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REVIEW

Circular RNAs and Bladder Cancer

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Abstract: Bladder cancer (BC) is the most common urinary system malignancy and is a serious threat to human health. Circular RNAs (circRNAs) are members of a newly defined class of noncoding RNAs (ncRNAs) that can regulate gene expression at the transcriptional or posttranscriptional level. Studies have shown that circRNAs are related to the clinicopathological characteristics, prognosis, and chemosensitivity of BC, and basic research has further confirmed that changes in the expression of circRNAs in BC are closely related to various tumor biological functions. CircRNAs promote tumor development by interacting with miRNAs to regulate transcription factors and both classical and nonclassical tumor signaling pathways. The nonclassical signaling pathways are related to cell cycle progression, epithelial–mesenchymal transition (EMT), extracellular matrix maintenance, and tumor stem cell maintenance. In this article, the relationships between circRNAs and the clinical characteristics of BC are reviewed, and the molecular mechanisms by which circRNAs promote tumor development are explored.

Keywords: circRNA, miRNA, bladder cancer, biomarker

Introduction

Bladder cancer (BC) is the most common malignant tumor in the urinary system and ranks 9th in global cancer incidence and 13th in global cancer-related mortality.[1,2] In 2018, an estimated 549,393 new cases were diagnosed,[3] 75% of which were non-muscle-invasive BC, and nearly 200,000 deaths from BC occurred.[4] In China, the mortality rate has increased significantly in the past few decades.[5] A high recurrence rate is a representative feature of BC.[6] Given the high incidence, recurrence rate and progression rate of BC, its five-year survival rate is still very low. Currently, surgical resection and chemotherapy are the main treatment methods for BC, but postoperative recurrence and the emergence of chemoresistance greatly limit the therapeutic effect of these treatments. Therefore, identifying a safe and effective molecular marker and treatment strategy is a pressing problem requiring resolution.

Noncoding RNAs (ncRNAs) are functional transcripts that are not translated into proteins and can be divided into two categories based on size: small ncRNAs (18–200 nucleotides) and long ncRNAs (lncRNAs, more than 200 nucleotides). Small ncRNAs, also known as microRNAs (miRNAs, usually 22–25 nucleotides), bind to miRNA response elements (MREs) in the 3′-untranslated region (UTR) of the target messenger RNA (mRNA) to either promote mRNA degradation or inhibit protein translation. Circular RNAs (circRNAs) are members of a newly defined class of ncRNAs with a covalently closed loop structure that has neither 5′-3′ polarity nor

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a polyadenylated tail.[7] These characteristics prevent them from being degraded by RNA exonucleases.[8] Therefore, circRNAs are more stable than linear RNAs. In addition, circRNAs can regulate gene expression at the transcriptional or posttranscriptional level. This article will discuss the role of several important circRNAs in BC, aiming to highlight new research directions for the prevention and treatment of BC.

CircRNA Biogenesis

CircRNAs can be divided into three types: 1) exonic circRNA (EcircRNA), 2) intronic circRNA (ciRNA) and 3) exon-intron circRNA (EIciRNA),[9–11] which are produced from exons, introns or both (Figure 1). EcircRNAs are located mainly in the cytoplasm, and ciRNAs and EIciRNAs are more abundant in the nucleus.[12] Among these three types of circRNAs, more than 80% are EcircRNAs.[12,13] CircRNAs are widely believed to be spliced at canonical splice sites in a manner dependent on backsplicing.[14] After pre-mRNA processing events are slowed, nascent mRNAs are processed through alternative pathways to promote backsplicing.[15] Looping of the intron sequence flanking the upstream splice acceptor site and the downstream splice donor site is the key step in circRNA formation.[12] CircRNA looping occurs via three mechanisms: 1) base pairing of inverted complementary sequences in downstream and upstream introns,[16,17] 2) binding of RNA-binding proteins to flanking introns via specific motifs,[18] and 3) lariat formation during exon skipping and internal backsplicing of the lariat.[16,19] These mechanisms can bring the upstream splice acceptor site and the downstream splice donor site into close proximity, resulting in looping of the circRNA.[12,14]

Relationships Among circRNAs, miRNAs and Target Genes

As a circular ncRNA, circRNAs are more stable than linear RNAs. An increasing number of scholars are referring to circRNAs as miRNA "sponges" because they competitively adsorb miRNAs owing to the presence of MREs, resulting in a reduction in the level of the target miRNA.[20] miRNAs are endogenous single-stranded small ncRNAs of approximately 19–25 nucleotides in length.[21] Recent literature has provided accumulating evidence that many miRNAs play roles similar to those of oncogenes or tumor suppressor genes and participate in the regulation of tumor cell proliferation, apoptosis, invasion, migration, angiogenesis, stem cell differentiation and other pathophysiological processes.[22–24] miRNAs inhibit posttranscriptional translation or degrade target sequences by incompletely or completely pairing with the 3′-UTR of the target mRNA, respectively, and these events regulate the expression of various cancer-related genes and thereby affect tumor biological characteristics.[22–24] Therefore, the circRNA/miRNA/target gene regulatory axis plays an important role in the biological characteristics of tumors. By targeting any of these molecules, the tumor characteristics can be changed, suggesting new research avenues for tumor prevention and treatment.

