Progress of research into circular RNAs in urinary neoplasms

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Circular RNAs (circRNAs) are a large class of endogenous RNA that form a covalently closed continuous loop without 5' or 3' tails and are diffusely expressed in mammalian cells. Through the development of high-throughput sequencing, microarray, and bioinformatics analyses, recent studies have shown that the expression of circRNAs is dysregulated in human tumor tissues and cells, as well as in the blood of patients, and closely correlates with the development of tumors. circRNAs can regulate the progression of tumors through various mechanisms. An increasing number of studies have shown that circRNAs may play critical roles in the early diagnosis, targeted therapy, and prognostic prediction of cancer as biomarkers or therapeutic targets. This review briefly describes the definitions and functions of circRNAs, and the main content includes the most recent progress in research into their function, regulation, and clinical relevance to bladder, renal, and prostate cancers. We also provide some novel ideas regarding the treatment of these diseases.

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27 **Abstract**

28   Circular RNAs (circRNAs) are a large class of endogenous RNA that form a covalently

29 closed continuous loop without 5' or 3' tails and are diffusely expressed in mammalian cells.

30 Through the development of high-throughput sequencing, microarray, and bioinformatics

31 analyses, recent studies have shown that the expression of circRNAs is dysregulated in human

32 tumor tissues and cells, as well as in the blood of patients, and closely correlates with the

33 development of tumors. circRNAs can regulate the progression of tumors through various

34 mechanisms. An increasing number of studies have shown that circRNAs may play critical roles

35 in the early diagnosis, targeted therapy, and prognostic prediction of cancer as biomarkers or

36 therapeutic targets. This review briefly describes the definitions and functions of circRNAs, and

37 the main content includes the most recent progress in research into their function, regulation, and

38 clinical relevance to bladder, renal, and prostate cancers. We also provide some novel ideas

39 regarding the treatment of these diseases.

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41 **Key words:** circRNA; bladder cancer; renal cancer; prostate cancer

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Introduction

47   Noncoding RNA (ncRNA) includes the major classes of housekeeping and regulatory

48   ncRNAs. Housekeeping ncRNAs include ribosomal RNA (rRNA), tRNA and small nuclear

49   RNA (snRNA). Regulatory ncRNAs can be classified according to length (< 200 or > 200 bp),

50   including small noncoding RNA that contain microRNA (miRNA), snRNA, piRNA, siRNA, and

51   long ncRNA (lncRNA). Circular RNAs (circRNAs; > 200 bp) are unusual endogenous

52   noncoding RNAs (*Bolha et al., 2017*) that were first reported by *Nigro et al. (1991)*. They were

53   initially considered to be splicing errors with no function (*Cocquerelle et al., 1993*), but through

54   the recent development of high-throughput sequencing, microarray, and bioinformatics analyses,

55   recent studies have shown that circRNAs may play pivotal roles in the occurrence and

56   progression of disease, including pancreatic cancer (*An et al., 2018*), breast cancer (*Zhao et al.,*

57   *2018*), epilepsy (*Gong et al., 2018*), and cardiovascular diseases (*Wang et al., 2017*). The present

58   review mainly highlights the most recent progress in research related to the functions, regulation,

59   and clinical relevance of circRNAs in bladder cancer (BC), renal cell carcinoma (RCC), and

60   prostate cancer (PCa) (Table 1) and provides novel ideas for future investigations and the

61   treatment of these diseases.

62

Survey methodology

64 We systematically searched titles in the PubMed database using the term, "circular RNA"

65 combined with "cancer," "guidelines," "prostate cancer," "renal cancer", "bladder cancer,"

66 "database," "data," and "identification." Publications that were unrelated to human circular RNA

67 were excluded. We did not refine factors such as journal, publishing date, or journal impact

68 factors during our search.

69 **Definition of circRNAs**

70 circRNAs comprise a class of non-coding RNA that have different structures from linear RNAs,

71 such as lncRNA and miRNA, and form covalently closed, continuous stable loop structures

72 without 3' or 5' ends. Back-splicing or lariat-circulating events might play vital roles in the

73 formation of integral circRNA. Most circRNAs are exons that stem from intergenic regions, but

74 a few originate from intergenic, intronic, antisense or untranslated regions (*Fu et al., 2018*).

