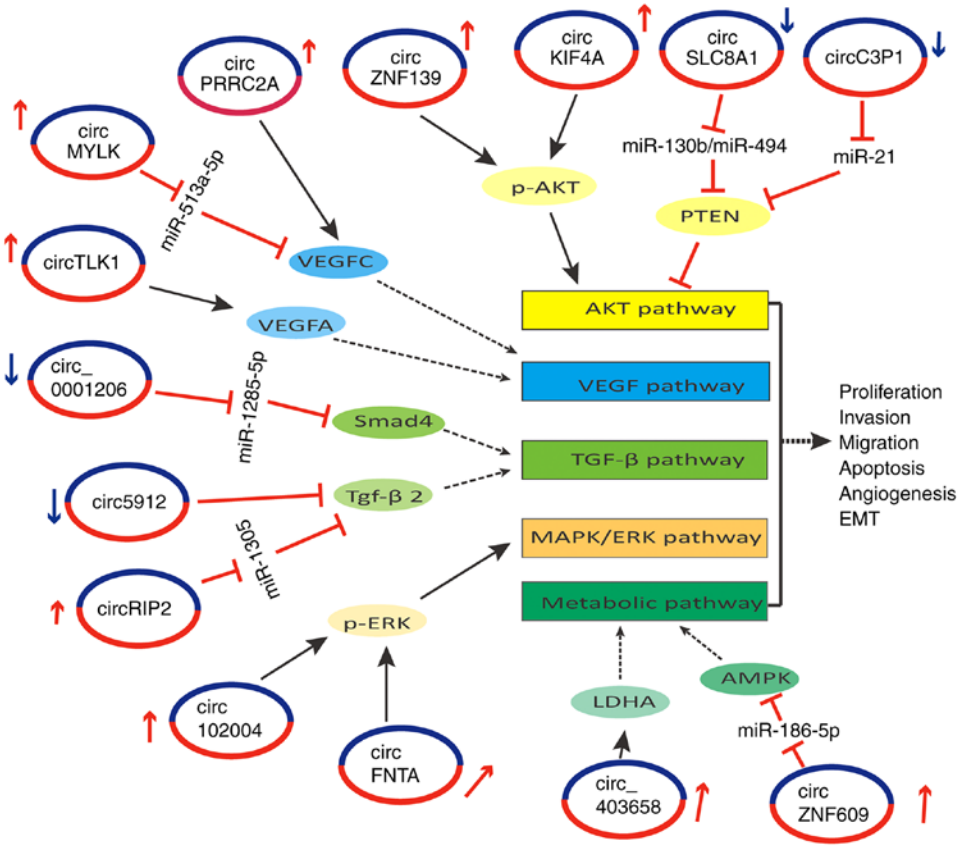

Figure 2. Representative diagram of circRNAs that interact with the circRNA-miRNA-mRNA regulatory network/RBPs and regulate oncogene or tumor suppressor signaling pathways. The diagram mainly shows that circZNF139 and circKIF4A activate the AKT pathway through p-AKT in BC, and that circFNTA, circ_403658 and circRIP2 activate the MAPK, metabolic and TGF-β signaling pathways through p-ERK, LDHA and miR-1305/TGF-β2, respectively, in BC. Furthermore, circ102004 and circZNF609 activate the MAPK and metabolic pathways through p-EKT and miR-186-5p/AMPK, respectively, in PCa. Moreover, circMYLK, circTLK1 and circPRRC2A activate the VEGF pathway through miR-513a-5p/VEGFC, VEGFA and VEGFC, respectively, in RCC. By contrast, circSLC8A1 and circ5912 deactivate the AKT and TGF-β pathways through miR-130b/miR-494/PTEN and TGF-β2, respectively, in BC. In addition, circ_0001206 deactivates the TGF-β pathway through miR-1285-5p/Smad4 in PCa, and circC3P1 deactivates the AKT pathway through miR-21/PTEN in RCC, which suggests that the circRNA-miRNA-mRNA interaction networks and RBPs that sponge circRNA serve a critical role in BC, PCa and RCC progression through signaling pathways. circRNA, circular RNA; EMT, epithelial-mesenchymal transition; RBP, RNA-binding protein; PCa, prostate cancer; BC, bladder cancer; RCC, renal cell cancer; miR, microRNA.

