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The Recent Research Progress of CircRNA in Bladder Cancer

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Abstract

Bladder cancer is a major public health problem in the world, and is one of the most common malignant tumors in the genito-urinary system. Due to its high incidence and mortality, it remains a serious threat to human health. In recent years, related researches on the occurrence of bladder cancer found a certain connection between the expression level of circRNA and development of bladder cancer. circRNA can accomplish the purpose of promoting or inhibiting the occurrence and progression of bladder cancer by affecting the expression of related miRNA and mRNA. Higher expression levels of some circRNAs such as circITCH, circACVR2A, circPICALM, and circZKSCAN1 demonstrate an improved prognostic survival of patients with bladder cancer. Higher expression of circBPTF and circPRMT5 correlated with worse prognosis in bladder cancer patients. This article highlights a relationship between CircRNA and bladder cancer.

Key words circRNA, miRNA, ceRNA, bladder cancer

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Introduction

With the scientific progress and the improvement in medical technology, number of diseases have been effectively prevented, and the overall health in the population has improved significantly. However, there are still several diseases that needs medical attention. Among them, solid tumors and their recurrence has been a major public health problem. Bladder cancer (Bca) is one of the most common malignant tumors in the genito-urinary system with a high recurrence rate and mortality [1], however the pathogenesis of Bca has not been fully elucidated. Protein-coding genes account for only 1%-2% of active transcription in the human genome, and most of the active transcription is non-coding RNA (ncRNA) that does not encode proteins [2]. With the progress in research, the role of a large number of ncRNAs in the occurrence and development of Bca has been confirmed [3-5]. The newly discovered circRNA is a regulatory endogenous ncRNA with a unique covalent loop structure, which is stable, conservative, and tissue-specific. It is expected to become a new marker and therapeutic target for tumor diagnosis and promote the development of precision medicine. This article highlights the latest research progress of circRNA in Bca, aiming to provide a new direction for in-depth study of the molecular mechanism of Bca occurrence and metastasis.

Bladder cancer

Concepts on bladder cancer and epidemiology characteristics

Bladder cancer (BC) refers to malignant tumor(s) that occurs on the bladder mucosa, and is mainly divided into three types: urinary epithelial cancer, squamous carcinoma, and adenocarcinoma. The highest percentage is urinary epithelial cancer, accounts for about 90% of total bladder cancer [1, 6]. According to statistics, bladder cancer is one of the most common malignant tumors in the urogenital system. It is ninth in position among the common cancer incidence in the world. It is the thirteenth for the cause of cancer-related death [7]. In China, the incidence and mortality of bladder cancer is first among the urinary system tumors, and with the advancement and changes in the lifestyle habits, the incidence and detection rate of bladder cancer has been increasing year by year [7, 8].

Diagnosis and treatment methods for bladder cancer in clinic

At present, there are numerous screening methods for bladder cancer clinically, such as urine cytological examinations, optical imaging, tumor marker testing, imaging examination, cystoscopy, biopsy, diagnostic transurethral resection of bladder tumor (TURBT) with surgery pathological examinations [9]. Among them, cystoscopy is a gold standard for the diagnosis of bladder cancer, and is very important especially before the resection of bladder tumor, which is essential for the complete resection of the bladder tumor during surgery. However, standard white light cystoscopy might miss up to 20% of bladder tumors [10]. Most common treatment methods for bladder cancer are surgical resection, which mainly include TURBT, radical cystectomy, bladder perfusion therapy, bladder irrigation immunotherapy etc. For poorly differentiated and partial well-differentiated bladder urinary epithelial cancer, TURBT remains the first choice. However, the recurrence rate within one year was 50% for high-risk bladder cancer after surgery, and the recurrence rate within 5 years after surgery remains high up to 90% [11, 12]. Therefore, a problem exists due to the long treatment duration and high postoperative recurrence rate. High interest in recent years and focus remains on fast, and accurate bladder cancer screening and diagnosis methods. Among them, the abnormal expression of circRNA may play an important role in the development of bladder cancer, and has certain application prospects in the diagnosis and treatment of bladder cancer.