75 According to their biogenesis, circRNAs can be categorized as exonic (ecircRNAs), circular

76 intronic (ciRNAs), retained-intron or exon-intron (EIciRNAs), and intergenic (*Bolha et al.,*

77 *2017*). Most circRNAs are located in the cytoplasm; however, some also reside in subcellular

78 compartments such as exosomes and mitochondria (*Tian et al., 2018;Szabo & Salzman,*

79 *2016;Shao et al., 2017; Chen et al ., 2017; Zhang et al., 2019*) (Fig. 1A). Intron length, exon

80 length, respective sequences, and RNA-binding proteins (RBPs) can affect the formation of

81 circRNAs (*Fu et al., 2018*).

82

83 **Functions of circRNAs**

84 **circRNAs can function as miRNA sponges**

85 circRNAs harbor miRNA binding sites within their sequences and can directly bind to miRNA,

86 inhibit combinations between miRNA and 3'-untranslated regions (3'-UTR) of target genes, and

87 abolish the effects of miRNA on gene expression (*Chen and Duan,2018; Li et al., 2018; Bian et*

88 *al., 2018*). This is the primary mechanism involved in the circRNA regulation of gene expression.

89 circ-SFMBT2 can serve as a sponge for miR-182-5p to regulate *CREB1* mRNA expression and

90 promote the proliferation of gastric cancer cells (*Sun et al., 2018*). circ-0000523 inhibits

91 colorectal cancer, and its overexpression attenuates the proliferation of cancer cells and induces

92 apoptosis. circ-0000523 can interact with miR-31 and inhibit the Wnt/β-catenin signaling

93 pathway, and thus, it can regulate the growth of colorectal cancer cells (*Jin et al., 2018*). circ-

94 NEK6 functions as an oncogenic circRNA in thyroid cancer as it is significantly up-regulated

95 and can promote the proliferation and invasion of cancer cells. The results of mechanical trials

96 have suggested that circ-NEK6 increases *FZD8* mRNA expression, activates the wnt signaling

97 pathway by interacting with miR-370-3p, which subsequently promotes the progression of

98 thyroid cancer (*Chen et al., 2018*). In addition, *Wang et al. (2018)* found that circ-DOCK1 is

99 distinctly upregulated in oral squamous cell carcinoma (OSCC) cell lines and OSCC tissues, and

100 that circ-DOCK1 downregulation can induce apoptosis in OSCC cell lines. circ-DOCK1 can also

101 increase *BIRC3* expression by acting as a sponge for miR-196a-5p, and then participating in the

102 process of OSCC apoptosis.

103

104 **Translation**

105 circRNA differs from linear RNA. Some circRNAs possess an open reading frame; hence, they

106 might be able to code proteins or peptides. One study has suggested that a circRNA (220 nt)

107 from the rice yellow mottle virus can encode a highly basic, 16-kDa protein (*AbouHaidar et al.,*

108 *2014*). One 2017 study found that consensus N^6-methyladenosine (m^{6}A) motifs and a single m^{6}A

109 site are sufficient to drive translation initiation, and proved that protein can be translated by

110 circRNAs in human cells. Further studies have indicated that the m^{6}A-driven translation of

111 circRNAs requires the initiation factor eIF4G2 and m6A reader YTHDF3. Methyltransferase

112 METTL3/14 can enhance, whereas demethylase FTO can inhibit m^{6}A-driven translation of

113 circRNAs (*Yang et al., 2017*). Moreover, others have found that circRNAs with internal

114 ribosome entry site elements (IRES) or prokaryotic ribosome-binding sites can encode peptides

115 (*Perriman and Ares, 1998; Chen and Sarnow, 1995*).

116

117 **circRNAs as gene transcribers and expression regulators**

118 Some circRNAs that circulate with introns "retained" between exons are called intron-containing

119 circRNAs, such as ciRNA and EIciRNA, which mainly reside in the nucleus, interact with U1

120 snRNP, and enhance the transcription of their parental genes in a cis-acting manner (*Li et al.,*

121 *2015*). In addition, some circRNAs, such as circ-ankrd52 and circ-sirt7, can accumulate at the

122   transcriptional sites of host genes, interact with RNA polymerase II (pol II) complexes, and then

123   regulate the transcription of the parental genes (*Chen, 2016*). In addition, the synthesis of back-

124   spliced circRNAs competes with pre-mRNA splicing and leads to lower levels of linear mRNA

125   that result in regulated gene expression (*Ashwal-Fluss et al., 2014*).

