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Current Status of Functional Studies on Circular RNAs in Bladder Cancer and their Potential Role as Diagnostic and Prognostic Biomarkers: A Review

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Worldwide, bladder cancer represents the ninth most common malignancy and is the 13th cause of cancer-associated death. Although surgery combined with chemotherapy and radiotherapy has improved patient outcomes, the prognosis remains poor for most patients with muscle-invasive bladder cancer. The exact mechanisms and critical regulators of bladder cancer remain unknown. Circular RNAs (circRNAs) are a distinct type of endogenous non-coding RNA. Recent studies have shown that circRNAs participate in many processes, including proliferation, invasion, migration, and apoptosis in multiple types of malignancy, including bladder cancer. Some circRNAs are dysregulated in bladder cancer and play essential roles in cancer progression. Importantly, some circRNAs may serve as diagnostic and prognostic biomarkers for bladder cancer. This review aims to summarize the findings from recent studies that have focused on the roles of human circRNAs in bladder cancer and discusses the clinical roles for circRNAs, including their potential roles as diagnostic or prognostic biomarkers.

MeSH Keywords: Biological Markers • Diagnosis • Prognosis • Urinary Bladder Neoplasms • Carcinoma, Transitional Cell • RNA, Untranslated

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Background

Worldwide, bladder cancer represents the ninth most common malignancy and the 13th cause of cancer-associated death [1]. In the USA, an estimated 81,190 cases of bladder cancer were diagnosed in 2018 and resulted in the death of 17,240 patients [2]. The most prevalent subtype of bladder cancer is urothelial or transitional cell carcinoma, which accounts for more than 90% of cases. About 70% of urothelial carcinomas are diagnosed as non-invasive or *in-situ* carcinomas, and the remaining 30% are diagnosed as muscle-invasive carcinomas, which are associated with a worse prognosis when compared non-invasive type or *in-situ* carcinoma of the bladder [3]. For patients with the non-invasive type, transurethral resection of the bladder cancer followed by subsequent treatment with Bacillus Calmette-Guérin (BCG) is recommended [4], and chemoradiation-based bladder preservation therapy is recommended for non-metastatic muscle-invasive bladder cancer [5]. Standard diagnostic methods for bladder cancer include cystoscopy, imaging examination, and assessment of urinary biomarkers. Urinary biomarkers may be an effective alternative or adjuvant method to cystoscopy for diagnosis of bladder cancer [6]. Further understanding of the mechanisms underlying the progression of bladder cancer and the identification of diagnostic and prognostic biomarkers are still required to improve clinical outcome for patients with bladder cancer.

Circular RNAs (circRNAs) are endogenous non-coding RNAs, which consist of a closed-loop structure, without a 5' cap and a 3' poly-A tail [7]. CircRNAs were first discovered in 1976 and were initially regarded as by-products of precursor mRNA [8]. Recently, circRNAs were found to be abundant in many species, including viruses, fungi, plants, and animals [9]. Data from previous studies have identified and proposed three classifications for circRNAs: exonic circRNAs (EcircRNAs); intronic circRNAs (ciRNAs); and exon-intron circRNAs (EIciRNAs) [10]. Four main functions have been described for circRNAs. First, EcircRNAs act mainly as microRNA (miRNA) sponges to enhance the expression levels of miRNA-target genes by adsorbing miRNA molecules [11]. For example, circITCH has been found to act as a sponge for miR-7, miR-17, miR-214, and miR-20a to enhance ITCH expression in lung cancer [12], esophageal squamous cell carcinoma [13], and colorectal cancer [14]. Second, ciRNAs and EIciRNAs play essential roles in regulating gene expression. For example, ci-ankrd52 promotes the transcription of its host gene (ANKRD52) by modulating the elongation activity of Pol II [15]. Third, circRNAs regulate the activity of RNA-binding proteins [16]. By interacting with c-myc, circ-Amotl1 promotes c-myc stability and increases the binding affinity of c-myc to promoters that include HIF-1α, Cdc25a, ELK-1, and JUN [16]. Fourth, some circRNAs have been reported to possess the ability to be translated into proteins. Hsa_circ_0001649, produced from the SHPRH gene, has been found to inhibit the tumorigenicity of gliomas by producing the functional protein, SHPRH-146aa [17].