CircRNA

CircRNA concept

The Sanger team discovered a new RNA molecule in the virus in 1976, which was named CircRNA [13]. CircRNA is a category of closed single-chain with covalent and without 5'-hats and 3'-polya tails. It is composed of exon and/or intron, which is not degraded by RNA exonuclease. It is one of the non-coded RNAs, and existed in the cells, serum exogenous bodies, and saliva having a huge potential for regulatory control [14, 15]. Researches found that CircRNA participated in the occurrence and development of cancer, high stability, and evolution conservative characteristics [16].

CircRNA biological occurrence and mechanism

CircRNA organisms mainly include four models: Splice looping of the exon lariat, Looping of intron pairs, Splice looping of the inner ring daughter lariat, Splice looping of internal ring rope, cyclization driven by RNA-binding proteins or trans factors [17]. Most circRNAs are encoded by known protein-coding genes and fall into three categories based on their structural composition: exon circRNA(EcircRNA), annular intron RNA(ciRNA), and exon-intron circRNA(EIciRNA) [18].

CircRNA plays different biological functions in different biological processes, mainly including five aspects [19]: (1) circRNA can be used as "molecular sponge", which is competitively combined with some miRNA (microRNA). To a certain extent, inhibitory effect of miRNA on mRNA indirectly promotes the expression of the target mRNA; (2) The complexes of circRNA combining with small ribonucleoprotein particles (snRNP) can further interact with RNA polymerase, to regulate the gene transcription; (3) CircRNA can interact with certain proteins to affect its function; (4) Some CircRNAs can translate into protein and performed some or other functions of the host gene; (5) CircRNA is a single-chain ring structure, which can form a dual chain structure with some mRNAs, thereby adjusting the expression of mRNA. Among them, circRNA as a "molecular sponge" combines some miRNA to promote the expression of target mRNA [20]. This is regarded as competing endogenous RNAS (ceRNA) early, that is, the ceRNA mechanism. In the ceRNA mechanism, circRNA and mRNA, which have a binding site with the same miRNA, have a positive adjustment relationship, which can indirectly predict the expression trend of target mRNA through the expression trend of circRNA, and vice versa [21-23].

Figure 1 shows the circRNA classification and mechanism of circRNA acting as a miRNA molecular sponge.

CircRNA plays a role in bladder cancer through the ceRNA mechanism

With the intensive study of identification of ceRNA and their role, it is found that multiple circRNAs can play a role in bladder cancer through the ceRNA mechanism. Here, we list some circRNAs that can play a role in bladder cancer through the ceRNA mechanism. **Table 1** shows the summary on circRNA associated with cancer. **Figure 2** shows that circRNAs regulate cell proliferation, apoptosis, invasion, migration and metastasis, angiogenesis, and cisplatin chemoresistance in BCa cells.

Study of partial tumor suppressor circRNA in bladder cancer

circHIPK3. circBCRC-2 (bladder cancer-related circular RNA-2, circBCRC-2), also known as circHIPK3, is a ring-shaped RNA that is mainly existed in the cytoplasm, which is formed by splicing of exons of the HIPK3 gene. In vitro, the excessive expression can effectively inhibit the migration and invasion of the bladder cancer cells. Its low expression level positively correlate with highly grade tumors and lymphatic metastasis in bladder cancer. circHIPK3 mainly utilizes the expression of heparanase (HPSE), which is used as a "molecular sponge", and plays the role of cancer suppressor gene in bladder cancer [24, 25].

circBCRC-3. circBCRC-3 (bladder cancer-related circular RNA-3, circBCRC-3) is a ring-shaped RNA derived from the PSMD1 gene. Over-expression can inhibit the proliferation of bladder cancer cells. circBCRC-3 mainly promotes the expression of the P27 through the "molecular sponge" as the "molecular sponge" of the MIR -182-5P and plays the role of cancer suppressor gene [24-27].

circUBXN7. circUBXN7 (hsa_circ_001380) is a circular RNA that expresses significantly down in the bladder cancer tissue and cell lines, and its lower level is positively related with bladder cancer staging, grading, prognosis. Excessive expression of circUBXN7 in vitro can significantly inhibit the cell proliferation, migration and invasion. Excessive expression of cancer cells in the body can inhibit tumor growth. circUBXN7 is mainly used as the expression of recombinant human beta-1, 4 -galactosyltransferase3 (B4GALT3) to play a role of cancer suppressor gene [28].

