

# Circular RNAs in prostate cancer: Biogenesis, biological functions, and clinical significance

Xiao Liu,<sup>1,2</sup> Yonghua Tong,<sup>1,2</sup> Ding Xia,<sup>1</sup> Ejun Peng,<sup>1</sup> Xiaoqi Yang,<sup>1</sup> Hailang Liu,<sup>1</sup> Tao Ye,<sup>1</sup> Xinguang Wang,<sup>1</sup> Yu He,<sup>1</sup> Zhangqun Ye,<sup>1</sup> Zhiqiang Chen,<sup>1</sup> and Kun Tang<sup>1</sup>

<sup>1</sup>Department of Urology, Tongji Hospital, Tongji Medical College, Huazhong University of Science and Technology, Wuhan 430030, China

**Circular RNAs (circRNAs) are covalently closed RNA molecules that play important regulatory roles in various tumors. Prostate cancer (PCa) is one of the most common malignant tumors in the world, with high morbidity and mortality. In recent years, more and more circRNAs have been found to be abnormally expressed and involved in the occurrence and development of PCa, including cell proliferation, apoptosis, invasion, migration, metastasis, chemotherapy resistance, and radiotherapy resistance. Most of the circRNAs regulate biological behaviors of cancer through a competitive endogenous RNA (ceRNA) regulatory mechanism, and some can exert their functions by binding to proteins. circRNAs are also associated with many clinicopathological features of PCa, including tumor grade, lymph node metastasis, and distant metastasis. In addition, circRNAs are potential diagnostic and prognostic biomarkers for PCa. Considering their critical regulatory roles in the progression of PCa, circRNAs would be the potential therapeutic targets. In this paper, the current research status of circRNAs in PCa is briefly reviewed.**

## INTRODUCTION

Prostate cancer (PCa) is the most common type of cancer and the second leading cause of cancer mortality in men.<sup>1</sup> In recent years, the incidence of PCa has significantly increased around the world, which seriously menaces men's health.<sup>1–3</sup> Clinically, PCa can be defined as local or advanced stage, and treatment methods include surgery, radiotherapy, androgen deprivation therapy (ADT), and chemotherapy. Although these therapies for PCa have been successful to a certain extent, the effects of these treatments are still limited. Once patients progress to metastatic castration-resistant PCa (mCRPC), overall survival (OS) will be significantly reduced.<sup>4</sup> Therefore, it is of great significance to find new molecular targets applied on the diagnosis and treatment of PCa.

Circular RNAs (circRNAs) are a novel class of non-coding RNA molecules with a single closed covalent loop. Unlike the linear RNA molecule, it lacks a 5' cap structure and a 3' polyadenylated tail structure.<sup>5</sup> In 1976, circRNA was first identified in RNA viruses and was thought to have no biological function.<sup>6,7</sup> Until recent years, with the development of RNA deep sequencing technology and bioinformatics, more and more circRNAs have been identified in normal and malignant human tissues or cells.<sup>8–12</sup> Salzman et al. have confirmed that

circRNAs are the major transcripts of a variety of human cell types.<sup>13</sup> Moreover, accumulating evidence suggests that circRNAs have been found to regulate gene expression at transcriptional, posttranscriptional, and translational levels, which are involved in multiple pathological processes of diseases, such as neurological dysfunction,<sup>14</sup> diabetes,<sup>15</sup> cardiovascular diseases,<sup>16</sup> and tumors.<sup>17</sup>

A series of studies suggest that circRNAs play pivotal roles in the occurrence and progression of PCa. In this article, we review the relevant literature and summarize the expression, biological functions, and clinical significance of circRNAs associated with PCa.