Studies have shown that circRNAs regulate the proliferation, invasion, migration, and apoptosis of multiple types of malignant cells [18]. The most abundant circRNA, ciRS-7, has been reported to be overexpressed and to act as an oncogenic circRNA to promote the proliferation of cancers, including colorectal cancer [19], hepatocellular carcinoma [20], lung cancer [21], and gastric cancers [22]. Also, circPVT1, which is also known as circ6, was found to promote the proliferation of head and neck carcinoma [23], gastric carcinoma [24], acute lymphoblastic leukemia [25], and osteosarcoma [26].

CircRNAs are highly conserved, stable, and specifically expressed in different organisms [27]. They form a covalently closed-loop structure, with resistance to RNA exonucleases and are more conserved and provide more stability than linear RNAs [28]. Also, circRNAs are specifically expressed in different species and organisms and are expressed during different stages of the disease [29]. Xu et al. investigated circRNA expression profiles of six different tissues and showed that each tissue expressed several unique circRNAs (36.92–50.04%), indicating that circRNA expression was tissue-specific [30]. In addition to tumor tissues, quantities of dysregulated circRNAs are present in human plasma, saliva, and circulating exosomes [31–33]. The presence of circulating circRNAs indicate their potential as non-invasive diagnostic and prognostic biomarkers [31–33]. Increasing numbers of circRNAs have been shown to be dysregulated in bladder cancer, and some of them might have future potential as biomarkers for bladder cancer. However, the potential mechanism and biological functions of most circRNAs in bladder cancer remain unknown. Therefore, this review aims to summarize the findings from recent studies that have focused on the roles of human circRNAs in bladder cancer and discusses the clinical roles for circRNAs, including their potential roles as diagnostic or prognostic biomarkers.

Expression of circRNAs in Bladder Cancer

Several studies have shown that circRNAs are dysregulated in bladder cancer. Using whole-transcriptome sequencing, Trine et al. identified 38,360 circRNAs in 457 bladder cancer samples [34]. Based on the location of their splice sites, the circRNAs were classified into four categories: 84.1% were derived from protein-coding exons; 0.9% were from non-coding RNAs; 5.1% were from 5'-untranslated regions (UTRs); and 1.6% were from 3'-UTRs [34]. By performing circRNA expression analysis of five matched bladder cancer samples and normal bladder tissue samples using high-throughput sequencing, Yang et al. identified 56 significantly differentially expressed circRNAs in bladder cancer tissue [35]. Li et al. identified 118

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Table 1. CircRNAs regulates the proliferation and progression of bladder cancer.

CircRNA	Gene symbol	Regulation of circRNA	miRNA sponge	Target gene/pathway	Function	Reference
circMYLK or hsa_circ_0002768	MYLK	Upregulated	miR-29a	VEGFA Ras/ERK signaling pathway	Proliferation(+) Migration(+) Invasion(+) EMT(+) Apoptosis(–)	40
circTCF25 or hsa_circ_0041103	TCF25	Upregulated	miR-103a-3p miR-107	CDK6	Proliferation(+) Migration(+)	41
hsa_circ_0058063	ATIC	Upregulated	miR-145	CDK6	Proliferation(+) Migration(+) Apoptosis(–) Cell cycle arrest(–)	44
circUVRAG or hsa_circ_0023642	UVRAG	Upregulated	miR-223	FGFR2	Proliferation(+) Migration(+)	47
circPTK2 or hsa_circ_0003221	PTK2	Upregulated	–	–	Proliferation(+) Migration(+)	48
circCEP128 or hsa_circ_0102722	CEP128	Upregulated	miR-145-5p	SOX11	Proliferation(+) Apoptosis(–)	49
circINTS4	INTS4	Upregulated	miR-146b	CARMA3	Proliferation(+) Migration(+) Apoptosis(–) Cell cycle arrest(–)	50
Cdr1as or ciRS-7 or hsa_circ_0001946 or Cdr1NAT	CDR1	Down-regulated	miR-135a	–	Proliferation(–) Migration(–) Invasion(–) Cell cycle arrest(+)	55
circHIPK3 or BCRC-2 or hsa_circ_0000284	HIPK3	Down-regulated	miR-558	HPSE	Migration(–) Invasion(–)	62
BCRC-3	PSMD1	Down-regulated	miR-182-5p	CDKN1B	Proliferation(–) Cell cycle arrest(+)	63