Bladder Cancer-Associated circRNAs in Clinical Practice

CircRNAs were first discovered in RNA viruses, and were long considered byproducts of mRNA splicing.[25] Advances in next-generation sequencing technology and bioinformatic approaches have led to the identification of thousands of circRNAs in different species.[26] Researchers

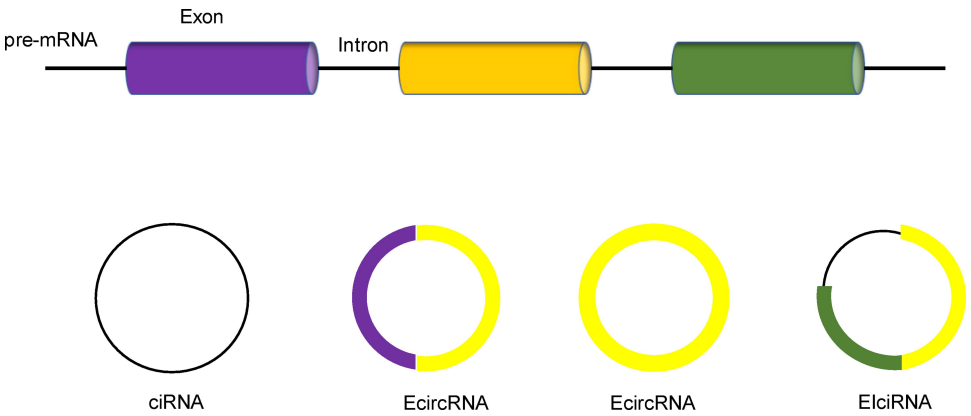


Figure 1 Three types of circRNAs produced from exons, introns or both.

have conducted many studies aimed at elucidating the function of circRNAs in different tumors. Additionally, numerous circRNAs have been found to be differentially expressed in BC tissues and healthy adjacent tissues. These discovered circRNAs have a tremendous potential role in future BC research. The following section introduces the roles and mechanisms of circRNAs in BC.

Relationships Between circRNAs and Clinicopathological Characteristics

Research has shown that the BC-related functions of circRNAs can be divided into two natures: tumor promotion and tumor suppression. Many circRNAs, including circ-BPTF, circTFRC, circPDSS1, circZFR, circPRMT5, circPTK2, circASXL1, and circCASC15, have been found to have increased expression levels in BC tissues and cell lines compared to healthy adjacent tissues, normal tissues and normal cell lines and to play a role in promoting tumor development. Further analysis showed that high levels of these circRNAs are closely related to the clinicopathological stage of BC, which describes the tumor status, including the tumor size, presence of local and distant metastasis, and tumor pathological grade, and affect the survival of BC patients.[27–34] Regarding tumor tissue classifications, the levels of circRNAs, including circ-BPTF, circTFRC, circZFR, circPTK2, and circASXL1, were found to be significantly higher in low-grade BC tissues than in high-grade BC tissues.[27,28,30,32,33] Regarding the pathological TNM stage, circRNAs, including circTFRC, circZFR, circPRMT5, circPTK2, circASXL1 and circCASC15, were positively correlated with the T stage when patients were stratified into Ta–1 and T2–4 subgroups.[28,30–34] Additionally, circTFRC, circZFR, circPRMT5, circPTK2 and circASXL1 were found to be closely related to lymph node status: BC patients with lymph node metastasis tended to have higher levels of these circRNAs.[28,30–33] In addition, circASXL1 is associated with distant metastasis, and patients with BC with distant metastasis have higher levels of circASXL1.[33] CircRNAs are related not only to pathological stage but also to clinical stage. For example, circPDSS1 levels differ across clinical stages of BC[29]—the higher the stage, the higher is the expression level. Clinically, BC tumors are divided into muscle-invasive and non-muscle-invasive tumors, and the former has worse outcomes. Compared with non-muscle-invasive BC tissue, muscle-invasive BC tissue has high levels of circ-BPTF.[27] Tumor recurrence is an important factor affecting outcomes, and circ-BPTF and circZFR have been found to be closely related to the recurrence of BC; recurrent tumor tissue exhibits higher levels of circRNA than primary tumor tissue.[27,30] In addition to the abovementioned findings regarding clinicopathological features, studies have shown that these circRNAs are not related to tumor size or vascular invasion. Because clinicopathological characteristics affect the prognosis of patients and circRNAs are closely related to the clinicopathological characteristics of BC, circRNAs may also be related to the prognosis of patients. Cumulative studies have confirmed that circ-BPTF, circTFRC, circZFR and circCASC15 are associated with overall survival in patients with BC;[27,28,30,34] circZFR, circPRMT5 and circCASC15 are associated with disease-free survival;[30,31,34] and hsa_circ_0137439 is associated with recurrence-free survival and overall survival.[35] In general, higher levels of these circRNAs are associated with less favorable patient survival.