## BIOGENESIS OF circRNAs

According to different origins, circRNAs can be classified into three main types: exonic circRNAs (ecRNAs),<sup>18</sup> exon-intron circRNAs (EIciRNAs),<sup>19</sup> and circular intronic RNAs (ciRNAs).<sup>20</sup> circRNAs are produced from precursor messenger RNAs (mRNAs) via a unique back-splicing process. To explain the back-splicing processes, Jeck et al. proposed two widely accepted circRNA cycle models: lariat-driven circularization and intron-pairing-driven circularization.<sup>21</sup> The lariat-driven circularization mode means that the splicing donor covalently binds to the splicing acceptor, which generate an exon-containing lariat and eventually form ecRNAs.<sup>22</sup> In the intron-pairing-driven circularization model, the two exons are brought close by complementary base pairs between introns, and spliceosome cuts away the exons and introns to form ecRNAs or EIciRNAs.<sup>19</sup> ciRNAs are produced by intron chains, which escape from the debranching and degradation in the process of back splicing.<sup>20</sup> RNA-binding proteins (RBPs) play an important role in the biogenesis of circRNAs by promoting or inhibiting intron pairing. Quaking (QKI) and myoblastin (MBL) proteins can promote circRNA circulation by binding to specific sequence sites in flanking introns and linking two flanking introns

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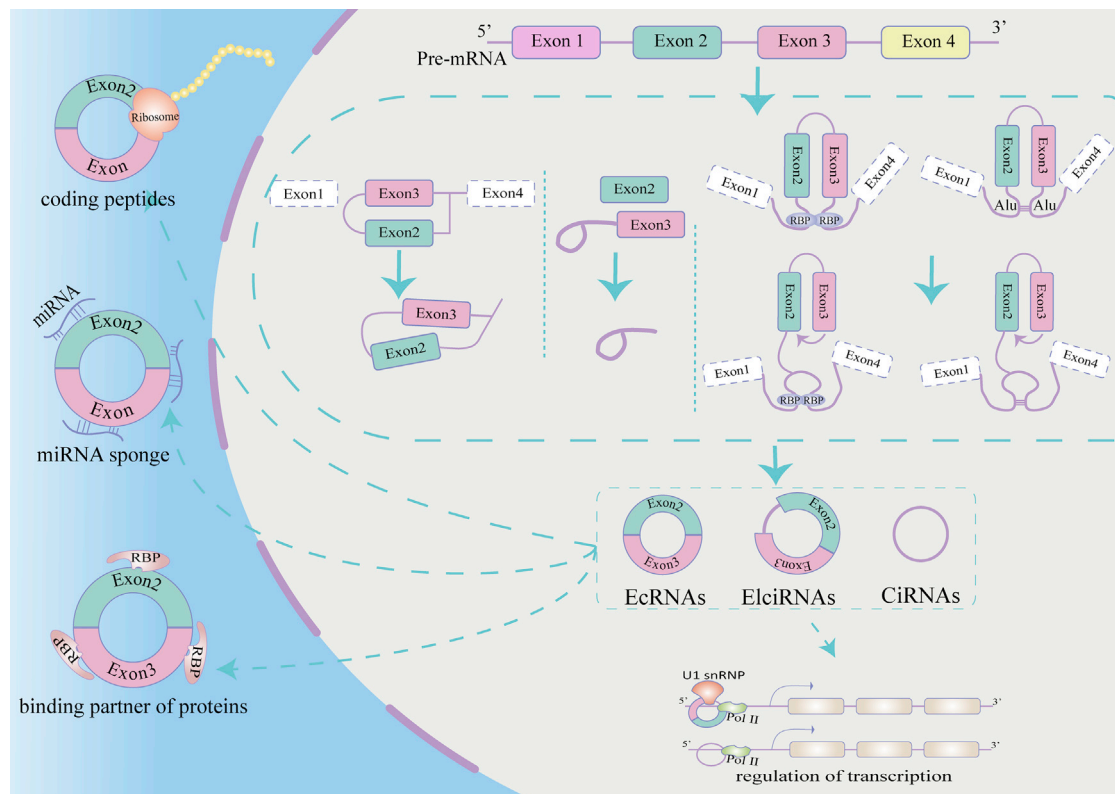
<sup>2</sup>These authors contributed equally

**Correspondence:** Dr. Kun Tang, PhD, Department of Urology, Tongji Hospital, Tongji Medical College, Huazhong University of Science and Technology, Wuhan 430030, China.

**E-mail:** [tangsk1990@163.com](mailto:tangsk1990@163.com)

**Correspondence:** Dr. Zhiqiang Chen, PhD, Department of Urology, Tongji Hospital, Tongji Medical College, Huazhong University of Science and Technology, Wuhan 430030, China.