circRNAs that were significantly differentially expressed in bladder cancer tissue samples when compared with non-tumor samples [36]. Yan et al. examined circRNA expression profiles in bladder cancer and normal bladder tissue samples using a circRNA-microarray assay and identified seven significantly differentially expressed circRNAs in the bladder tumors [37]. Huang et al. identified 469 significantly differentially expressed circRNAs in bladder cancer, including 285 upregulated circRNAs and 184 down-regulated circRNAs [38].

CircRNAs Regulate Bladder Cancer Progression and Cell Proliferation

The findings from several studies have shown that circRNAs are correlated with the proliferation, invasion, migration, and apoptosis of bladder cancer. Table 1 lists the circRNAs identified in bladder cancer, classified according to their role as oncogenes or anti-oncogenes, based on their different functions.

CircRNAs as Oncogenes in Bladder Cancer

CircMYLK

CircMYLK, also known as hsa_circ_0002768, is spliced from the MYLK gene [39]. By screening circRNA expression profiles, Zhong et al. found that the circMYLK levels were significantly increased in bladder cancer tissue samples than in matched normal bladder tissue samples and that the circMYLK levels were correlated with bladder cancer stage [40]. In bladder cancer cells studied *in vitro*, upregulation of circMYLK enhanced tumor cell growth and migration, whereas circMYLK knockdown resulted in the opposite effects. *In vivo* studies

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showed that circMYLK upregulation promoted the growth of xenograft tumors [40]. By performing bioinformatics analysis, immunoprecipitation experiments, and luciferase reporter assays, circMYLK was shown to bind to miR-29a [40]. Further studies have shown that circMYLK regulates the expression of vascular endothelial growth factor A (VEGFA), induces epithelial–mesenchymal transition (EMT), and activates Ras/ERK signaling [40]. These findings support that circMYLK may promote the development of bladder cancer by its effects on the miR-29a/VEGFA pathway.

CircTCF25

CircTCF25, also known as hsa_circ_0041103, is overexpressed in tissue samples of bladder cancer samples and bladder cancer cell lines *in vitro* [41]. In bladder cancer cells, overexpression of circTCF25 resulted in increased cell proliferation and promoted cell migration when compared with control cells, as shown by 5'-ethynyl-2'-deoxyuridine and wound-healing assays, respectively [41]. Also, overexpression of circTCF25 resulted in down-regulation of miR-103a-3p expression [41]. CDK6, a member of the serine-threonine-kinase family, participates in cell cycle regulation and is essential for the transition to the G1 phase [42,43]. Over-expression of CDK6 has been found in bladder cancer [41,44], osteosarcoma [45], pancreatic cancer [46], oral squamous cell carcinomas [42], and gastric cancer [43]. In bladder cancer tissues and cells, both CDK6 and circTCF25 were upregulated, and circTCF25 overexpression resulted in increased CDK6 expression [41]. These findings indicate that circTCF25 may promote the development of bladder cancer by regulating the miR-103a-3p/CDK6 pathway [41].