Cumulative studies have shown that many of the circRNAs discussed below act as tumor suppressors to inhibit BC. The expression levels of these circRNAs in primary BC tissues and BC cell lines are significantly reduced compared to those in adjacent tissues or normal cell lines. Moreover, the expression levels of these circRNAs are significantly negatively correlated with clinicopathological characteristics. CircFNDC3B, circACVR2A, circRIP2, circSLC8A$_1$, circHIPK3, hsa_circ_0018069, circPICALM and circ-ZKSCAN1 are associated with pathological T stage.[36–43] As the T stage advances, the expression levels of these circRNAs decrease significantly.[36–43] Additionally, the expression levels of circFNDC3B, hsa_circ_0071662, circACVR2A, circRIP2, circHIPK3, circPICALM, circ-ZKSCAN1 and circMTO1 in patients with lymph node metastasis were found to be lower than those in patients with negative lymph nodes.[36–38,40,42–45] Similarly, the expression levels of hsa_circ_0071662 and CircRIP2 in patients with distant metastasis and of CircHIPK3 in patients with vascular invasion were found to be lower than those in patients without distant metastasis and vascular invasion, respectively.[38,40,44] Compared with low-grade bladder tumors, high-grade bladder tumors were found to exhibit lower levels of circFNDC3B, circACVR2A, circSLC8A$_1$, circHIPK3, hsa_circ_0018069, circPICALM, circ-ZKSCAN1, hsa_circ_0077837 and hsa_circ_0004826.[36,37,39–43,46] Additionally, the hsa_circ_0018069 expression level in muscle-invasive BC

was found to be higher than that in non-muscle-invasive BC.[41] Regarding survival, low levels of circFNDC3B, hsa_circ_0071662, circACVR2A, circRIP2, circPICALM, circ-ZKSCAN1 and circMTO1 are related to poor overall survival;[36–38,42–45] similarly, circ-ZKSCAN1 and circMTO1 are positively correlated to disease-free survival;[43,45] and hsa_circ_0077837 and hsa_circ_0004826 are also positively correlated with recurrence-free survival.[46] In summary, regardless of whether the levels of circRNAs in BC tissue are increased or decreased, these circRNAs are closely related to clinicopathological characteristics (Table 1).

The close relationship between the expression levels of circRNAs and the clinicopathological characteristics of BC suggests that circRNAs will become diagnostic markers and prognostic predictors. However, molecular testing of tissues still has limitations for clinical application. Interestingly, circRNA expression in serum or urine has been found to be useful in evaluating clinicopathological features. In addition to identifying bladder tumors, hsa_circ_0137439 levels in urine can distinguish muscle-invasive from non-muscle-invasive BC.[35] Serum has_circ_0003221 and hsa_circ_0000285 levels can also be used to identify bladder tumors,[32,47] and the elevated serum levels of circFARSA, circSHKBP1 and circBANP in recurrent BC suggest that circRNAs can be used to verify tumor recurrence.[48] In conclusion, the ability to detect the expression levels of circRNAs in serum and urine further increases the possibility of utilizing circRNAs as diagnostic and prognostic markers in BC.

circRNAs and Chemosensitivity

Chemotherapy is an important component of cancer treatment. Methyl jasmonate is a cyclopentanoic acid compound originally isolated from jasmine plants and is the most active anticancer derivative of natural jasmonate.[49] Recently, an increasing number of basic studies have confirmed that methyl jasmonate exerts notable antitumor effects in many cancers, including colorectal cancer, non-small-cell lung cancer, gastric cancer, and prostate cancer, by inducing cancer cell apoptosis and blocking invasion, migration, and angiogenesis. Methyl jasmonate may thus be a promising new anticancer drug.[50–53] One study showed that methyl jasmonate induces the expression of circRNA BCRC-3, which is derived from the PSMD1 gene. Overexpressed circRNA BCRC-3 in BC cells sponges miR-182-5p, thereby increasing the expression level of P27 (also called cell cycle-dependent kinase inhibitor 1B); this ultimately results in cell cycle inhibition in tumor cells and exerts an antitumor effect.[54] Similarly, gambogic acid (GA), a natural product from Gambia, has been shown to perform an antitumor function in various tumors. In BC, GA induces the expression of circRNA BCRC4, which is expressed at low levels in BC. Increased expression of circRNA BCRC4 enhances the expression of miR-101 and subsequently downregulates EZH2 (which conventionally promotes tumor progression).[55] Eventually, the sensitivity of BC cells to apoptosis is enhanced.[55] In summary, antitumor drugs induce changes in the expression of circRNAs and thus inhibit tumor progression.

The sensitivity of tumors to chemotherapy can affect the survival and prognosis of patients. Dysregulation of circRNAs in BC induces chemoresistance. For example, the expression level of circELP3 is increased in bladder tumors, which consequently increases cisplatin resistance.[56] Overexpression of circFNTA can regulate FNTA and KRA by interacting with miR-370-3p and increasing the chemotherapeutic resistance of BC to cisplatin.[57] CircRNA Cdr1as mitigates APAF1 activity by binding to miR-1270, thereby increasing the sensitivity of cells to cisplatin.[58] The ABC transport pathway is an important mechanism mediating tumor chemoresistance. Activity of this pathway reduces drug sensitivity by reducing the accumulation of drugs in tumor cells. Several studies have reported that the expression of ABC transport proteins in BC is upregulated, which can mediate multidrug resistance in tumors.[59–64] Studies have shown that hsa_circ_102336, which is highly expressed in BC, binds to and inhibits miR-515-5p, thereby regulating the ABC transport pathway and subsequently the resistance of BC to cisplatin.[65] In addition to affecting cisplatin resistance, circHIPK3 expression was found to be negatively correlated with gemcitabine resistance in bladder tumors, and overexpression of circHIPK3 was found to result in increased resistance of bladder tumors to gemcitabine.[66] Additionally, hsa_circ_0000285 can promote chemosensitivity to cisplatin in BC. Compared with patients with chemosensitive bladder tumors, those with chemoresistant bladder tumors have lower expression of hsa_circ_0000285, suggesting that hsa_circ_0000285 increases chemosensitivity in BC.[47] The above studies indicate that circRNAs are involved in the drug resistance of bladder tumors (Table 2) and will become important targets for reversing tumor drug resistance.