**E-mail:** [zhqchen\\_8366@163.com](mailto:zhqchen_8366@163.com)



**Figure 1. Biogenesis and functions of circRNAs**

The non-canonical back-splicing process generates three types of circRNAs: ecircRNAs, ElciRNAs, and ciRNAs. circRNAs regulate the transcription by interacting with RNA pol II. circRNAs can be translated into polypeptides. circRNAs serve as miRNA sponges. circRNAs mediate RBP actions.

together.<sup>9,23,24</sup> In contrast, adenosine deaminase acting on RNA 1 (ADAR1) can bind to double-stranded RNA, destabilize RNA pairing, and thereby inhibit circRNAs biogenesis.<sup>25,26</sup> In short, the biogenesis of circRNAs is regulated by many factors, such as enzymes, intronic sequences, and transcription factors.<sup>23,26–28</sup>

## FUNCTIONS OF circRNAs

Plenty of studies have explored the potential functions of circRNAs. Five main functions of circRNAs have been revealed: sponging microRNAs (miRNAs),<sup>8</sup> acting as protein sponges or decoys,<sup>10,12</sup> adjusting alternative splicing,<sup>9</sup> encoding a peptide or protein,<sup>11</sup> and regulating transcription of parental genes.<sup>29</sup> Serving as miRNAs sponges is the most common function of circRNAs.<sup>8</sup> With multiple miRNA response elements, circRNA can competitively bind miRNA acting as intracellular competitive endogenous RNA (ceRNA) to regulate the expression of related genes. For instance, ciRS-7 targets miR-7 and upregulates HOXB13, the target of oncogenic miR-7, thereby promoting growth and metastasis of cancer.<sup>30</sup> Interestingly, a miRNA stabilization mechanism has also been suggested for circRNAs.<sup>31,32</sup> In addition, acting as protein sponges or decoys is also an important function for circRNAs. In 2014, Ashwal-Fluss et al. found that circMbl could sponge out the excess MBL protein by binding to it.<sup>9</sup> Some circRNAs have also been identified to regulate

alternative splicing. A circRNA from the SEPALLATA3 gene promotes the recruitment of splicing factors to the transcripts and regulates splicing of its cognate mRNA.<sup>33</sup> Furthermore, increasing studies indicate that circRNAs participate in the different biological processes by translating into proteins (Figure 1). Although circRNAs lack the 7-methylguanosine (m7G) cap at the 5' end and poly(A) tail at the 3' end, they could complete the translation through an internal ribosome entry site (IRES) element-dependent or m6A modification-dependent manner.<sup>11,34,35</sup> For example, circ-ZNF609 has an open reading frame (ORF) and is translated into a polypeptide chain in a splicing-dependent and cap-independent manner.<sup>11</sup> Some circRNAs are found to regulate gene transcription. For example, circEIF3J and circPAIP2 can promote expression of their parental genes in a *cis*-acting manner. Mechanistically, an ElciRNA-U1 snRNP complex interacts with polymerase II (pol II) at the promoters of parental genes to enhance transcription.<sup>29</sup>

## DETECTION METHODS OF circRNAs

The determination of circRNAs presents challenges. A two-step strategy is currently recommended for the validation of circRNAs, which has been proved successful in the application of miRNAs.<sup>36</sup> This approach should include the following steps: (1) discovery and identification of circRNAs using RNA sequencing (RNA-seq) or

microarray technology; (2) validation of circRNAs using reverse transcription quantitative polymerase chain reaction (RT-qPCR) and Sanger sequencing.