126

127   **Protein binding**

128   circRNAs can bind, store, sequester, and interact with proteins to regulate the expression and

129   translation of genes. Many circRNAs interact with RNA binding proteins (RBPs). For example,

130   the circRNA, circ-Mbl, and its flanking introns have conserved muscleblind (MBL) protein

131   binding sites that firmly and specifically bind MBL. Modulating MBL levels significantly affects

132   the biosynthesis of circ-Mbl (*Ashwal-Fluss et al., 2014*). *Du et al. (2016)* reported that high

133   levels of circ-Foxo3 expression in non-cancer cells are associated with cell cycle progression.

134   More concretely, aberrant circ-Foxo3 expression represses cell cycle progression by binding to

135   the cell cycle proteins cyclin-dependent kinase 2 (*CDK2*) and cyclin-dependent kinase inhibitor 1

136   (*P21*), which results in the formation of a ternary complex and subsequently blocks cell cycle

137   progression. *Chen et al. (2019)* found high levels of circ-AGO2 and human antigen R (HuR)

138   expression and associated them with poor outcomes among patients with gastric cancer. circ-

139   AGO2 promotes the growth, invasion, and metastasis of cancer cells in *vitro* and in *vivo*. The

140   mechanisms involve physical interactions between circ-AGO2 and HuR protein to promote its

141   activation and enrichment on the 3'-untranslated region of target genes. This in turn results in

142   decreased circ-AGO2 binding and the inhibition of gene silencing modulated by circ-

143   AGO2/miRNA that correlates with cancer progression.

144

circRNAs and bladder cancer (BC)

146   BC is the most prevalent among malignant tumors of the urinary system. The incidence of BC is

147   the highest among urogenital tumors in China, and it is second only to PCa in Western countries.

148   The incidence of BC in males is 3 to 4-fold higher than that in females (*Bray et al., 2018*), and it

149   increases annually, with the incidence reaching a peak at ages between 50 and 70 years. Hence,

150   biomarkers are urgently needed to diagnose and treat BC. circ-RNA shows considerable

151   potential to serve as such biomarkers. Many studies have indicated that circRNAs are involved in

152   the occurrence and progression of BC through multiple mechanisms.

153

Inhibitor activities

155   circRNAs function as sponges for miRNA to upregulate target gene expression and inhibit the

156   progression of BC (Fig. 1B). circ-HIPK3 is a circ-RNA derived from Exon2 of the *HIPK3* gene

157   (*Zheng et al., 2016*). Silencing circ-HIPK3 can significantly inhibit the growth of human cells by

158   directly binding to and inhibiting miR-124 activity (*Zheng et al., 2016*). Dysregulated circ-

159   HIPK3 expression correlates with the occurrence and progression of human diseases (*Cao et al.,*

160   *2018;Yu et al., 2018*) and circ-HIPK3 functions differ among diseases. *Li et al. (2017)* found

161 that circ-HIPK3 is significantly decreased in BC tissues and cell lines, while it negatively

162 correlates with BC grade, invasion, and lymph node metastasis. The overexpression of circ-

163 HIPK3 effectively inhibits the migration, invasion, and angiogenesis of BC cells *in vitro* and

164 suppresses BC growth and metastasis *in vivo*. Mechanistic studies have shown that circ-HIPK3

165 harbors two vital binding sites for miR-558 and can abundantly sponge miR-558 to suppress the

166 expression of *HPSE*, *VEGF*, *MMP9*, thereby suppressing the progression of BC. Therefore, circ-

167 HIPK3 might be a novel biomarker for treating BC. *Chi et al. (2019)* reported that circ-000285

168 derived from *HIPK3* inhibits BC. Analysis using quantitative real-time polymerase chain

169 reaction (qRT-PCR) has shown that circ-000285 is downregulated in BC tissues, cell lines, and

170 sera derived from patients with BC. In addition, the expression of circ-000285 is decreased

171 almost three-fold among patients who are resistant to cisplatin compared with those who are

172 cisplatin-sensitive. Additionally, circ-0000285 is associated with tumor size, differentiation,

173 lymph node metastasis, distant metastasis, and TNM stage. Collectively, these findings indicate

174 that circ-000285 can serve as a biomarker for BC diagnosis and chemotherapy, as well as a

175 prognostic predictor. circ-BCRC4 is an important inhibitor of BC because its overexpression

176 attenuates cancer cell proliferation and induces apoptosis. circ-BCRC4 also interacts with miR-

177 101 to downregulate EZH2 expression and induce cancer cell apoptosis (*Li et al., 2017*).