Hsa_circ_0058063

Hsa_circ_0058063, located at chr2: 216177220-216213972 with a length of 1640 base pairs (bp), that originates from the ATIC gene [39]. Sun et al. found that hsa_circ_0058063 was upregulated in bladder cancer tissue samples when compared with non-tumor samples [44]. In bladder cancer cells, has-circ_0058063 down-regulation inhibited cell proliferation and migration, and enhanced apoptosis, by directly inhibiting the expression of miR-145, which targets the CDK6 gene [44]. BALB/c nude mice that expressed has_circ_0058063 short-hairpin RNA (shRNA) had reduced weight and size of tumor xenografts, miR145 expression was upregulated, and CDK6 expression was inhibited, indicating that hsa_circ_0058063 was involved in the progression of bladder cancer by regulating the miR-145/CDK6 axis [44].

CircUVRAG

CircUVRAG, also known as hsa_circ_0023642, is an EcircRNA that that originates from the UVRAG gene [39]. CircUVRAG expression has been shown to be significantly increased in bladder cancer cells, and circUVRAG silencing inhibits bladder cancer cell proliferation and migration. *In vivo* studies have shown that circUVRAG downregulation resulted in significantly reduced tumor xenograft volumes and weights when compared controls [47]. Also, circUVRAG silencing promoted miR-223 expression, which inhibited the expression of the FGFR2 gene, demonstrating that circUVRAG regulated FGFR2 levels by sponging miR-223 in bladder cancer [47].

Hsa_circ_0003221

Hsa_circ_0003221 is an EcircRNA from the PTK2 gene located at chr8: 141856358-141900868. Xu et al. detected the expression levels of hsa_circ_0003221 in bladder tumor samples, matched normal samples, and blood samples from 40 patients with bladder cancer and showed that hsa_circ_0003221 expression was significantly upregulated in bladder cancer tissue when compared with matched normal bladder tissue [48]. In the same study, hsa_circ_0003221 levels were significantly associated with lymphatic metastasis and silencing hsa_circ_0003221 with small-interfering RNA (siRNA) significantly inhibited bladder cancer cell proliferation, and overexpression of hsa_circ_0003221 had the opposite effects [48]. These results showed that hsa_circ_0003221 can serve as an oncogene by promoting bladder cancer cell proliferation, but the functional mechanisms of hsa_circ_0003221 in bladder cancer require further investigation [48].

CircCEP128

CircCEP128, also known as hsa_circ_0102722, is spliced from the CEP128 gene. Wu et al. found that circCEP128 was significantly over-expressed in tumor specimens from patients with bladder cancer [49]. Further studies showed that circCEP128 knockdown reduced bladder cancer cell proliferation and increased cell apoptosis [49]. Mechanistically, circCEP128 was found to serve as a sponge of miR-145-5p and to upregulate the level of the miR-145-5p-target gene, SOX11 [49].

CircINTS4

CircINTS4 has been shown to be upregulated in bladder cancer tissue samples when compared with matched normal bladder tissues [50]. Functional studies showed that circINTS4 promoted proliferation and induced apoptosis in bladder cancer cell lines by regulating the miR-146b/CARMA3 pathway, and circINTS4 activated NF-kB signaling and suppressed P38 MARK-signaling in bladder cancer cells [50].

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CircRNAs as Anti-Oncogenes in Bladder Cancer

Cdr1as

Cdr1as (ciRS-7 or Cdr1NAT) is the most well-known circRNA. Recent studies have shown that ciRS-7 can serve as an oncogenic circRNA by binding to miR-7 to promote the progression of several malignant tumors, including lung cancer [21,51], gastric cancer [22], colorectal cancer [19,52], esophageal cancer [53,54], and hepatocellular carcinoma [20]. However, Cdr1as was found to have a different role in bladder cancer. Li et al. detected Cdr1as levels in tumor samples and matched normal control tissue from 94 patients with bladder cancer [55]. The expression of Cdr1as was shown to be significantly down-regulated in bladder cancer tissue samples, and *in vitro* studies showed that Cdr1as overexpression reduced cell proliferation rates and blocked cell cycle in bladder cancer cell lines [55]. Using *in vivo* studies that involved the subcutaneous injection of bladder cancer cell lines infected with a Cdr1as-overexpressing adenovirus in nude mice, the tumor volumes and weights significantly decreased in the Cdr1as-overexpression group, consistent with the *in vitro* findings [55]. In a follow-up study, Cdr1as was found to exert anti-oncogenic functions by binding to miR-135a [55].