The total RNA samples treated with RNase R after the removal of ribosomal RNA and polyadenosylated mRNA are the preferred samples for the preparation of circRNA-seq library.<sup>21,37–39</sup> However, in many circRNA databases, RNase R was not processed.<sup>38,40–43</sup> Next-generation sequencing is a powerful way to map the whole genome of circRNAs. However, next-generation sequencing may have transcription mistakes produced from the reverse transcriptase or ligation, while the bioinformatics threshold or algorithm also affects the specificity and sensitivity.<sup>44,45</sup> For circRNAs with longer sequences (>300–500), the commonly used sequencing by synthesis technique (Illumina) is less reliable due to random transcriptional errors.<sup>46</sup> The novel third-generation sequencing, based on single-molecule sensing technology, has significantly longer read lengths and shorter sequencing times. Although there is still a certain error rate, they have the potential to promote the detection of circRNAs in the future.<sup>46</sup> In fact, the error rate of the newest single-molecule sequencing is less than five errors per billion base pairs.<sup>47</sup> RNA-seq can be used to find potential new circRNAs, but microarray can only detect characteristic circRNAs with the corresponding probes. On the other hand, microarray technology has a higher detection efficiency of circRNA than RNA-seq.<sup>48</sup>

The validation of circRNA candidates is the process of the identification between circRNA and linear RNA. The first step in the validation of circRNA candidates is to demonstrate the circularity of the transcript, which requires the design of specific divergent primers to detect circRNAs with RT-qPCR.<sup>49</sup> A further verification step is to observe the stability of circRNA via digesting the RNA samples with RNase R.<sup>50</sup> Notably, some linear RNAs are incompletely digested by RNase R.<sup>51</sup> Sanger sequencing can also be used to verify the specific back splicing of circRNAs. For Sanger sequencing, it is noted that trans-spliced linear RNA might display the same sequence as back splicing of circRNA.<sup>52</sup> Northern blotting is a gel electrophoresis method used for circRNA validation, which can separate circRNAs from their normal counterparts.<sup>8,53,54</sup> The specificity of the results in the Northern blotting is optimized by quantifying the entire circRNA length. In addition to the previously mentioned methods, complete functional proof of circRNAs can be provided through cell experiments.<sup>49,55,56</sup>

## RESEARCH OF circRNAs IN PCa

We systematically searched the Web of Science, PubMed, and Embase to identify all relevant literature published in English. The following search terms were used to identify any relevant studies: "circular RNA," "circRNA," "prostate cancer," "prostate neoplasm," "prostate tumor," and "prostate adenocarcinoma." We also used the combined Boolean operators "AND" or "OR" in the title/abstract. The amount of research on circRNAs has increased rapidly, while that on protein-coding genes has remained stable (Figure 2A). Similar trends are observed in the context of general oncology (Figure 2B) and PCa (Fig-

ure 2C). Most of these studies were published in the past 4 years. Besides, many circRNAs related to PCa were further verified by RT-qPCR (Figure 2D). These findings indicate that circRNAs and their roles in the development of PCa are attracting increasing attention.

## circRNA EXPRESSION PROFILES IN PCa

The advancement of high-throughput sequencing and bioinformatics has contributed to the discovery of circRNAs in PCa. Quantities of circRNAs that are dysregulated in PCa cell lines and tissues have been identified (Table 1). For example, 177 differentially expressed circRNAs were identified via a genome-wide circRNA-based microarray analysis of six pairs of PCa and adjacent normal tissues, among which 134 circRNAs were downregulated and 43 circRNAs were upregulated.<sup>57</sup> Through circRNA chromatin immunoprecipitation, Ge et al. found 88,750 circRNAs in five pairs of PCa and adjacent normal tissues, among which 749 were differentially expressed.<sup>58</sup> Xia et al. identified 1,021 circRNAs differentially expressed in four pairs of PCa and adjacent normal prostate tissues, and the combination of prostate specific antigen (PSA) levels and the two differentially expressed circRNAs significantly increased the sensitivity and specificity (84.5% and 90.9%, respectively) compared with PSA alone.<sup>59</sup> Moreover, high-throughput sequencing was used to identify 827 upregulated and 1,279 downregulated circRNAs associated with PCa mesenchymal transformation in the PCa cell line.<sup>60</sup> In another study, Zhang et al. analyzed the difference of circRNAs in three PCa cells (RWPE-1, 22RV1, and PC-3) by high-throughput circRNAs sequencing. A total of 9,545 circRNAs were detected and hundreds of differentially expressed circRNAs were identified.<sup>61</sup> Some databases are often used to identify differentially expressed circRNAs, like the Gene Expression Synthesis Database (GEO). Using the GSE140927 dataset, Wu et al. identified 60 circRNAs differentially expressed between PCa tissues and normal tissues, and used bioinformatics to predict three circRNA-miRNA-mRNA interaction axes.<sup>62</sup>