Table I. circRNAs act as oncogenes in bladder, prostate and renal cancer: Summary of circRNAs, including their ID number, host genes, mechanisms, functions and clinical applications.

A, Bladder cancer

circRNAs	Host gene	Biological function	Target	Clinical applicant	(Refs.)
circ_403658	ZNF292	Promote tumor growth, increase lactate production, LDH activity, ATP production and glucose uptake of cell	LDHA, VEGFR and VEGF	Target	(10)
circPRMT5 (circ_101320)	PRMT5	Enhance tumor metastasis, increase expression of Vimentin, SNAIL1	miR-30c	DFS, target	(65)
cTFRC (circ_0001445)	TFRC	Promote cell proliferation and invasion	E-cadherin, miR-107	OS, target	(66)
circRIP2 (circ_0005777)	RIP2	Promote tumor growth, metastasis and increase expression of TGF-β2, N-cadherin, Vimentin, smad3 and p-smad3	miR-1305, TGF-β2 and smad3		(13)
circRGNEF (circ_0072995)	RGNEF	Enhance tumor and metastasis	miR-548 and KIF2C		(19)
circVANGL1	VANGL1	Promote tumor growth	miR-1184 and IGFBP2		(20)
circFNTA (circ_0084171)	FNTA	Promote tumor metastasis and decrease cisplatin chemosensitivity, increases the expression of p-ERK1/2 and p-MEK1/2	miR-370-3p and KRAS		(70)
circ_0023642	UVARG	Promote tumor growth and metastasis, increase the expression of EGFR	miR-490-5p and ERα		(17)
circ_103809	ZFR	Increase BCSC oncosphere formation, migration and invasion	miR-511		(22)
circELP3	ELP3	Promote tumor growth and cisplatin resistance	hypoxia		(71)
circ_0068871	FGFR3	Enhance tumor growth and the expression of p-STAT3 FGFR3	miR-181a-5p and		(16)
circZNF139 (circ_0001727)	ZNF139	Increase cell proliferation, migration and invasion. Promote the expression level of p-AKT and PI3K	p-AKT and PI3K		(23)
circKIF4A (circ_0007255)	KIF4A	Promote tumor growth and metastasis, enhance expression of p-AKT and PI3K	miR-375/1231 and NOTCH2		(14)
circ_0008532	MTGR1	Promote tumor growth and metastasis, reduce the expression of Notch1, NICD-1 and HES1	miR-155-5p/330-5p		(15)
circ_0003221 (circPTK2)	PTK2	Promote cell proliferation and migration		Biomarker	(61)

B, Prostate cancer

circRNAs	Host gene	Biological function	Target	Clinical applicant	(Refs.)
circHIPK3 (circ_0000284)	HIPK3	Increase cell proliferation and invasion, and inhibit apoptosis	miRNA-338-3p and ADAM17		(5,42)
circ0005276	XIAP	Increase tumor growth and increase expression of N-cadherin	XIAP and FUS		(41)
circ102004	USP22	Increase cell proliferation, invasion and migration, improve expression of p-ERK, p-AKT, p-JNK, JNK, β-catenin, BCL2 and MMP2			(43)
circABCC4 (circ_0030586))	ABCC4	Increase cell proliferation, invasion and migration	miR-1182 and FOXP4		(39)
circFOXO3 (circ_0006404)	FOXO3	Increase cell proliferation and inhibit apoptosis	miR-29a-3p and SLC25A15		(63)

Table I. Continued.