circSLC8A1. circSLC8A1 is a ring-shaped RNA that is significantly downregulated in bladder cancer tissue, which can inhibit proliferation, migration and invasion of bladder cancer cells. Its low expression is positively associated with bladder cancer, which are mainly used as 'molecular sponge' of miR-494 to adjust the expression of PTEN and plays the role of cancer [29].

circITCH. circITCH is the famous circular RNA that is formed by splicing of ITCH (itchy E3 ubikuitin protein ligase) gene exon. The expression of circITCH is significantly lowered in bladder cancer tissue and cell lines. Its excessive expression inhibits proliferation, migration, and invasion in bladder cancer cells. High expression of circITCH also results in tumor growth and metastasis, and its expression level is proportional to the healing survival time in the bladder cancer. circITCH adjusts the suppressor genes role of p21 and PTEN (P21 and phosphatase tensin homologue) in bladder cancer, which mainly through the "molecular sponge" of MIR -17 and MIR -24 [30].

circACVR2A. circACVR2A (HSA_CIRC_ 001073) is a ring-shaped RNA that is mainly located in the cytoplasm. It is expressed at lower level in the bladder cancer tissue and cell lines. Overexpression of circACVR2A significantly inhibits proliferation, migration and invasion of bladder cancer cells. In vivo, overexpression can inhibit tumor growth and lymphatic metastasis, and its low expression has a certain correlation with poor healing. circACVR2A is mainly targeted by the "molecular sponge" as the mir-626 (eyes absent 4, EYA4), thereby playing the role of cancer suppressor gene [31].

circPICALM. circPICALM is mainly from the cell transcripts of PICALM gene exon 9 to 12. Its expression is downregulated in bladder cancer tissue and cancer cell lines. Overexpression of circPICALM results in significant inhibition in the migration and invasion ability of bladder cancer cells. Its low expression positively correlate with the pathological staging, classification, and lymph node metastasis of bladder tumors. It also has a certain correlation with overall survival of patients with bladder cancer. It is projected as a putative prognostic biomarker before bladder cancer resection. circPICALM mainly regulates the expression of STEAP4 (six transmembrane epithelial antigen of the prostate 4, STEAP4) by 'molecular sponge' of MIR-1265, and play a role in the role of cancer suppressor gene in bladder cancer [32].

circZKSCAN1. circZKSCAN1 is a ring-shaped RNA, which is mainly located in the cytoplasm. It expression is lowered in bladder cancer tissue and cell lines. Forced expression can inhibit proliferation, migration and invasion of bladder cancer cells, however its lower expression is positively associated with poor tumor survival rate, high recurrence, and positive tumor metastasis. circZKSCAN1 mainly regulates the expression of p21 through the 'molecular sponge' as miR -1178-3P, and play a role in the cancer suppressor gene in bladder cancer [33].

circMTO1. circMTO1 is an important circRNA frequently downregulated in bladder cancer tissue. Lower circMTO1