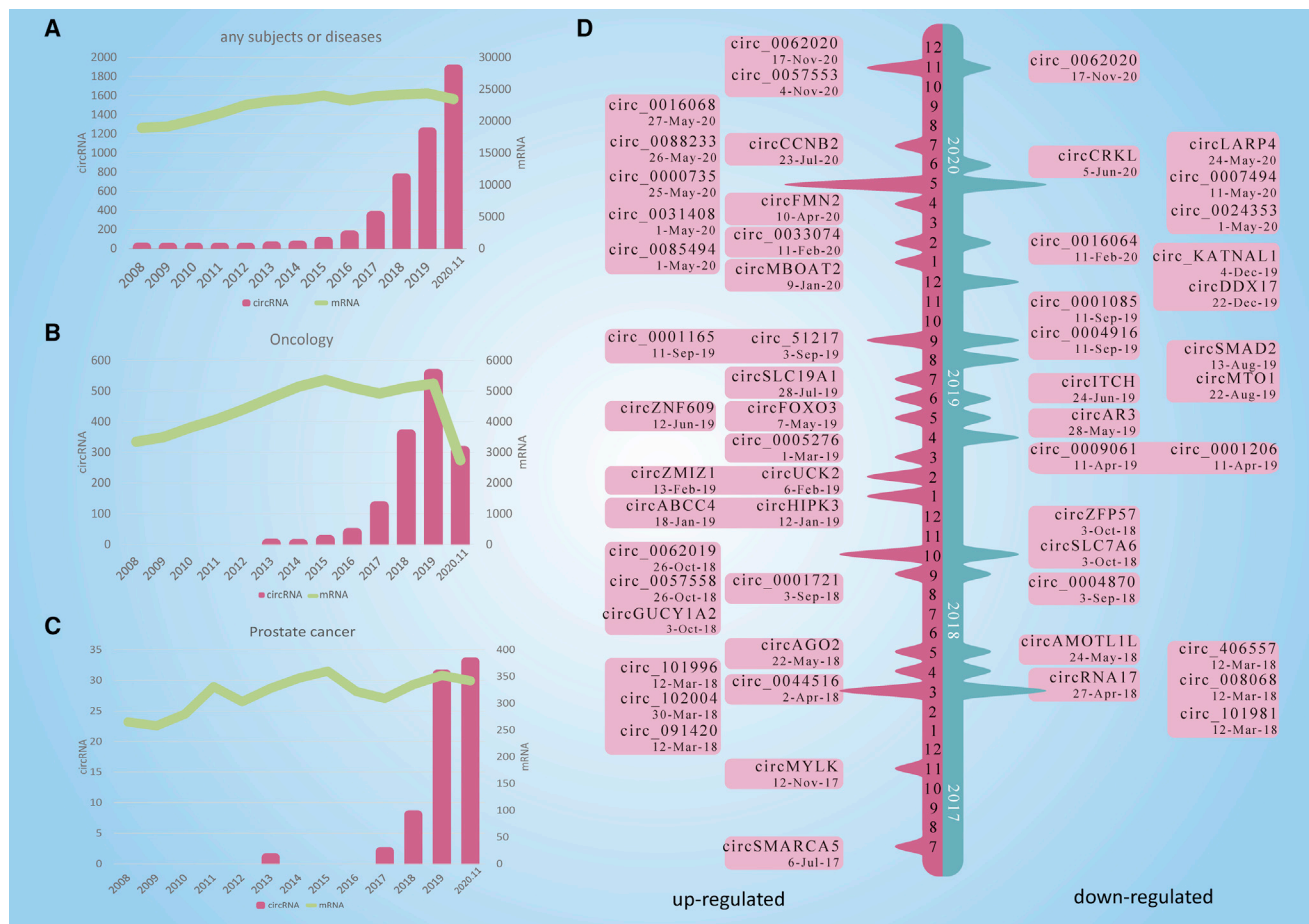
In general, there are a large number of aberrantly expressed circRNAs between PCa tissues and normal tissues. In most studies, the number of circRNAs downregulated was higher than those upregulated.