B, Prostate cancer

circRNAs	Host gene	Biological function	Target	Clinical applicant	(Refs.)
circHIPK3 (circ_0000284)	HIPK3	Increase cell proliferation and invasion, and inhibit apoptosis	miRNA-338-3p and miR-1238 and LHX2		(5,42)
circFMN2 (circ_0005100)	FMN2	Increase tumor growth and reduce the expression of E-cadherin			(64)
circZNF609	ZNF609	Increase cell proliferation, invasion and migration, improve ratio of p/t-AMPK and the level of YAP1	miR-186-5p		(38)
circ_0044516	COL1A1	Increase cell proliferation, invasion and migration	miR-29a-3p	Diagnosis	(62)

C, Renal cancer

circRNAs	Host gene	Biological function	Target	Clinical applicant	(Refs.)
circPCNXL2 (circ_406752)	PCNXL2	Enhance tumor growth	miR-153 and ZEB2	Target and diagnosis	(49)
circPRRC2A (circ_406752)	PRRC2A	Enhance tumor growth, increase expression of N-cadherin, Snail and vimentin, VEGFC	miR-514a-5p/6776-5p and TRPM3	OS	(50)
circMYLK (circ_0141940)	MYLK	Enhance tumor growth and metastasis, increase expression of VEGFC	miR-513a-5p and VEGFC		(51)
circTLK1 (circ_0004442)	TLK1	Improve tumor growth and metastasis, increase expression of N-cadherin, vimentin and VEGFA	miR-136-5p and CBX4		(52)
circ_001895	CTBP1	Increase tumor growth, improve expression of N-cadherin	miR-296-5p and SOX12	OS	(53)
circ-EGLN3 (circ_0031594)	EGLN3	Increase cell proliferation, invasion and inhibit apoptosis	miR-1299 and IRF7	OS, biomarker/ target	(55,60)
circ_0039569	CCL2	Promote cell proliferation, migration and invasion	miR-34a-5p and CCL22	Biomarker	(72)
circ_0085576	ASAP1	Enhance tumor growth and metastasis	miR-498 and YAP1	OS, DFS	(67)

circRNA, circular RNA; BCSC, bladder cancer stem cell; OS, overall survival; DFS, disease-free survival; miR, microRNA.

Table II. circRNAs act as tumor suppressors in bladder, prostate and renal cancer: Summary of circRNA names, including their ID number, host genes, mechanisms, functions and clinical applications.

A, Bladder cancer

circRNAs	Host gene	Biological function	Target	Clinical applicant	(Refs.)
circFAM114A2 (circ_0001546)	FAM114A2	Reduce tumor growth	miR-762 and ΔNP63	Biomarker and target	(25)
circACVR2A	ACVR2A	Reduce tumor growth and metastasis	miR-626 and EYA4	OS and target	(26)
circPTPRA (circ_102984/0006117)	PTPRA	Reduce tumor growth	KLF9 and miR-636	Biomarker and target	(27)
circFUT8 (circ_0003028)	FUT8	Suppress tumor metastasis and inhibit expression of Slug	miR-570-3p and KLF10		(28)
circ_0071662	TPPP	Reduce cell proliferation and invasion, and deactivate AKT pathway	miR-146-3p, HPGD and NF2	Biomarker	(30)
circSLC8A1 (circ_0000994)	SLC8A1	Reduce tumor growth and metastasis, inhibit expression of p-Akt and MMP-9	miR-130b/494 and PTEN	Biomarker and target	(31)
circ5912 (circ_0005912)	FIP1L1	Increase tumor growth and metastasis, reverses TGF-β2-induced EMT			(37)
circCdr1as (CiRS-7)	LINC00632	Reduce tumor growth and increase cisplatin chemosensitivity	miR-1270 and APAF1	Biomarker	(74)
circ_0006260	SLC41A2	Reduce tumor growth	miR-653 and March1		(32)
circPICALM (circ_0023919)	PICALM	Reduce tumor growth and metastasis, decrease pFAK/FAK ratio and decrease expression of β-catenin, Vimentin, ZEB1, Slug and N-cadherin	miR-1265 and STEAP4		(36)
circNR3C1(circ_0001543)	NR3C1	Reduce tumor growth	miR-27a-3p and cyclin D1		(33)
circ-ZKSCAN1 (circ_0001727)	ZKSCAN1	Reduce tumor growth and metastasis	miR-1178-3p and p21	OS, DFS	(34)
circ-Foxo3 (circ_0006404)	Foxo3	Promote cell apoptosis and inhibit proliferation, enhance expression of cleaved-caspase 3 and ratio of Bax/Bcl2	miR-191-5p		(73)
circ_0068307	ALG3	Reduce tumor growth	miR-147 and c-Myc		(29)
circCDYL	CDYL	Decrease cell proliferation and migration, reduce expression of c-Myc			(7)
circ_0077837/0004826	EPB41L2/UTRN	Reduce cell proliferation, migration and invasion		OS, RFS	(68)
circHIPK3 (circ_0000284)	HIPK3	Inhibit cell viability and enhance cell apoptosis induced by gemcitabine		Target, DFS	(75)