CircHIPK3

CircHIPK3, derived from the HIPK3 gene, is also known as bladder cancer-related circular RNA-2 (BCRC-2) [39]. Recent studies have shown that circHIPK3 can promote cell proliferation and metastasis in cancers, including nasopharyngeal carcinoma [56], colorectal carcinoma [57], hepatocellular carcinoma [58], lung cancer [59], and ovarian cancers [60]. Conversely, circHIPK3 behaves as an anti-oncogene in osteosarcoma [61] and bladder cancer [62]. Li et al. showed that circHIPK3 expression was lower in bladder cancer tissue samples than in normal bladder tissue [62]. Overexpression of circHIPK3 significantly inhibited bladder cancer cell migration *in vitro* and suppressed bladder cancer growth *in vivo*. Functionally, circHIPK3 inhibited miR-558 activity, thereby leading to an increased expression level of the HPSE gene [62].

Bladder cancer-related circRNA-3 (BCRC-3)

BCRC-3 is derived from the PSMD1 gene. BCRC-3 levels are significantly lower in bladder cancer tissue samples compared with normal bladder tissue [63]. In bladder cancer cells, BCRC-3 overexpression inhibited cell proliferation and induced cell cycle blocking [63]. Consistent with the *in vitro* findings, BCRC-3 overexpression negatively regulated bladder cancer tumor growth *in vivo* [63]. MiR-182-5p, an oncogene upregulated in several types of cancer [64–66], was confirmed to absorb BCRC-3 in dual-luciferase reporter assays [63]. P27 (CDKN1B), an essential factor that negatively regulates cell cycle progression, was established to bind to miR-182-5p using a dual-luciferase reporter assay, which suggested that BCRC-3 inhibits bladder cancer progression through the miR-182-5p/p27 pathway [63].

Potential Role of circRNAs as Diagnostic and Prognostic Biomarkers for Bladder Cancer

Early diagnosis can significantly improve the opportunity for a cure in patients with cancer. Prognostic evaluation is essential for early intervention in cases involving poor prognostic factors, and for developing appropriate treatment plans. Therefore, the identification of biomarkers that enable cancer prognosis and early diagnosis is urgently needed. CircRNAs are significantly dysregulated in many human tumors and exhibit cell and tissue specificity. However, even within the same type of carcinoma, the expression profiles of circRNAs vary according to tumor size, stage, and the presence or absence of metastasis [29,30]. Based on these characteristics, circRNAs are ideal diagnostic and prognostic biomarkers for malignant tumors. Based on their value as prognostic biomarkers, circRNAs can be classified into biomarkers that are suggestive of poor prognosis or good prognosis, as shown in Table 2.

CircRNA Biomarkers Associated with Poor Prognosis in Bladder Cancer

CircVANGL1

CircVANGL1 is derived from the VANGL1 gene [39], and circVANGL1 has been shown to promote the progression of osteoporosis through binding to miR-217 and increasing RUNX2 expression [67]. In bladder cancer cells, circVANGL1 silencing has been shown to inhibit cell proliferation and arrest the cell cycle [68]. *In vivo* studies showed that circVANGL1 silencing suppressed bladder cancer cell migration, and mechanistically, circVANGL1 suppressed miR-605-3p activity, increasing VANGL1 expression [68]. Also, circVANGL1 expression has been shown to be increased in bladder cancer tissue samples when compared with normal bladder tissue [68]. The high circVANGL1 level was correlated with poorer overall survival (OS) than the low circVANGL1 level in patients with bladder cancer, which suggested that circVANGL1 might be a promising diagnostic and prognostic biomarker in patients with bladder cancer [68].

Has_circ_0000144

Has_circ_0000144 originates from the SLAMF6 gene [39]. A recent study showed that has_circ_0000144 promoted the proliferation of bladder cancer cells by decreasing miR-217

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Table 2. Circular RNAs that can potentially serve as prognostic biomarkers for bladder cancer.