178 circRNAs also function as sponges of miRNAs to upregulate target gene expression and inhibit

179 BC progression (Fig. 1B). For example, recent studies suggest that circ-ITCH expression is

180 significantly downregulated in several cancer cell lines and tumor types (*Luo et al., 2018*;*Wang*

181   *et al., 2018*). Enforced circ-ITCH expression can significantly suppress BC cell proliferation,

182   migration, invasion, and metastasis, as well as induce apoptosis and G1/S cell cycle arrest *in*

183   *vitro* and *in vivo*. Mechanistically, circ-ITCH enhances the expression of miR-17, miR-224 target

184   gene *p21* and *PTEN* by "sponging" miR-17 and miR-224, which suppresses the aggressive

185   biological behavior of BC (*Yang et al., 2018*). *Xie et al. (2018)* found that low levels of circ-

186   BCRC-3 are expressed in BC tissues and cell lines, and that enhanced circ-BCRC-3 expression

187   can attenuate BC cell proliferation *in vitro* and *in vivo*. Mechanistically, circ-BCRC-3 enhances

188   the expression of miR-182-5p target gene cyclin-dependent kinase inhibitor 1B (*p27*) by

189   "sponging" miR-182-5p, which attenuates the aggressive biological behaviors of BC. Methyl

190   jasmonate (MJ), which has anticancer effects, can suppress BC progression by increasing circ-

191   BCRC-3 expression. Hence, circ-BCRC-3 functions as a tumor inhibitor that suppresses BC

192   progression through the miR-182-5p/p27 axis, which would be a novel target for BC therapy.

193   circ-UBXN7 is also a novel supressor of BC, and miR-1247-3p is a carcinogenic factor, of which

194   *B4GALT3* is a target. Recent findings suggest that circ-UBXN7 is significantly downregulated in

195   BC tissues compared with matched non-tumor tissues, and that circ-UBXN7 expression is

196   related to the pathological stage, grade, and prognosis of BC. Others have shown that circ-

197   UBXN7 directly binds miR-1247-3p, and can reverse the oncogenic effects induced by miR-

198   1247-3p. Mechanistically, circ-UBXN7 can function as a competitive endogenous RNA (ceRNA)

199   of miR-1247-3p that enhances *B4GALT3* expression, consequently inhibiting BC cell viability

200   and invasion. Consequently, the circ-UBXN7-miR-1247-3p-B4GALT3 regulatory network

201   should be a potential target for treating BC (*Liu et al., 2018*). *Liu et al. (2018)* reported that circ-

202 FNDC3B also functions as a tumor suppressor in BC. circ-FNDC3B is a highly stable and

203 cytoplasmic circRNA derived from exons 5 and 6 of the *FNDC3B* gene locus that is expressed at

204 low levels in BC cell lines and tissues, and associated with pathological T stage, grade,

205 lymphatic invasion, and the overall survival rates of patients. Functional experiments have

206 shown that overexpressed circ-FNDC3B significantly inhibits the proliferation, migration,

207 invasion, growth and lymphatic metastasis of tumors both *in vitro* and *in vivo*. Mechanical

208 experiments have shown that miR-1178-3p is a carcinogenic factor that targets the 5'UTR of

209 *G3BP2*. circ-FNDC3B can function as a miR-1178-3p sponge that directly binds to miR-1178-3p

210 to regulate the expression of *G3BP2*, inhibit the SRC/FAK signaling pathway, and suppress the

211 development of BC.

212

213 **Promoter activities**

214 circRNAs are not only inhibitors but also promoters of BC. circRNA can elevate target gene

215 expression by combining with miRNA and thus promote BC progression (Fig. 1B). *Zhong et al.*

216 *(2016)* used microarrays to determine circRNA expression profiles in BC tissues and found that

217 circ-TCF25 is upregulated. Furthermore, circ-TCF25 overexpression can downregulate miR-

218 103a-3p and miR-107, increase *CDK6* expression and promote BC cell proliferation and

219 migration *in vitro* and *in vivo*. Hence, circ-TCF25 might be a novel promising marker for BC.