B, Prostate cancer

circRNAs	Host gene	Biological function	Target	Clinical applicant	(Refs.)
circRNA17 (circ_0001427)	PDLIM5	Inhibit tumor growth, metastasis and enzalutamide-resistant	miRNA-181c-5p and ARv7		(11)

Table II. Continued.

B, Prostate cancer					
circRNAs	Host gene	Biological function	Target	Clinical applicant	(Refs.)
circAMOTL1L (circ_000350)	AMOTL1L	Inhibit tumor growth, increase expression of Pcdha8 and E-cadherin	miR-193a-5p and Pcdha8		(46)
circ_0001206	CRKL	Inhibit tumor growth	miR-1285-5p and Smad4		(45)
circ-ITCH	ITCH	Inhibit tumor growth	miR-17-5p and HOXB13		(47)
circFoxo3	Foxo3	Inhibit tumor growth, metastasis and chemoresistance to docetaxel			(76)
circ_0004870	RBM39			Biomarker	(69)
C, Renal cancer					
circ-AKT3 (circ_0017252)	AKT3	Inhibit tumor growth and metastasis	miR-296-3p and E-cadherin		(58)
circC3P1	C3P1	Inhibit cell proliferation, migration, invasion and ratio of p/t-PI3K, p/t-AKT, p/t-p65, and p/t-IκBα	miR-21 and PTEN		(56)
cRAPGEF5 (circ_0001681)	RAPGEF5	Inhibit tumor growth and metastasis	miR-27a-3p and TXNIP	OS, RFS	(59)
circUBAP2 (circ_0001846)	UBAP2	Reduce cell proliferation, migration and invasion	miR-148a-3p and FOXK2		(57)

circRNA, circular RNA; BCSC, bladder cancer stem cell; OS, overall survival; DFS, disease-free survival; RFS, recurrence-free survival; miR, microRNA.

that circ_0006260 inhibits tumor progression by upregulating membrane-associated ring finger 1 (MARCH1) in BC, an effect that could be reversed by miR-653. MARCH1 belongs to the E3 ligase family (32). In addition, cyclin D1 and p21, which control the cell cycle, are upregulated by miR-27a-3p and miR-1178-3p, resulting in the facilitation of tumor progression. By contrast, circNR3C1 and circZKSCAN1 act as a sponge for miR-27a-3p and miR-1178-3p to repress the cell development induced by miR-27a-3p and miR-1178-3p, respectively, in BC (33,34).

EMT plays a crucial role in the metastasis of BC (35). Indeed, circ phosphatidylinositol binding clathrin assembly protein (PICALM) inhibits cell metastasis and reduces the expression of β-catenin, vimentin, zinc finger E-box binding homeobox 1 (ZEB1), Slug and N-cadherin, which were found to be associated with EMT in BC; however, those effects could be reversed by miR-1265. circPICALM is derived from the PICALM gene (36). Notably, circRNA acts as a double agent in BC. For instance, circ5912 sabotages tumor growth *in vitro* and *in vivo*, and reduces the TGF-β2-induced EMT process. In addition, circ5912 attenuates early stage cancer progression, but promotes cancer development following the occurrence of distant metastasis (Fig. 2) (37).