Table 1 CircRNAs and Clinical Characteristics

CircRNAs	CircRNA Expression in Bladder Cancer	Tumor Grade	Pathological T Stage	Lymph Node Metastasis	Distant Metastasis	Vascular Invasion	Clinical Stage	Muscle Invasion	Tumor Recurrence	Overal Survival	Disease-Free Survival	Recurrence-Free Survival	
CircBPTF	Up-regulation	•						•	•				
CircTFRC	Up-regulation	•	•	•						•			
CircZFR	Up-regulation	•	•	•					•	•	•		
CircPTK2	Up-regulation	•	•	•									
CircASXL1	Up-regulation	•	•	•	•								
CircPRMT5	Up-regulation		•	•							•		
CircCASC15	Up-regulation		•							•	•		
CircPDSS1	Up-regulation						•						
hsa_circ_0137439	Up-regulation											•	
CircRNDC3B	Down-regulation	•	•	•						•			
CircACVR2A	Down-regulation	•	•	•						•			
CircRIP2	Down-regulation		•	•	•					•			
CircSLC8A1	Down-regulation	•	•										
CircHIPK3	Down-regulation	•	•	•		•							
CircPICALM	Down-regulation	•	•	•						•			
Circ-AKSCAN1	Down-regulation	•	•	•						•	•		
CircMTO1	Down-regulation			•						•	•		
hsa_circ_0071662	Down-regulation			•	•					•			
hsa_circ_0077837	Down-regulation	•										•	
hsa_circ_0004826	Down-regulation	•										•	
hsa_circ_0018069	Down-regulation	•	•					•					

Note: •, represented that circRNA has the relationship with corresponding clinical characteristic.

Table 2 CircRNAs and Chemotherapy Drugs

CircRNAs	Gene Symbol	Chemosensitivity	Chemotherapy Drugs	Pathways
CircELP3		Inhibition	Cisplatin	Unknown
CircFNTA		Inhibition	Cisplatin	MiR-370-3p/FNTA and KRA
Cdr1as		Promotion	Cisplatin	MiR-1270/APAF1
CircHIPK3		Inhibition	Gemcitabine	Unknown
Hsa_circ_102336	*TAF4B*	Inhibition	Cisplatin	MiR-515-5p/ABC transport pathway
Hsa_circ_0000285	*HIPK3*	Promotion	Cisplatin	Unknown

CircRNAs in Regulating the Biological Activity of Bladder Cancer

Cumulative studies have found that circRNAs interact with miRNAs to regulate the expression of target molecules and play an important role in the development of various biological characteristics of BC, including angiogenesis, invasion, metastasis, and chemoresistance.[37,67–72] Understanding the mechanisms by which circRNAs affect the abovementioned biological functions of BC will help to identify important therapeutic targets.

Classical Tumor Signaling Pathways

Classical tumor signaling pathways are major pathways regulating the biological activity of tumors to promote tumor development and progression. Accumulating studies