## FUNCTIONS AND MECHANISMS OF circRNAs IN PCa circRNAs and hallmarks of cancer

In 2011, some scholars proposed 10 cancer characteristics that lead to the gradual transformation of normal cells into cancer cells, with important and positive implications for cancer research.<sup>71</sup> We briefly summarized the circRNAs involved in the critical phases of PCa tumorigenesis and progression (Table 2). These circRNAs get involved in diverse processes of PCa, including cell proliferation, apoptosis, invasion, migration, metastasis, chemical resistance, and radiation resistance.

### Cell proliferation

Tumor cells can maintain an active proliferative state by activating the cell proliferation signaling pathway.<sup>71</sup> The PI3K/Akt signaling pathway plays an important role in the regulatory of cell proliferation, and its over-activation facilitates the proliferation, metastasis, and



**Figure 2. Research of circRNAs related to PCa**

(A–C) The amount of research, as quantified by the annual number of peer-reviewed publications, has been relatively stable for mRNAs (celadon line), but not for circRNAs (purple bars), in the following categories: (A) overall, for any subject or disease; (B) oncology; and (C) PCa. (D) Increasing numbers of novel circRNAs were identified from 2017 to December 2020.

recurrence of PCa.<sup>107,108</sup> Alterations of the PI3K/Akt pathway occur in 42% of localized prostate tumors and 100% of metastatic prostate tumors.<sup>109,110</sup> The mammalian target of rapamycin (mTOR) kinase is a downstream signaling molecule of the PI3K/Akt pathway.<sup>111,112</sup> circMBOAT2 upregulates mTOR expression by sponging miR-1271-5p, further activates the PI3K/Akt signaling pathway, and thereby promotes PCa cell proliferation and metastasis.<sup>85</sup> A study found that circ\_ITCH can inhibit the activation of the PI3K/AKT/mTOR pathway, thus inhibiting the proliferation and progression of PCa cells.<sup>103</sup> It is noted that circ\_ITCH exerts similar function in various cancers.<sup>113–116</sup> In addition, phosphatase and tensin homologues (PTEN) is a well-known negative regulator of the PI3K/Akt pathway.<sup>117</sup> A study found the loss of PTEN in 44% of primary prostate carcinomas.<sup>118</sup> Zhang et al. found that PTEN is low expressed in PCa tissues, while hsa\_circ\_0007494 could suppress the proliferation of PCa cells by upregulating the expression of PTEN.<sup>101</sup> Moreover, Huang et al. proposed that circABCC4 promotes proliferation and invasion of PCa cells through circABCC4/miR-1182/FOXP4 axis.<sup>75</sup>

Chen et al. also found that circHIPK3/miR-193A-3P/MCL1 axis contributes to the proliferation and migration of PCa cells.<sup>78</sup> It is worth noting that circRNAs can promote the proliferation of cancer cells through multiple signaling pathways. For example, circ\_SLC19A1 can promote proliferation and metastasis of PCa cells through two signaling pathways, circ\_SLC19A1/miR-497/SEPT2 and circ\_SLC19A1/miR-326/MAPK1.<sup>89,92</sup> This phenomenon suggests that the regulatory role of circRNA in tumor progression is more likely to be reticular than linear. Besides, circ-102004 was verified to inhibit the proliferation and migration of PCa cells.<sup>74</sup> It has also been reported that circZMIZ1 can promote the proliferation of PCa cells.<sup>87</sup>

In addition, dysregulation of cell cycle regulators contributes to the unrestricted growth and proliferation of tumor cells.<sup>71</sup> CDC25B activates the cyclin-dependent kinase (CDK) complex and plays a crucial role in cell cycle control.<sup>119</sup> For example, circHIPK3 promotes G2/M transition and induces PCa cell proliferation by sponging miR-338-3p and increasing CDC25B expression, thus playing a carcinogenic role in