3. circRNAs in PCa

circRNAs act as an oncogene in PCa. The circRNA-miRNA-mRNA axis plays a vital role in PCa progression. A disintegrin and metalloprotease 17, as a downstream of the Notch signaling pathway, was found to be highly expressed in PCa and to increase cell proliferation and invasion. Notably, its effect could be promoted by circ homeodomain interacting protein kinase 3 (HIPK3) or impaired by miR-338-3p. circHIPK3 is derived from the HIPK3 gene (5). Another study demonstrated that circZNF609 enhances PCa cell growth and metastasis, and increases the ratio of p/total-AMP-activated protein kinase (AMPK) by upregulating miR-186-5p, which promoted tumor progression through the activation of the AMPK signaling pathway (38). Furthermore, forkhead box p4 (FOXP4), a member of the FOXO family, was found to promote PCa progression *in vitro*, an effect that could be reversed by miR-1182 or enhanced by circ ATP-binding cassette subfamily C member 4 (ABCC4). circABCC4 (circ_0030586) is derived from the ABCC4 gene (Table I) (39).

circRNAs also interact with RBPs in PCa. Fused in sarcoma (FUS), a nuclear DNA/RNA-binding protein that regulates different steps of gene expression, acts as an oncogene in multiple cancer types (40), is overexpressed in PCa, and by binding to circ0005276, upregulates X-linked inhibitor of apoptosis (XIAP), the host gene of circ0005276. Furthermore, XIAP and circ0005276 enhance tumor growth and improve the expression of N-cadherin in PCa (41). circHIPK3 facilitates the G_2/M transition of PCa cells by modifying cell division cyclin 25, which causes G_2/M cell cycle arrest (42). In addition, circ102004 promotes PCa tumor growth *in vitro* and *in vivo* by increasing the levels of p-ERK, p-AKT, p-JNK, JNK and β-catenin, which have been found to be positively correlated with tumor aggressiveness; circ102004 is derived from oncogene ubiquitin-specific peptidase 22 (Fig. 2) (43).

circRNAs act as a tumor suppressor in PCa. Previous evidence has confirmed that Smad4, as a central mediator of the TGF-β signaling pathway, represses androgen receptor (AR) transactivation and exhibits low expression in PCa (44). circ_0001206 is derived from the CRKL gene, and was found to reduce PCa development by regulating Smad4; however, this effect could be reversed by miR-1285-5p (Fig. 2) (45). circRNA also acts as a reservoir for miRNA in PCa. For example, circRNA17 (circ_0001427) enhances the function of miR-181c-5p to suppress AR-splicing variant 7 (ARv7) expression and improves the ability of miR-181c-5p to inhibit tumor progression. ARv7 has been found to be positively correlated with enzalutamide resistance in PCa (11).

circRNA can both sponge miRNA and interact with RBPs in PCa. For instance, P53 and RNA-binding protein 25 (RBM25; a transcriptional target of p53) increase the expression of circ_000350 [circ angiomotin-like 1 (circAMOTL1L)] in PCa. circAMOTL1L and RBM25 impair cell mobility and diminish the level of vimentin and β-catenin in PCa. circAMOTL1L is derived from the AMOTL1 gene. In addition, circAMOTL1L inhibits tumor growth and enhances the expression of protocadherin α8 (Pcdha8) in PCa; however, these effects could be reversed by upregulating miR-193a-5p or depleting p53. Pcdha8 is a tumor suppressor and a member of a subset of the cadherin superfamily (Table II) (46). In addition, circ itchy E3 ubiquitin protein ligase-overexpression reduces PCa growth by sponging miR-17-5p to rescue the degradation of homeobox protein Hox-B13 (HOXB13) *in vitro* and *in vivo* (47). HOXB13 has been verified to act as an oncogene in PCa.

4. circRNAs in RCC

circRNAs act as an oncogene in RCC. The activation of the EMT process and VEGF signaling pathway contributes to tumor initiation (48). The expression of ZEB2 is upregulated by circ pecanex 2 (PCNXL2) or downregulated by miR-153 in RCC. In addition, circPCNXL2 (circ_406752) is derived from the PCNXL2 gene, and enhances tumor growth *in vitro* and *in vivo*, while its effect can be reversed by miR-153 (49). The expression of N-cadherin, Snail and vimentin could be increased by circ proline rich coiled-coil 2A (PRRC2A) and circ myosin light chain kinase (MYLK), which abolish the tumor suppression effect of miR-514a-5p/miR-6776-5p and miR-513a-5p, respectively, in RCC. In addition, circPRRC2A and circMYLK have been shown to facilitate tumor progression by upregulating transient receptor potential cation channel subfamily M member 3 (TRPM3) and VEGFC, respectively. TRPM3 has been reported to act as an oncogene in metastatic RCC. VEGFC is a member of the VEGF family and circPRRC2A is derived from the PRRC2A gene (Fig. 2) (50,51). Chromobox 4, as a SUMO E3 ligase, upregulates the level of VEGFA, and represses cell growth and metastasis in RCC following circTLK1-silencing or miR-136-5p-overexpression. Circ tousled-like kinase 2 (TLK1; circ_0004442) is derived from the back-splicing of the TLK1 mRNA (52).