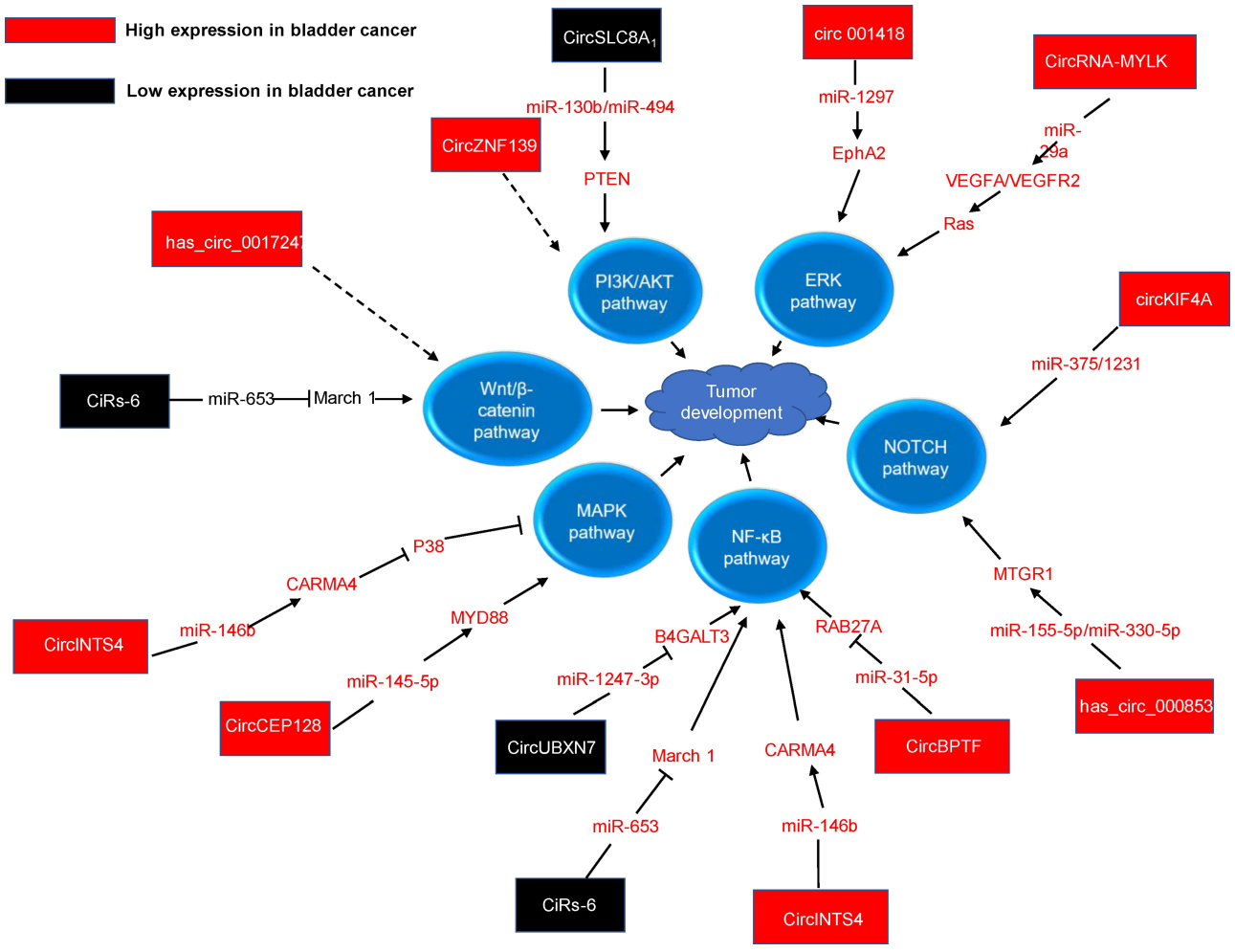


Figure 2 The detailed mechanisms of circRNAs on tumor classic pathways.

have shown that circRNAs are involved in classical tumor signaling pathways by interacting with miRNAs (Figure 2).

The PI3K/AKT/mTOR pathway plays a key role in cell survival, cell physiology, and pathological changes, and activation of this signaling pathway can promote tumor progression.[73] PTEN is a negative regulator of the PI3K/AKT/mTOR pathway, and it can regulate cell growth, proliferation, energy metabolism, and the immune response.[74,75] CircZNF139 is highly expressed in BC cells and promotes the development of BC through the PI3K/AKT signaling pathway.[76] The decreased expression of circSLC8A$_1$ in BC reduces its interaction with miR-130b/miR-494, resulting in decreased PTEN expression and, consequently, increased activity of the downstream PI3K-AKT/PKB signaling pathway.[39] In BC, PTEN is also regulated by circ-ITCH, and low expression of circ-ITCH reduces its interaction with miR-17 or miR-224, thereby increasing the PTEN level.[77]

Extracellular signal-regulated kinase (ERK) is generally considered a key regulator of biological activity in cells.[78] It plays a key role in regulating various cellular functions, for example, promoting cell proliferation, differentiation and survival in response to extracellular signals.[78] In addition, cumulative studies have shown that activation of ERK-related signaling leads to tumor formation and progression and is considered a promising target for tumor treatment.[79–81] Elevated expression of circRNA MYLK in BC enhances sponging of miR-29a to activate VEGFA/VEGFR2 and the downstream Ras/ERK signaling pathway, which promotes tumor development.[82] In addition, circRNA001418 is overexpressed in BC, thus reducing the miR-1297 level; this reduction results in an increase in EphA2 expression to activate the downstream ERK1/ERK2 signaling pathway, which promotes tumor progression.[83]

The NOTCH pathway has been shown to play both tumor-promoting and tumor-suppressing roles. In tumors, NOTCH1 functions as a tumor suppressor, while NOTCH2 acts as an oncogene that promotes tumor cell proliferation and metastasis through various mechanisms, including epithelial–mesenchymal transition (EMT) and cell cycle regulation.[84] Overexpression of circKIF4A in BC can promote tumor development by sponging miR-375/1231, which consequently upregulates NOTCH2 expression.[85] Similarly, hsa_circ_0008532 is overexpressed in BC and directly interacts with miR-155-5p and miR-330-5p to upregulate the MTGR1 expression and the downstream NOTCH signaling pathway.[86]

NF-κB can induce regulatory signals in response to different stimuli and has been shown to play a key regulatory role in the physiological and pathological processes of various diseases, including cancer.[87] Compared with normal urethral epithelium, superficial BC tissue exhibits increased levels of NF-κB, while invasive BC tissue exhibits decreased levels; thus, the NF-κB-related pathway may function as a "double-edged sword" in tumor development.[88] Circ-BPTF, which is highly expressed in BC, inhibits the oncogene *RAB27A* by directly interacting with miR-31-5p and weakening its inhibition of *RAB27A*, an action related to the regulation of NF-κB.[28] CircUBXN7 inhibits miR-1247-3p and upregulates the B4GALT3 expression, which can inhibit NF-κB expression.[89] Low expression of circUBXN7 in BC could thus result in increased NF-κB signaling to promote tumor progression.[89]