CircRNA	Gene symbol	Regulation of circRNA	miRNA sponge	Target gene/protein/pathway	Biomarker	Reference
circVANGL1 or hsa_circ_0002623	VANGL1	Upregulated	miR-605-3p	VANGL1	Poor prognosis	68
hsa_circ_0000144	SLAMF6	Upregulated	miR-217	RUNX2	Poor prognosis	69
circBPTF or hsa_circ_0000799	BPTF	Upregulated	miR-31-5p	RAB27A	Poor prognosis	70
circPRMT5	PRMT5	Upregulated	miR-30c	SNAIL1/E-cadherin signaling pathway	Poor prognosis	71
circGprc5a or hsa_circ_02838	–	Upregulated	–	Gprc5a protein	Poor prognosis	74
cTFRC or hsa_circ_0001445	TFRC	Upregulated	miR-107	TFRC	Poor prognosis	76
circMTO1 or hsa_circ_0007874 or hsa_circ_104135	MTO1	Down-Regulated	miR-221	–	Good prognosis	79
circITCH or hsa_circ_0001141 or hsa_circ_001763	ITCH	Down-Regulated	miR-17 miR-224	p21 PTEN	Good prognosis	85
circUBXN7 or hsa_circ_0001380	UBXN7	Down-Regulated	miR-1247-3p	B4GALT3	Good prognosis	87
circLPAR1 or hsa_circ_0087960	LPAR1	Down-Regulated	miR-762	–	Good prognosis	88
circFNDC3B or hsa_circ_0006156	FNDC3B	Down-Regulated	miR-1178-3p	G3BP2/SRC/FAK signaling pathway	Good prognosis	89

expression, thereby increasing expression of the miR-217-target gene, RUNX2, *in vitro* [69]. Also, has_circ_0000144 was significantly upregulated in bladder cancer tissue samples [69]. Based on Kaplan–Meier survival analysis, patients with high has_circ_0000144 levels had a worse OS than patients with a low has_circ_0000144 level, supporting the view that has_circ_0000144 might be a promising prognostic biomarker in patients with bladder cancer [69].

CircBPTF

CircBPTF, derived from exons in the BPTF gene, is over-expressed in bladder cancer cells [70]. Functional analysis, using specially designed siRNAs, showed that circBPTF blockade resulted in reduced cell proliferation and migration when compared with control cells by binding to miR-31-5p, which then modulated RAB27A levels [70]. The circBPTF level was upregulated in patients with bladder cancer, and Kaplan–Meier curve analysis showed that the circBPTF level was inversely correlated with patient survival rates and circBPTF expression levels were associated with the TNM stage and tumor recurrence [70].

CircPRMT5

CircPRMT5, located at chr14: 23395341-23396023, was originally identified as a significantly overexpressed circRNA in bladder cancer tissues by microarray analysis, with more than a six-fold expression change, which was later verified by quantitative reverse-transcriptase polymerase chain reaction (qRT-PCR) analysis [71]. Functional studies also showed that circPRMT5 knockdown inhibited epithelial-mesenchymal transition (EMT) of bladder cancer cell lines through the miR-30c/SNAIL1/E-cadherin axis [71]. Furthermore, levels of circPRMT5 were significantly upregulated in bladder cancer tissue samples compared with matched normal bladder tissues, and upregulation of circPRMT5 occurred more commonly in patients with shorter overall survival (OS) from bladder cancer [71]. Higher circPRMT5 levels were significantly associated with lymphatic metastasis and advanced tumor stage [71]. Exosomes are vesicles with a diameter of 40–100 nm that are released by cells into the extracellular microenvironment [72]. Recent findings suggested that circRNAs are abundant in exosomes, indicating that they can potentially act as biomarkers for cancer diagnosis and targeted therapy [73]. Chen et al. found that circPRMT5

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expression was enriched in serum exosomes and urine exosomes from patients with bladder cancer [71].