The abnormal activation of transcription factors promotes the proliferation and differentiation of tumor cells (24). For example, SRY-box transcription factor 12

(SOX-12), which was overexpressed in ccRCC, was upregulated by circ_001895 or downregulated by miR-296-5p. Furthermore, the high expression of circ_001895 led to increased tumor growth and metastasis by regulating SOX-12, and improving the expression of N-cadherin, while those effects could be reversed by miR-296-5p (53). The interferon regulatory factors (IRFs) are a family of master transcription factors that regulate pathogen-induced innate and acquired immune responses (54). By contrast, the IRF7 overexpression in RCC was found to facilitate tumor progression *in vitro*, and to be increased by circ-egl-9 family hypoxia inducible factor 3 (EGLN3) or repressed by miR-1299; circ-EGLN3 (circ_0031594) is derived from the EGLN3 gene (Table I) (55).

circRNAs act as tumor suppressors in RCC. Cell signaling transduction plays a vital role in the occurrence of RCC. circ complement component 3 precursor pseudogene (C3P1) is derived from exons 27-29 of the complement component 3 precursor pseudogene, decreases the ratio of p/total-PI3K, p/t-AKT, p/total-p65 and p/total-IκBα, promotes the expression of Bcl-2, cleaved caspase-3 and cleaved caspase-9, and consequently inhibits tumor progression in kidney cancer. These circC3P1-induced effects could be reversed by the upregulation of miR-21 through targeting PTEN in RCC (Fig. 2) (56). FOXK2 was found to translocate to the nucleus, be dependent on the AKT-mTOR signaling pathway, be expressed at a low level in ccRCC, and impair tumor cell proliferation and metastasis; however, its effect could be enhanced by circ_0001846 or attenuated by miR-148a-3p (57).

Notably, circRNAs can sponge miRNAs to protect RBP degradation in RCC. The overexpression of circ-AKT3 leads to the inhibition of tumor growth and metastasis, and sponges miR-296-3p to avoid the mRNA degradation of E-cadherin. circ-AKT3 (circ_0017252) is derived from the AKT3 gene locus (58). circ Rap guanine nucleotide exchange factor 5 (RAPGEF5; circ_0001681) is derived from the RAPGEF5 gene, and could be upregulated by thioredxin interacting protein (TXNIP) or downregulated by miR-27a-3p in RCC cells. circRAPGEF5 overexpression leads to a repressive effect on the progression and aggressiveness of RCC by upregulating TXNIP; however, these effects could be reversed by miR-27a-3p. In addition, patients with RCC and high circRAPGEF5 expression have been associated with an improved overall survival (OS) and recurrence-free survival (RFS) rate (Table II) (59).

5. circRNAs act as biomarkers for the diagnosis and prognosis of BC, PCa and RCC

In the past few decades, tumor diagnosis and prognosis have largely depended on radiography testing and pathological examinations. Nowadays, circRNA also acts as a biomarker for the diagnosis and prognosis of urological neoplasms. For example, circEGLN3 can distinguish ccRCC from normal tissues with 97% accuracy (60). circRNAs abundantly exist in exosomes of patients with urological cancer, which indicates that they can play a diagnostic role in liquid biopsies. The level of circ protein tyrosine kinase 2 (circ_0003221) was increased in the lymph nodes of a nude mouse model and *in vivo*, as well as in the blood of patients with BC, and promoted the progression of BC (61). Similarly, the expression of circ_0044516, circFOXO3 and circ formin 2 (circ_0005100) was increased in the blood of patients with PCa, and promoted tumor progression by sponging miR-29a-3p and miR-1238, respectively (Table I) (62-64).