In addition to the abovementioned pathways, other classical pathways have been found to be regulated through circRNAs in BC. For example, circCEP128, which is highly expressed in BC, inhibits the expression of miR-145-5p, thereby upregulating MYD88 and other downstream proteins in the MAPK signaling pathway.[90] In addition, overexpression of hsa_circ_0017247 in BC increases Wnt/β-catenin signaling activity and promotes tumor progression.[91] These two pathways are involved in the development of numerous types of tumors. Additionally, some circRNAs are involved in more than one tumor signaling pathway in BC. The low expression of circRNA CiRs-6 in BC reduces March 1 expression by interfering with the interaction between miR-653 and March1, which can activate the NF-κB and Wnt/β-catenin signaling pathways.[92] CircINTS4, which is highly expressed in BC, promotes the expression of CARMA4 by sponging miR-146b, thereby activating the NF-κB signaling pathway and inhibiting p38-MAPK signaling.[93] In summary, the classical tumor signaling pathway is important and involved in the regulation of tumorigenesis and tumor progression. In BC, circRNAs are closely associated with classical tumor signaling pathways and contribute to the regulation of BC progression.

Nonclassical Tumor Pathways

In addition to classical tumor pathways, many circRNA-related pathways in BC have been found to be involved in the regulation of the cell cycle, EMT, extracellular matrix,

and tumor stem cell-related functions in BC, resulting in promotion of tumor cell malignancy (Figure 3).

Regulation of the Cell Cycle

Tumor cells actively proliferate, and the cell cycle is closely related to cell proliferation. The cell cycle is regulated mainly by cyclins, cyclin-dependent protein kinases (CDKs), and CDK inhibitors.[94] Many circRNAs have been found to be involved in the cell cycle in BC cells. Overexpression of circNR3C1 in BC was found to reduce the expression of cyclinD1 via sponging of miR-27a-3p; a similar relationship was found between hsa_circ_0058063, CDK6, and miR-145-5p.[95,96] Therefore, low expression of circNR3C1 and hsa_circ_0058063 in BC accelerate the G1-to-S phase transition of tumor cells and enhance cell proliferation owing to decreased sponging of their target miRNAs and subsequently increased expression of cyclinD1 and CDK6, respectively.[95,96] High expression levels of p21, a cyclin-dependent kinase inhibitor, can induce cell cycle arrest. The expression of p21 in BC tissues was significantly reduced compared with that in adjacent normal tissues.[97] Studies have shown that circRNAs are involved in regulating p21 expression. In BC, reductions in the Cdr1as, circ-ZKSCAN1, and circ-ITCH expression levels weakened p21 activity via reducing binding to their respective target miRNAs (miR-135a, miR-1178-3p, miR-17, and miR-224), which ultimately led to downregulated expression of p21.[77,98] The KIF2C protein is involved in the inhibition of cell cycle progression and mitosis.[99] It is localized mainly in the cytoplasm throughout the cell cycle and participates in the DNA repair process.[99] Studies have shown that *KIF2C* is associated with tumor progression.[100–102] In BC, elevated expression of circRGNEF increases sponging of miR-548, which prevents the expression of its targetKIF2C and consequently promotes tumor progression.[103] In summary, in BC, different circRNAs participate in the regulation of different cell cycle-related proteins, ultimately leading to accelerated tumor proliferation.