220 circ-BPTF is a novel circRNA derived from *BPTF* exons, and it is significantly upregulated in

221 BC, compared with adjacent normal tissues and cell lines. Patients who express more circ-BPTF

222   have higher BC tumor grades and poorer prognoses. Functionally, circ-BPTF knockdown

223   reduces tumor progression *in vitro* and *in vivo*. Mechanistically, mimics of miR-31-5p, which is

224   a target miRNA of circ-BPTF, can partially reverse the effects of circ-BPTF. Furthermore,

225   *RAB27A* is a target of miR-31-5p, and circ-BPTF weakens the anti-oncogenic effects of miR-31-

226   5p and consequently promotes *RAB27A* expression. Therefore, attenuating circ-BPTF expression

227   might be a promising direction to pursue as a strategy for treating BC (*Bi et al., 2018*). *Zeng et al.*

228   *(2019)* found that levels of circ-VANGL1 BC are higher in BC than in adjacent normal tissues.

229   Functionally, silencing circ-VANGL1 significantly attenuates BC cell proliferation, cell cycle,

230   migration, and invasion *in vitro* and suppresses tumor growth *in vivo*. Mechanistically, circ-

231   VANGL1 directly binds to miR-605-3p. The interaction between circ-VANGL1 and miR-605-3p

232   inhibits miR-605-3p expression, by elevating that of *VANGL1* that facilitates BC progression.

233   *Sun et al. (2019)* reported that circ-0058063 is upregulated in BC tissues, and that silencing circ-

234   0058063 attenuates the migration capacity of cancer cells, increases cell apoptosis rates, and

235   arrests cells at the G0/G1 phase *in vitro*, thereby suppressing tumor growth *in vivo*.

236   Mechanistically, circ-0058063 can negatively modulate miR-145-5p as a sponge, and elevate

237   *CDK6* expression to promote BC progression.

238   Microarray analysis has shown that the circRNA, circ-MYLK, is significantly upregulated in BC.

239   Levels of circ-MYLK are associated with the progression of BC stage and grade. Functionally,

240   circ-MYLK overexpression noticeably enhances BC cell invasive and migratory capabilities.

241   Moreover, upregulating circ-MYLK can promote the epithelial-mesenchymal transition (EMT)

242   of BC. Mechanistically, circ-MYLK overexpression enhances the expression of CD31, S100A4,

243   VEGFA, snail, N-cadherin, vimentin, Ras, p-RAF-1, p-MEK1/2, pERK1/2, and suppresses that

244   of E-cadherin and ZO-1. circ-MYLK functions as a ceRNA for miR-29a, thus activating

245   VEGFA/VEGFR2 and the downstream Ras/ERK signaling pathway to exert these effects (*Zhong*

246   *et al., 2017*). *Huang et al. (2018)* identified circ-0000144 as a novel oncogene in BC, because its

247   expression is significantly upregulated in BC, compared with adjacent non-tumor tissues, and

248   high levels of circ-0000144 expression are associated with a poor prognosis. Functionally, circ-

249   0000144 knockdown attenuates BC cell proliferation and invasion *in vitro*, and reduces tumor

250   volumes *in vivo*. Mechanistically, circ-0000144 is a sponge for miR-217, and *RUNX2* is a target

251   of miR-217. circ-0000144 enhances *RUNX2* expression by repressing miR-217 and thus exerts

252   oncogenic activities in BC.

253   circ-UVRAG is derived and cyclized by some exons from the *UVRAG* gene. A recent study

254   indicated that circ-UVRAG is up-regulated in BC lines. Functionally, silencing circ-UVRAG

255   suppresses tumor formation and metastasis. Mechanistically, miR-223 is a downstream binding

256   target of circ-UVRAG, and miR-223 can target FGFR2. Downregulated circ-UVRAG promotes

257   miR-223 expression, which weakens *FGFR2* expression in BC. Therefore, circ-UVRAG might

258   serve as a good diagnostic biomarker of BC, and contribute to targeted BC therapy (*Yang et al.,*

259   *2019*). Overall, the above evidence suggests that circRNAs have the potential to serve as novel

260   biomarkers for the diagnosis, therapy, and prognostic prediction of BC.

261   At present, these studies have mainly investigated conventional functions (ceRNA mechanisms)

262   of circRNAs in BC. Unconventional functions of circRNAs, such as translation and protein

263   binding, should be further explored. Defining these functions will contribute to a deeper

264   understanding of the mechanisms underlying the involvement of circRNAs in cancer

265   development.