circ protein arginine methyltransferase 5 (PRMT5; circ_101320) and circ_0001445 have been shown to facilitate the progression of BC by sponging miR-30c and miR-107, respectively. Furthermore, patients with BC and a high level of circPRMT5 and circ_0001445 displayed poor disease-free survival (DFS) and OS rate (65,66). The overexpression of circ_0085576 has been shown to increase RCC tumor progression following Yes1-associated transcriptional regulator upregulation and miR-498-silencing. In addition, patients with ccRCC and a high level of circ_0085576 had a poor OS and DFS rate; circ_0085576 is derived from the ArfGAP with SH3 domain ankyrin repeat and PH domain 1 gene (67). By contrast, circ_0004826 and circ_0077837, which are spliced from the utrophin and erythrocyte membrane protein band 4.1-like 2 genes, respectively, are usually expressed at a low level in BC, inhibit tumor cell development and act as a biomarker for OS and RFS in patients with BC (Table II) (68). circRNAs can also act as biomarkers for the effect of drug treatment. circ_0004870 is an exonic circRNA located on chromosome 20, which has been found to be downregulated in enzalutamide-resistant cells and expressed at a low level in an AR-positive cell line (LNCaP clone 1/9), thus acting as a biomarker for the effect of enzalutamide treatment in PCa (69)

6. circRNAs act as therapeutic targets for BC, PCa and RCC

The overexpression of circ_0084171 and circELP3 result in an increase in tumor growth and promotion of cisplatin resistance in BC. In addition, circ_0084171 improves the expression of p-ERK1/2 and p-MEK1/2 in BC, while those effects could be reversed by miR-370-3p (Fig. 2) (70,71). Furthermore, circ_0039569 is derived from the C-C motif chemokine ligand 22 (CCL22) gene, is highly expressed in RCC and promotes tumor development after sponging miR-34a-5p or over-regulating CCL22. Furthermore, the inhibition of circ_0039569 may enhance the drug sensitivity of RCC cells; however, the study suggesting this did not provide any details to prove it (Table II) (72).

By contrast, the overexpression of CDR1 antisense RNA (Cdr1as; circ_0001946) and circ-Foxo3 has been shown to increase cell apoptosis and decrease cisplatin chemoresistance reduced by miR-1270 and miR-191 in BC, consequently suppressing tumor development. circ-Foxo3 is derived from FOXO3 mRNA, and Cdr1as is formed by back-splicing of the cerebellar degeneration-related protein 1 gene (73,74). A different study illustrated that the overexpression of circHIPK3 has been shown to lead to an increased sensitization of BC cells to gemcitabine and act as a biomarker for DFS in patients with BC (75). In addition, the apoptosis and chemosensitivity of docetaxel in androgen-dependent PCa cells could be increased by the overexpression of circFoxo3. Furthermore,

the upregulation of circfoxo3 enhanced the chemosensitivity of PCa-bearing mice to docetaxel and prolonged the life span of these mice (Table II) (76).

7. Conclusion

In conclusion, circRNAs, as a family of non-coding RNAs that can form a loop with joined 3'heads and 5'tails, are characterized by abundant, highly stable, evolutionarily conserved and tissue-specific expression. Several studies have shown that circRNAs play a crucial role in tumor growth, metastasis and treatment resistance (12). circRNAs have shown an ability to help determine the pathogenesis, and serve as a biomarker for the diagnosis and prognosis, of urological cancer. Clinical trials using treatment and diagnostic methods involving circRNAs are now being conducted, including trials in hepatocellular carcinoma and myocardial infarction (77,78). However, a number of limitations in the recently published studies of circRNAs were identified. For example, circZNF139 and circ-ZKSCAN1 are identical circRNAs that are known as circ_0001727, but display opposite roles in BC (23,34). In addition, circ-Foxo3 serves as both an oncogene and tumor suppressor in PCa (63,76), and circ5912 serves as a double agent in BC (37). Therefore, the function of circRNAs in tumors of the urinary system remains largely unclear and further research is required.

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Availability of data and materials

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Authors' contributions

LY reviewed the publications and drafted the manuscript. LY and JZ designed and drew the diagram. GZ and XZ revised the manuscript and confirmed the authenticity of all the raw data. All authors read and approved the final version of the manuscript.

Ethics approval and consent to participate

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Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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