CircGprc5a

CircGprc5a expression has been shown to be increased in bladder cancer tissue samples and bladder cancer cells than in non-tumor samples, and circGprc5a levels are significantly correlated with metastasis and poor OS [74]. Unlike the more common mechanism of action for circRNAs, which can act as miRNA sponges, circGprc5a was shown to be translated into a peptide (circGprc5a-peptide) that bound to the Gprc5a membrane protein in bladder cancer cells [74]. Also, Gprc5a promoted bladder cancer cell maintenance *in vitro*, cell proliferation, and cell migration by activating signaling through a G protein-coupled receptor (GPCR) [74]. As a superfamily of cell-surface signaling proteins, GPCRs play important roles in cancer progression [75]. These findings suggest that circGprc5a can promote bladder cancer cell proliferation through the circGprc5a-peptide–Gprc5a axis [74].

CTFRC

CTFRC, also known as has-circ-0001445, is derived from the TFRC gene. Su et al. found that bladder tumor samples expressed higher levels of cTFRC than matched non-tumor samples. Furthermore, a high cTFRC level was associated with reduced OS in patients with bladder cancer, when compared with patients with bladder cancer who had a low cTFRC level. Mechanistically, it is likely that overexpression of cTFRC promoted bladder cancer cell proliferation and mediated EMT through the miR-107/TFRC pathway [76].

CircRNA Biomarkers Associated with Improved Prognosis in Bladder Cancer

CircMTO1

The MTO1 gene produces circMTO1, which has been shown to be down-regulated in hepatocellular carcinoma [77], colon cancer [78], and bladder cancer [79]. CircMTO1 expression was shown to be reduced in 87.4% of hepatocellular carcinoma tissue samples when compared with normal tissue samples and decreased circMTO1 was significantly associated with a worse prognosis for patients with hepatocellular carcinoma [77]. CircMTO1 has been shown to inhibit the proliferation of colorectal cancer cells *in vitro* by negatively regulating Wnt/β-catenin signaling [78]. Also, lower circMTO1 expression correlated with a poor OS [78]. Li et al. examined circMTO1 levels in 117 patients with bladder cancer, and showed that circMTO1 levels were significantly lower in bladder cancer tissue samples than in normal bladder tissue samples [79]. Patients with lower circMTO1 expression had a reduced OS when compared with patients with higher circMTO1 expression levels [79]. Also, circMTO1 is involved in chemoresistance in breast cancer [80] and glioblastoma [81]. Liu et al. found that circMTO1 suppressed tumor growth, and reversed monastrol resistance in breast cancer cell lines by suppressing the TRAF4/Eg5 axis [80]. Rao et al. found that circMTO1 level was lower in temozolomide-resistant glioblastoma tissue samples. Overexpression of circMTO1 significantly suppressed cell proliferation, promoted cell apoptosis, and reduced temozolomide chemoresistance in glioblastoma cells [81].

Circ-ITCH

CircITCH is generated from the ITCH gene, and is a well-studied circRNA, that has been shown to inhibit the progression of lung cancer[12], esophageal cancer [13], colorectal cancer [14], breast cancer [82], and papillary thyroid cancers [83], through the inhibition of Wnt/β-catenin signaling. Furthermore, circITCH serves as an independent prognostic biomarker in hepatocellular carcinoma [84]. In a study performed in 72 patients with bladder cancer, circITCH was shown to be significantly down-regulated in bladder cancer tissue samples when compared with levels in matched non-tumor samples [85]. CircITCH levels were shown to be positively correlated with the histological tumor grade, and patients with lower circITCH expression had a reduced OS [85]. Functionally, circITCH overexpression significantly suppressed bladder cancer cell proliferation by binding to miR-17/miR-224 [85].

CircUBXN7

CircUBXN7 was identified initially as a significantly down-regulated circRNA in bladder cancer samples through high-throughput sequencing [86]. Then, Liu et al. used qRT-PCR and showed that circUBXN7 levels were reduced in bladder cancer tissue samples when compared with matched non-tumor samples [87]. Patients with lower circUBXN7 levels were found to have a worse OS than those with a higher circUBXN7 level [87]. Functionally, circUBXN7 inhibited miR-1247 activity, resulting in an increased B4GALT3 level.