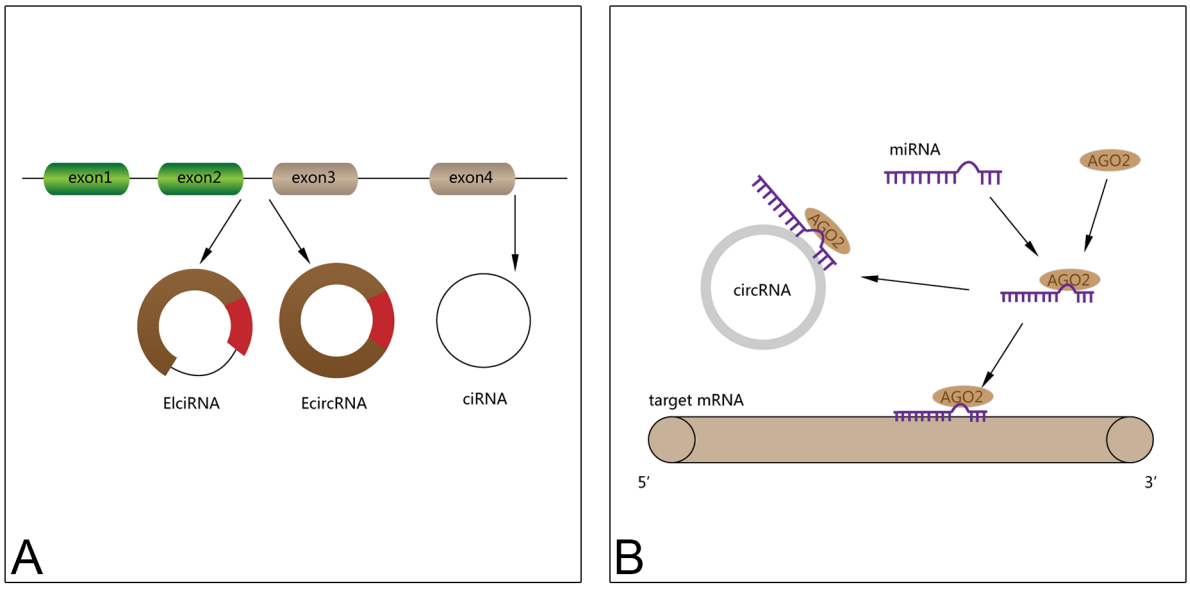

Figure 1. Schematic diagram for circRNA classification (A) and mechanism of circRNA acting as a miRNA molecular sponge (B).

expression positively correlate with bladder cancer metastasis and poor survival. It was shown that circMTO1 was able to sponge miR-221 and overexpression of circMTO1 negatively regulate the E-cadherin/N-cadherin pathway to inhibit bladder cancer cells EMT by competing for miR-221 [34].

NR3C1. It was demonstrated that circNR3C1 possessed four targeting sites of miR-27a-3p and could effectively sponge miR-27a-3p to suppress the expression of cyclin D1, which can inhibit cell cycle progression and proliferation of bladder cancer cells [35].

CRIM1. circCRIM1could effectively sponge miR-182 to suppress the expression of Foxo3a, which can inhibit invasion and migration of cancer cells to some extent [36].

Study of cancer-promoting circRNAs in bladder cancer

circVANGL1. CIRCVANGL1 (HSA_CIRC_002623) is a ring-shaped RNA and its expression is high in the bladder cancer tissue and cell lines. Loss of expression of VANGL1 in vitro can inhibit the proliferation, migration, and invasion of bladder cancer cells. Mechanistically, circVANGL1 promotes IGFBP2 (insulin like growth factor binding protein 2, IGFBP2) to promote the role of cancer genes through the miR-114 'molecular sponge' [37].

circUVRAG. circUVRAG is a ring-shaped RNA mostly found in cytoplasm with high expression in bladder cancer cell lines. Knockdown of circUVRAG in bladder cancer cells resulted in the inhibition of tumor growth, metastasis in mouse xenograft model. circUVRAG is essentially used as the 'molecular sponge' of miR-223 to adjust FGFR2 (Fibroblast growth factor receptor 2, FGFR2) [38].

circTFRC. circTFRC is a ring-shaped RNA expressed in the bladder cancer tissue and cell lines. High expression of circTFRC promote proliferation, invasion and induction of epithelial-mesenchymal transition (EMT) of bladder cancer cells; whereas higher levels positively correlate with the s tumor grading, T staging and lymphatic metastasis in bladder cancer patients. circTFRC regulates the role of TFRC (transferin receptor, TFRC)