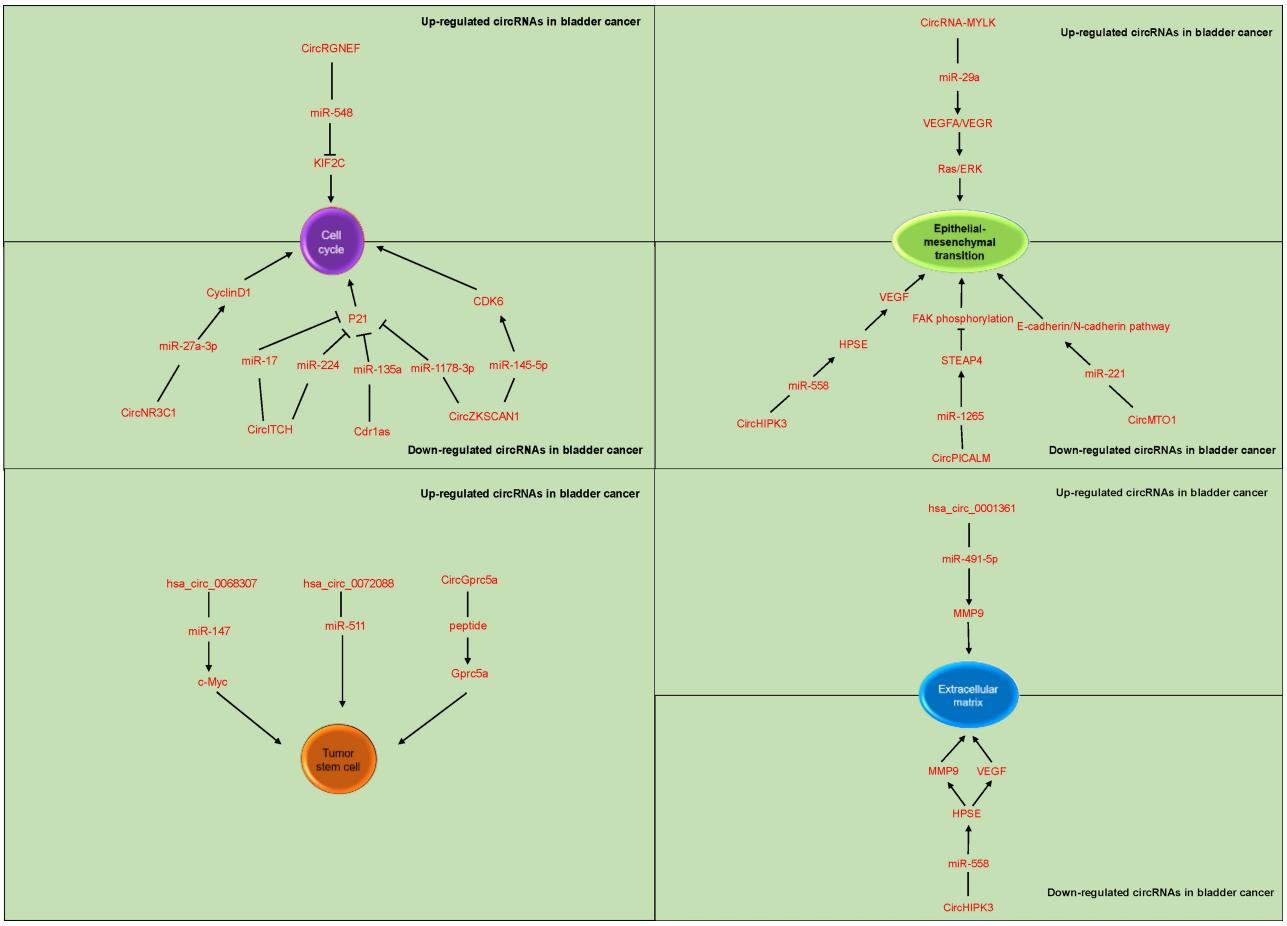


Figure 3 The detailed mechanisms of circRNAs on cell cycle, epithelial–mesenchymal transition, tumor stem cells and extracellular matrix.

Regulation of EMT

The invasion and migration of tumor cells are closely related to EMT.[104] CircRNAs also participate in tumor cell invasion and migration by regulating EMT.[104] CircRNA-MYLK, which is highly expressed in BC, was found to sponge miR-29a to activate VEGFA/VEGFR signaling and downstream Ras/ERK pathways to promote EMT.[82] In addition, VEGFA expression is increased via sponging of miR-205-05p by upregulated circ0001429 in BC.[105] In addition to increased expression of VEGFA, increased expression of VEGF also promotes EMT in BC.[40] CircHIPK3 was found to be expressed at low levels in BC, and circHIPK3 inhibits HPSE expression by sponging miR-558; therefore, the expression of the target mRNA VEGF is suppressed, resulting in inhibition of EMT.[40] Low expression of circHIPK3 in BC increases the expression of VEGF and promotes EMT.[40] FAK is a nonreceptor tyrosine kinase that contains multiple tyrosine phosphorylation sites, and phosphorylated FAK contributes to downstream signal transduction.[106] Robust activation of the FAK signaling pathway is generally believed to promote EMT progression in tumors.[107] One study showed that circPICALM sponges miR-1265 to promote the expression of its target STEAP4, and overexpressed STEAP4 can bind FAK to prevent autophosphorylation of the Y397 phosphorylation site on FAK and consequently inhibit EMT in bladder tumors.[42] In BC, circPICALM is expressed at low levels; thus, EMT is promoted through the above mechanism.[42] In addition, FAK is regulated by circFNDC3B via its interaction with miR-1178-3p, resulting in inhibition of G3BP2 and its downstream SRC/FAK signaling pathway.[36] Low expression of circFNDC3B in BC abrogates its inhibitory effect on SRC/FAK.[36] However, data regarding the effect of circFNDC3B on EMT are lacking, but it has been speculated that circFNDC3B affects EMT via FAK signaling. Low expression of circMTO1 in BC results in reduced binding of circMTO1 to miR-221, which alleviates the inhibition of the E-cadherin/N-cadherin pathways and subsequently promotes both EMT and the invasion and migration of bladder tumors.[45] In summary, in bladder tumors, different circRNAs contribute to metastasis by inducing increases in the expression of EMT-related molecules, thereby promoting EMT.

Regulation of Tumor Stem Cells

Cancer stem cells retain the ability to drive tumor formation, metastasis, and drug resistance. Because of these characteristics, tumors are difficult to eliminate. CircRNA_103809 (hsa_circ_0072088) is essential in the maintenance of BC stem cell functions, including self-renewal and invasion and migration ability, by directly interacting with miR-511.[108] CircGprc5a is upregulated in BC and BC stem cells.[109] In BC stem cells, circGprc5a interacts with peptides and binds to Gprc5a, a key factor in bladder CSCs, in a peptide-dependent manner.[109] Gprc5a is highly expressed in BC stem cells and promotes their self-renewal and metastasis.[109] Expression of hsa_circ_0068307 is upregulated in tumor cell lines, and inhibiting the expression of this circRNA can slow cell invasion and proliferation.[110] In BC stem cells, hsa_circ_0068307 knockdown upregulates miR-147 expression, and resulting in inhibition of c-Myc expression to hinder the differentiation of BC stem cells.[110] In summary, circRNAs play an important role in BC stem cell maintenance and are important candidate molecules for eliminating BC stem cells and treating BC.