266

267

268   **circRNA and renal cancer**

269   Renal cancer also is a common urological tumor that was responsible for over 403,000 new

270   diagnoses in 2018 and an estimated 175,000 deaths worldwide (*Bray et al., 2018*). Therefore,

271   identifying novel biomarkers for the diagnosis and treatment of renal cancer might reduce its

272   mortality. circRNAs play major roles in RCC (*Xiong et al., 2019*) (Fig. 1B).

273   Clear cell RCC (ccRCC) is a common pathological type of renal carcinoma. *Wang et al. (2018)*

274   showed that circ-0001451 is significantly down-regulated in ccRCC tissues, and that it correlates

275   with the clinicopathological features (including clinical stage, tumor stage, lymph node, and

276   metastasis) and overall survival of patients with ccRCC. Functional experiments have confirmed

277   that circ-0001451 knockdown promotes the proliferation of ccRCC cell lines and inhibits

278   apoptosis *in vitro*, indicating its potential as novel diagnostic biomarker of ccRCC and a

279   potential target for ccRCC treatment. However, the mechanism of ccRCC suppression requires

280   further investigation. Estrogen receptor beta (ERβ) is a carcinogenic factor in ccRCC. Increased

281   ERβ expression is associated with a more advanced stage and a poor prognosis for patients with

282   ccRCC. Mechanistically, ERβ represses circ-ATP2B1 expression by inhibiting its host gene

283   ATP2B1 and directly binding to the ERE (-1765 to -1760 nt) on the 5'-promoter of ATP2B1.

284   Moreover, ERβ-circ-ATP2B1 might function by interacting with miR-204-3p, resulting in

285   decreased miR-204-3p and increased FN1 mRNA expression that promotes ccRCC progression

286   (*Han et al., 2018*). *Wang et al. (2017)* reported that androgen receptors (*AR*) interact with circ-

287   HIAT1 and promote ccRCC development. Overall survival of is worse among patients with

288   ccRCC who express low, compared with high levels of circ-HIAT1. Functionally, *AR* promote

289   ccRCC cell proliferation, migration and invasion. Mechanistically, *AR* suppress circ-HIAT1

290   expression by inhibiting its host gene (*HIAT1*) at the transcriptional level and directly binding to

291   the ARE on the *HIAT1* promoter, regulating miR-195-5p/29a-3p/29c-3p expression, and thereby

292   enhancing *CDC42* mRNA expression to promote ccRCC progression. In summary, the above

293   evidence suggests that circRNAs could serve as prognostic biomarkers and therapeutic targets

294   for ccRCC. Many circRNAs exist in RCC, but only a few have been investigated. The manifold

295   functions and mechanisms of circRNAs in RCC should be further explored in depth. In addition,

296   conventional functions such as ceRNA mechanisms and unconventional functions such as

297   translation and protein binding warrant further investigation.

298

299   **circRNA and prostate cancer (PCa)**

300   PCa is frequently diagnosed in elderly men. One report has indicated that about 1.3 million new

301   diagnoses of PCa and 359,000 associated deaths will occur worldwide during 2018 (*Bray et al.,*

302   *2018*), and that morbidity and mortality rates will continue to increase. circRNAs play vital roles

303   in PCa development (Fig. 1B). The relative mRNA expression of circRNAs can be modulated by

304   upstream or downstream factors to regulate PCa progression. Notably, miR-145 is a tumor

305   suppressor in cancer, *He et al. (2018)* found using microarray analysis that miR-145

306   overexpression promotes the expression of circRNA-101981, circRNA-008068, and circRNA-

307   406557, and suppresses that of circRNA-101996 and circRNA-091420 in PCa LNCaP cells.

308   Therefore, circRNAs can be regarded as regulatory factors in PCa development. circMYLK is

309   not only a cancerogenic factor in BC but also in PCa. *Dai et al. (2018)* found significantly

310   upregulated circ-MYLK expression in PCa tissues and cancer cell lines. Functionally,

311   upregulated circRNA-MYLK significantly promotes tumor cell proliferation, invasion, and

312   migration while decreasing cell apoptosis, whereas circ-MYLK knockdown reverses these

313   processes. Mechanistically, circ-MYLK promotes PCa cell proliferation, colony formation,

314   invasion, and migration by downregulating miR-29a expression. *Kong et al. (2017)* found high

315   expression levels of circ-SMARCA5 in PCa samples compared with matched noncancerous

316   prostate tissues, indicating that circ-SMARCA5 could be an oncogenic circRNA. Functional

317   experiments have shown that silencing circ-SMARCA5 in PCa cells suppresses proliferation,

318   increases the amount of cells in G1 phase, decreases that in S phase, and elevates apoptosis rates.