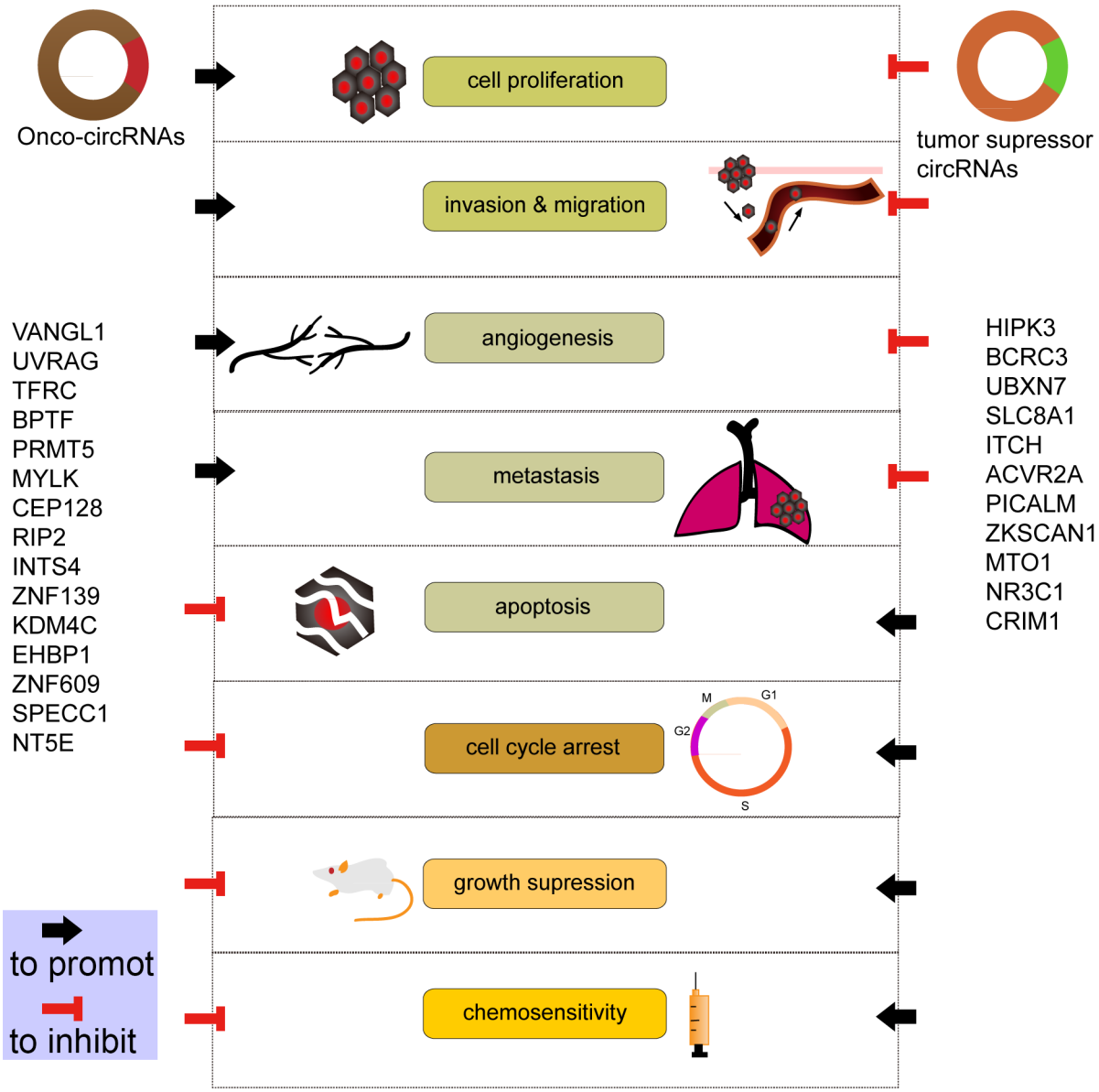

Figure 2. circRNAs regulate cell proliferation, apoptosis, invasion, migration and metastasis, angiogenesis, and cisplatin chemoresistance in BCa cells.

Table 1. Summary on circRNA associated with cancer.