CircLPAR1

In 125 patients with bladder cancer, circLPAR1 was shown to be significantly down-regulated in bladder cancer tissue samples compared with its level in paired control normal bladder tissue samples [88]. Univariate and multivariate Cox regression analysis showed that low circLPAR1 levels were associated with poorer disease-specific survival (DSS) than high circLPAR1 levels [88]. Functionally, hsa_circ_0014717 overexpression significantly suppressed bladder cancer invasion by negatively regulating miR-762 expression [88].

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CircFNDC3B

CircFNDC3B was shown to be significantly down-regulated in bladder cancer tissue samples compared with its level in matched non-tumor samples, using high-throughput sequencing [83]. Also, circFNDC3B expression was found to be significantly lower in 56 bladder cancer samples when compared with matched normal bladder tissue samples [89]. Significant associations have been shown between circFNDC3B expression and TNM stage, histopathological grade, and the occurrence of lymphatic metastasis [89]. Furthermore, the low circFNDC3B level was significantly associated with a reduced OS rate, when compared with high circFNDC3B expression [89].

CircRNAs as Biomarkers of Chemotherapy Resistance in Bladder Cancer

Data from several studies have shown that some circRNAs are associated with the sensitivity of bladder cancer to chemotherapy. For example, by sequencing and qRT-PCR, Su et al. showed that circELP3 was upregulated in bladder cancer cells cultured under hypoxia and that hypoxia-induced circELP3 expression promoted proliferation and reduced apoptosis in bladder cancer cells [90]. Additionally, hypoxia-induced circELP3 promoted cisplatin resistance by regulating bladder cancer cells *in vitro* [90]. Chi et al. showed that levels of hsa_circ_0000285 were significantly lower in bladder cancer tissue samples than in matched normal bladder tissue samples [91]. Also, levels of hsa_circ_0000285 were lower in patients with cisplatin-resistant bladder cancer than in patients with cisplatin-sensitive bladder cancer [91]. Cisplatin-based chemotherapy remains the mainstay of treatment for bladder cancer, and cisplatin resistance results in poor prognosis in patients with advanced bladder cancer. Therefore, it is essential to continue to explore the clinical implications of the role of circRNAs in cisplatin resistance, and to investigate potential biomarkers and treatment targets and the effects of circRNAs on chemoresistance in patients with bladder cancer.

Conclusions

This review has summarized what is currently known of the roles of circRNAs in human bladder cancer in regulating cell proliferation, invasion, and metastasis, and highlighted their potential clinical role of circRNAs in the diagnosis, prognosis, and response to chemotherapy of bladder cancer. As described in this review, circRNAs exhibit an extensive range of biological functions, including sponging miRNAs, regulating transcription and the activities of RNA-binding proteins, and undergoing translation. Currently, several circRNAs are involved in the pathogenesis of bladder cancer, and some of them may function as promising biomarkers. Further insights into the molecular mechanisms associated with the progression of bladder cancer progression may lead to breakthroughs in clinical applications for treating bladder cancer. However, several limitations and challenges need to be resolved. Currently, there is a lack of uniform nomenclature for circRNAs, which can lead to duplicated studies by different research groups. Also, current circRNA databases are limited. Although some databases contain information for annotating circRNAs and predicting interactions among circRNAs, miRNAs, and proteins, such as circBase [39], starBase v2.0 [92], deepBase v2.0 [93], CircInteractome [94], and Circ2Traits [95], no circRNA database has been developed for tumor prognosis, which makes it challenging to evaluate the functions of circRNAs in different types of malignant tumors. Also, due to the high technical costs, there is a lack of circRNA expression profile data obtained from microarrays or RNA-seq assays for a large number of samples. Finally, the exact contribution of circRNA to the pathogenesis and progression of bladder cancer is likely to be complicated and, currently, only limited roles have been identified. Therefore, more circRNAs should be investigated in terms of their functions, mechanisms of action, and their potential clinical applications.

Conflict of interest

None.

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