319   However, the mechanisms of circ-SMARCA5 in PCa have not been investigated in detail.

320   Presently, studies into the roles of circRNA in PCa are scarce, and further detailed investigations

321   into the mechanisms of circRNAs are required because circRNAs have the potential to serve as

322   therapeutic and prognostic targets of PCa.

323

Conclusion

325   circRNA expression markedly differs between cancer and healthy cells. circRNA function as

326   oncogenic factors or tumor suppressors that participate in cancer occurrence and progression

327   through a multitude of mechanisms. Dysregulated circRNA expression is inextricably associated

328   with cancer development. The expression of circRNAs correlates with clinical stage, tumor stage,

329   lymph node metastasis, and the prognosis of patients with cancer. circRNAs functionally

330   influence the proliferation, invasion, migration, cell cycle progression, apoptosis, and drug

331   resistance of cancer cells. circRNAs mechanistically act as sponges of miRNAs to indirectly

332   regulate target gene expression. Moreover, circRNAs can function upstream as proteins that

333   regulate target gene expression. circRNAs participate in cancer development through all these

334   mechanisms. Therefore, measures are needed to decrease cancerogenic circRNAs and/or enhance

335   the expression of circRNA tumor-suppressors as novel targets of cancer therapy.

336

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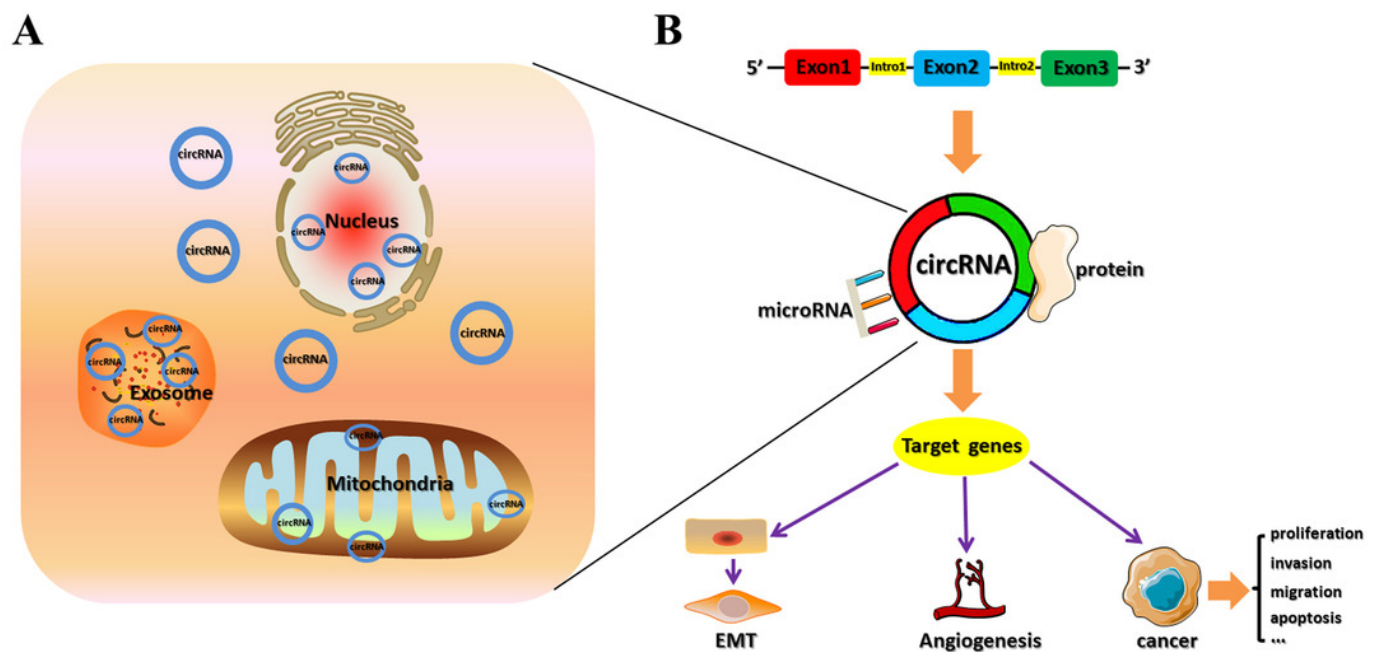
Figure 1

Locations and functions of circRNAs.