Classification	circRNA	ceRNA	Target gene	Function	References
Tumor supressor circRNAs	HIPK3	miR-588	HPSE	To inhibit cancer cell migration, invasion and angiogenesis	[24, 25]
	BCRC3	miR-182-5p	p27	To inhibit the growth and proliferation of cancer cells and induced G0/ G1 phase arrest	[24-27]
	UBXN7	miR-1247-3P	B4GALT3	To inbibit cancer cell proliferation, migration, invasion and tumor growth	[28]
	SLC8A1	miR-130b,miR-494	PTEN	To inhibit cancer cell proliferation, migration, invasion and tumor growth	[29]
	ITCH	miR-17/miR-224	P21/PTEN	To inhibit cancer cell proliferation, migration, invasion, tumor growth and metastasis	[30]
	ACVR2A	miR-626	EYA4	To inhibit cancer cell proliferation, migration, invasion, tumor growth, lymphatic metastasis	[31]
	PICALM	miR-1265	STEAP4	To inhibit cancer cell migration, invasion and lymphatic metastasis	[32]
	ZKSCAN1	miR-1178-3P	p21	To inhibit the proliferation, migration and invasion of cancer cells and induced G1/ S phase arrest	[33]
	MTO1	miR-221	E-cadherin/ N-cadherin pathway	To inhibit bladder cancer cells' EMT by competing for miR-221	[34]
	NR3C1	miR-27a-3p	cyclin D1	To inhibit cell cycle progression and proliferation of bladder cancer cells in vitro, as well as suppress tumor growth in vivo	[35]
Onco-circRNAs	VANGL1	miR-1184	IGFBP2	To promote the proliferation, migration and invasion of cancer cells	[36]
	UVRAG	miR-223	FGFR2	To promote cancer cell proliferation, metastasis, tumor growth	[37]
	TFRC	miR-107	TFRC	To promote cancer cell proliferation, invasion, lymphatic metastasis, and induces EMT of bladder cancer cells	[38]
	BPTF	miR-31-5p	RAB27A	To promote cancer cell migration and invasion	[39]
	PRMT5	miR-30c	SNAIL1	To promote cancer cell migration, invasion, lymphatic metastasis, and induces EMT of bladder urothelial cancer cells	[40]
	MYLK	miR-29a	VEGFA	To accelerate cell proliferation, migration, tube formation of HUVEC and rearranged cytoskeleton	[41]
	CEP128	miR-145-5p	SOX11	To further promote cell proliferation and inhibits cell apoptosis of bladder cancer	[42, 43]
	RIP2	miR-1305	TGF-β2	Effective circRIP2 activity accelerates bladder cancer progression via inducing EMT	[44]
	INTS4	miR-146b	CARMA3	To control multiple pathological processes, including cell proliferation and migration, the cell cycle and apoptosis to promotes tumorigenesis in bladder cancer	[45]
	ZNF139	-	PI3K/AKT pathway	To promote cell proliferation, migration and invasion via activation of PI3K/AKT pathway in bladder cancer	[46]

through the 'molecular sponge' of MIR-107, and play a role in oncogenes in bladder cancer [39].

circBPTF. circBPTF (hsa_circ_0000799) is a ring-shaped RNA from the reverse editing of the precursor gene BPTF (Bromodomain PHD finger transcription factor, BPTF). It is located in the cytoplasm of tissues and cell lines. Over-expression of circBPTF significantly promotes migration of bladder cancer cells and high circBPTF expression is associated with poor survival, higher tumor grade and tumor recurrence rate of patients with bladder cancer. circBPTF regulates the role of Rab27 (Ras -Related protein Rab-27A, RAB27A) through the 'molecular sponge' of miR-31-5p [40].

circPRMT5. circPRMT5 is a ring-shaped RNA increased in cancer tissue, serum, and urinary exosomes of the patients with urothelial carcinoma. circPRMT5 positively correlates with poor survival such as advanced clinical stage of patients and the decrease in/or decreased survival rate, which can predict the lymphatic metastasis. circPRMT5 indirectly adjusts SNAIL1 (recombinant snail homolog 1) by 'molecular sponge' of MIR-30C. A study found that the expression of circPRMT5 is not significantly increased in other human cancers. The result indicates that circPRMT5 expression in urothelial carcinoma may be tumor-specific. Therefore, circPRMT5 may become a specific biomarker that predicts lymphatic metastasis in urothelial carcinoma [41].

circRNA-MYLK. circRNA-MYLK and VEGFA have been shown to significantly upregulate and co-expressed in bladder cancer. circRNA-MYLK levels were related to the progression stage and grade of bladder cancer. circRNA-MYLK could directly bind to miR-29a and release the suppression for target VEGFA, which activates VEGFA/VEGFR2 signaling pathway. Increased expressing circRNA-MYLK accelerated cell proliferation, migration, tube formation of HUVEC and rearranged cytoskeleton. In addition, up-regulating circRNA-MYLK promoted epithelial-mesenchymal transition (EMT) [42].