Regulation of Extracellular Matrix Maintenance

The extracellular matrix is an important component of the tumor microenvironment. Many studies have confirmed that the extracellular matrix has an important effect on tumor growth, invasion, migration, angiogenesis, and other behaviors.[111–113] One report indicated that circHIPK3 inhibits HPSE expression by interacting with miR-558.[40] However, in BC, a decrease in circHIPK3 expression leads to an increase in HPSE expression, which promotes the expression of MMP9 and VEGF to remodel the extracellular matrix and thereby advance tumor development.[40] In addition, in BC, elevated expression of hsa_circ_0001361 upregulates MMP9 expression, which may affect the extracellular matrix by interacting with miR-491-5p.[114] In summary, in BC, circRNAs have important roles in maintaining the extracellular matrix and promote tumor development by changing its composition.

Regulation of Transcription Factors

The literature discussed below indicates that in BC cells, circRNAs are involved in regulating the activity of transcription factors that control the expression of molecules related to tumor biology (Table 3). Myc, as a transcription factor, was found to be upregulated by hsa_circ_0067934 in BC via its sponging of miR-1304, and increased Myc expression activates growth factor-related molecules, such as VEGFR.[115] As a member of the myc gene family, c-Myc is regulated by circCDYL in BC via direct

Table 3 CircRNAs and Transcript Factors

CircRNAs	Gene Symbol	CircRNA Expression in Bladder Cancer	Target miRNAs	Transcript Factors
CircCDYL		Down-regulation	miRNA-105-5p	c-myc
CircFUT8		Down-regulation	miR-570-3p	KLF10
CircPTPRA		Down-regulation	miR-636	KLF9
CircFAM114A2		Down-regulation	miR-762	ΔNP63
CircCEP128		Up-regulation	miR-145-5p	Sox11
CircDOCK1		Up-regulation	miR-132-3p	Sox5
CircCASC15		Up-regulation	miR-1224-5p	CREB1
hsa_circ_0067934	*PRKCI*	Up-regulation	miR-2304	Myc
hsa_circ_0058063	*ATIC*	Up-regulation	miR-486-3p	FOXP4
hsa_circ_0000144	*SLAMF6*	Up-regulation	miR-217	RUNX2

interactions of circCDYL with miR-105-5p and activates cell cycle-related molecules.[116] The current literature describes many circRNAs that have been found to be involved in regulating the activity of transcription factors, including transcriptional activators and repressors, in BC, but detailed information about the molecular transcripts that are regulated by these transcription factors is lacking. For example, in BC, circCEP128 and circDOCK1 are involved in mediating the expression of the Sox family transcription factors Sox11 and Sox5 by sponging miR-145-5p and hsa-miR-132-3p, respectively.[117,118] The Sox family of proteins comprises transcriptional regulators involved in the development of various tissues.[119–121] In addition, the KLF family comprises a group of evolutionarily conserved transcription factors that regulate a series of cellular processes, such as cell proliferation, apoptosis, differentiation, and metabolism.[122–125] CircFUT8 and circPTPRA are involved in regulating the KLF family members KLF10 and KLF9 by directly binding to miR-570-3p and miR-636, respectively.[126,127] CircRNA_0058063 (hsa_circ_0058063) directly interacts with miR-486-3p to regulate the levels of the FOXP4 transcription factor, and circCASC15 promotes the activation of CREB1 by sponging miR-1224-5p.[34,128] Low expression of circFAM114A2 in BC weakens miR-762-mediated inhibition of ΔNP63, a major isomer of the transcription factor TP63.[129] High expression of hsa_circ_0000144 in BC increases its direct binding to miR-217, thereby abrogating its inhibitory effect on the transcription factor RUNX2 and subsequently increasing RNX2 expression.[130] In summary, circRNAs participate in the regulation of transcription factors related to BC tumors, but most research has not focused on which transcript is affected by these transcription factors; therefore, more in-depth studies are required.

Conclusions

An increasing number of studies have shown that some circRNAs are differentially expressed in BC tissues and that their dysregulation is related to the clinicopathological characteristics of BC patients. By acting as transcriptional regulators, these circRNAs are associated with the expression of target miRNAs and proteins related to BC cell proliferation, invasion, and metastasis and contribute to the development of BC. Given their unique advantages, such as superior stability, higher abundance, and presence in different body fluids, circRNAs are promising diagnostic and prognostic biomarkers as well as potential therapeutic targets for BC. In addition, circRNAs are involved in the development of tumor chemoresistance, although the detailed mechanisms of circRNAs in BC chemoresistance are unknown. Clarifying the detailed mechanism of chemoresistance is a highly important task to improve BC prevention and treatment. We believe that the discovery of additional circRNAs will lead to a new era of gene-targeted therapy.

Data Sharing Statement

Data sharing not applicable to this article as no datasets were generated or analysed during the current study.

Author Contributions

All authors contributed to data analysis, drafting or revising the article, gave final approval of the version to be published, and agree to be accountable for all aspects of the work.

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Disclosure

The authors declare that they have no competing interests for this work. Disclosure of potential conflicts of interest: None.

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