(A) Primarily, circRNAs are located in the cytoplasm, but some reside in subcellular compartments such as exosomes and mitochondria. (B) Function of circRNAs. circRNAs serve as sponges that directly bind miRNA or protein to regulate gene expression and activate signaling pathways, thus participating in the development of bladder, renal, and prostate cancers.

Summary of circRNAs in bladder, renal, and prostate cancers.

Cancer type	circRNA	miRNA	Downstream	Function	Reference
Bladder cancer	circ-HIPK3	miR-558	HPSE, VEGF, MMP9	Inhibits migration, invasion, and angiogenesis of cancer cells *in vitro*, as well as tumor growth and metastasis *in vivo*.	*Li et al., 2017*
	circ-BCRC4	miR-101	EZH2	Attenuates proliferation of cancer cells and induces apoptosis.	*Li et al., 2017*
	circ-ITCH	miR-17 miR-224	P21, PTEN	Induces G1 cell cycle arrest and apoptosis, inhibiting BC cell proliferation, invasion, and migration *in vitro*, as well as tumor growth *in vivo*.	*Yang et al., 2018*
	circ-BCRC-3	miR-182-5p	P27	Attenuates proliferation, cell cycle progression of BC cell *in vitro*; inhibits tumor growth *in vivo*.	*Xie et al., 2018*
	circ-UBXN7	miR-1247-3p	B4GALT3	Inhibits cancer cell proliferation, invasion, and migration *in vitro*;	*Liu et al., 2018*

			repenses tumor growth *in vivo*.	
circ-FNDC3B	miR-1178-3p	G3BP2	Inhibits cancer cell proliferation, migration, invasion, tumor growth, and lymphatic metastasis *in vitro* and *in vivo*.	*Liu et al., 2018*
circ-TCF25	miR-103a-3p and miR-107	CDK6	Promotes cancer cell proliferation, migration *in vitro*, tumor growth, and metastasis *in vivo*.	*Zhong et al., 2016*
circ-BPTF	miR-31-5p	RAB27A	Promotes cancer cell invasion, migration *in vitro*, and tumor growth *in vivo*.	*Bi et al., 2018*
circ-VANGL1	miR-605-3p	VANGL1	Promotes cancer cell proliferation, migration, metastasis, cell cycle progression *in vitro*, and tumor growth *in vivo*.	*Zeng et al., 2019*
circ-0058063	miR-145-5p	CDK6	Promotes cancer cell proliferation, migration, metastasis, and cell cycle progression; inhibits apoptosis *in vitro*.	*Sun et al., 2019*
circ-MYLK	miR-29a	CD31, S100A4,	Promotes cancer cell	*Zhong et al.,*

			ZO-1, VEGFA, Ras, p-Raf-1, p-MEK1/2, p-ERK1/2	proliferation, invasion, and migration, inhibiting apoptosis *in vitro*; facilitates tumor growth, EMT, and metastasis *in vivo*.	*2017*
	circ-0000144	miR-217	RUNX2	Promotes cancer cell proliferation, invasion, and migration *in vitro*, as well as tumor growth *in vivo*.	*Huang et al., 2018*
	circ-UVRAG	miR-223	FGFR2	Promotes cancer cell proliferation, migration, and metastasis *in vitro*, as well as tumor growth *in vivo*.	*Yang et al., 2019*
Renal cell cancer	circ-0001451	-	-	Suppresses cancer cell proliferation; promotes apoptosis *in vitro*.	*Wang et al., 2018*
	circ-ATP2B1	miR-204-3p	FN1	Suppresses cancer cell invasion *in vitro* and tumor growth *in vivo*.	*Han et al., 2018*
	circ-HIAT1	miR-195-5p miR-29a-3p miR-29c-3p	CDC42	Suppresses cancer cell invasion and migration *in vitro*, as well as tumor growth *in vivo*.	*Wang et al., 2017*

Prostate cancer	circ-MYLK	miR-29a	-	Promotes cancer cell proliferation, invasion, and migration; decreases apoptosis *in vitro*.	***Dai et al., 2018***
	circ-SMARCA5	-	-	Promotes cancer cell proliferation and cell cycle progression *in vitro*.	***Kong et al., 2017***