Circular RNA CEP128. circCEP128 acts as a ceRNA for miR-145-5p, which could upregulate SOX11 and further promotes cell proliferation and inhibits apoptosis of bladder cancer cells [43, 44].

RIP2. In vitro and in vivo studies suggest that circRIP2 enables to promote bladder cancer progression via inducing EMT. It was found that circRIP2 enables to sponge miR-1305 to elevate Tgf-β2 in bladder cancer, and inducing EMT via TGF-β2/smad3 pathway [45].

INTS4. circINTS4 was found to control multiple pathological processes, including cell proliferation and migration, cell cycle and apoptosis promoting bladder tumorigenesis. circINTS4 directly binds to miR-146b to inhibit its activity by targeting 3'-UTR of CARMA3 mRNA. In addition, circINTS4 could activate the NF-kB signaling pathway and suppress the p38-MAPK signaling pathway in a CARMA3-mediated manner in bladder cancer cells [46].

ZNF139. Bioinformatics research suggests that ZNF139/circZNF139 facilitates its effects on the proliferation, clonal expansion, migration, and invasive potential of bladder cancer cells [47].

KDM4C. circKDM4C directly interacts with miR-200b-3p and miR-200c-3p as a miRNA sponge, enhancing the expression of ZEB1 and promotes mesenchymal phenotype [48].

EHBP1. Mechanistically, circEHBP1 overexpression promote TGFbR1 expression by attenuating miR-130a-3p to activate the TGF-b/SMAD3 signaling pathway, further elevating VEGF-D secretion and ultimately facilitating lymphangiogenesis and lymph node metastasis in bladder cancer [49].

ZNF609. In bladder cancer patients, increased expression of circZNF609 correlate with poor survival. In vitro and in vivo, forced expression of circZNF609 enhance bladder cancer cell proliferation, migration, and cisplatin chemo-resistance. Mechanistically, circZNF609 alleviated the inhibition effect on target CDC25B expression by sponging miR-1200 [50].

SPECC1. Increased expression of circSPECC1 contribute to poor prognosis of bladder cancer. Knockdown of circSPECC1 impairs proliferation and migration of bladder cancer cells. Mechanically, circSPECC1 sponge miR-136-5p to promote the mRNA and protein expression of GNAS [51].

NT5E. Decreased miR-502-5p reversed the circNT5E silencing-mediated inhibition of bladder cancer cell growth and migration. The study suggested that circNT5E may act as a pro-oncogene in the development and progression of bladder cancer and it may become a useful tumor biomarker and promising therapeutic target for treatment [52].

Conclusion

Studies from circRNA highlighted in bladder cancer demonstrate that the expression of circRNA may be related to biological behavior (proliferation, migration, invading), pathological staging or typing (differentiation level, pathological staging and lymph nodes), and prognosis of survival status in bladder cancer patients. Among the above mentioned various bladder cancer-related circRNA, circITCH, higher expression levels of circACVR2A, circPICALM, circMTO1, circNR3C1 and circZKSCAN1, exhibit better prognostic survival status of patients with bladder cancer. Higher levels of circBPTF and circPRMT5 correlate with the worse prognosis in bladder cancer patients. This result suggests that screening, diagnosis, and prognosis of bladder cancer can be performed on circRNA at the same time, which will increase the accuracy of the results. Among them, the carcinogenic effect of circPRMT5 may be a specific event in bladder cancer, which is expected to be developed as a specific biomarker related to bladder cancer. Mechanistic studies on circRNA's in bladder cancer suggest and indirect control downstream target mRNA by 'molecular sponge' as related miRNA, that is, circRNA-miRNA-mRNA type ceRNA mechanism pathway. This mechanism path explores the cause of the incidence of bladder cancer from the perspective of multi-gene synergy, which could provide new ideas for the diagnosis and treatment of bladder cancer. But how to achieve individualized diagnosis and treatment of bladder cancer by detecting the level of specific circRNA expression levels, further research is still needed.

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Ethical policy

All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. Informed consent was obtained from all individual participants included in the study. Approval from institutioalethical committee was taken.

Availability of data and materials

All data generated or analysed during this study are included in this publication.

Author contributions

SL designed the study and was responsible for the writing of the original draft. XLX and SL edited and approved the final

manuscript.

Competing interests

All authors declare no competing interests.

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