**Table 1. Overview of circRNAs identified by RNA-seq and microarray in PCa**

Sample	Special treatment	Detection method	GEO database	Data source	Total circRNA	Number of circRNA differently expressed (fold change $\geq 2$ )	circRNAs validated by qRT-PCR	Reference	Year
One pair PCa and PCN tissues	-	circRNA microarray	GSE155792	circRNA microarray	170,340	-	five	Deng et al. <sup>63</sup>	2020
Three pair PCa and PCN tissues	RNase R	circRNA microarray	-	circRNA microarray	-	15 (three upregulated, 12 downregulated)	one	Li et al. <sup>64</sup>	2020
Four pair PCa and PCN tissues	RNase R	ceRNA microarray	-	ceRNA microarray	88,371	1,021 (117 upregulated, 904 downregulated)	three	Xia et al. <sup>59</sup>	2018
Five pairs HGT and LGT	-	circRNA microarray	-	circRNA microarray	-	2,238(1,238 upregulated, 1,000 downregulated)	five	Yang et al. <sup>65</sup>	2019
Five pair PCa and PCN tissues	-	circRNA microarray	-	circRNA microarray	12,532	95 (71 upregulated, 24 downregulated)	three	Song et al. <sup>66</sup>	2019
Five pair PCa and PCN tissues	RNase R	circRNA microarray	-	circRNA microarray	7,385	988 (436 upregulated, 552 downregulated)	five	Shang et al. <sup>67</sup>	2020
Five pair PCa and PCN tissues	-	circRNA microarray	-	circRNA microarray	88,750	749 (261 upregulated, 487 downregulated)	-	Ge et al. <sup>58</sup>	2020
Six pair PCa and PCN tissues	-	circRNA microarray	-	circRNA microarray	9,599	177 (43 upregulated, 134 downregulated)	six	Rochow et al. <sup>57</sup>	2020
Blood samples from the six patients and six healthy persons	RNase R	circRNA microarray	-	circRNA microarray	-	109 (69 upregulated, 42 downregulated)	eight	Li et al. <sup>68</sup>	2020
H-k LNCaP cells and normal LNCaP cells	RNase R	Sanger sequencing	GSE72844	RNA-seq	4,389	139 upregulated and 93 downregulated	six	Fei et al. <sup>28</sup>	2017
LNCaP cell line	RNase R	circRNA microarray	GSE118959	circRNA microarray	13,617	930 (278 upregulated, 588 downregulated)	10	Greene et al. <sup>69</sup>	2019
LNCaP-miR-145 cells and LNCaP-NC	-	circRNA microarray	-	circRNA microarray	10,743	267 upregulated, 149 upregulated	five	He et al. <sup>70</sup>	2018
PC-3M IE8 cells	RNase R	circRNA microarray	-	bioinformatics analysis	4,788	827 upregulated and 1,279 downregulated	four	Yan et al. <sup>60</sup>	2020
RWPE-1, 22RV1 and PC3 cell lines	RNase R	RNA-seq	-	RNA-seq and bioinformatics analysis	9,545	-	20	Zhang et al. <sup>61</sup>	2018

HGT, high-grade (Gleason > 8) PCa tissues; LGT low-grade (Gleason < 6) PCa tissues; PCN, PCa tissues paired adjacent normal prostate tissues; H-k, HNRNPL-knockdown; NC, normal control.

HGT and LGT taken from the two different areas within the same PCa sample.

PCa.<sup>90</sup> Another study also confirmed that circHIPK3 can promote PCa cell proliferation through the circHIPK3/miRNA-338-3P/ADAM17 axis, thus promoting the occurrence of PCa cell malignancy.<sup>79</sup> KLF5 is a tumor suppressor in the progression of PCa.<sup>120</sup> circCRKL can inhibit the cell cycle progression in PCa by regulating miR-141/KLF5 and plays a tumor suppressor role in PCa.<sup>100</sup> Besides, Kong et al. also found that circSMARCA5 promotes cell cycle, inhibits cell apoptosis, and acts as an oncogene in PCa.<sup>72</sup> Further studies showed that circSMARCA5 could promote glycolysis and proliferation of PCa cells through circSMARCA5/miR-432/PDCD10 axis, thus accelerating the process of PCa.<sup>91</sup> Moreover, the overexpression of circFMN2 can reduce the percentage of G0/G1 phase of PCa cells, increase the percentage of PCa cells in G2 phase, and inhibit cell apoptosis.<sup>67</sup>

### Apoptosis

Apoptosis and autophagy are the main mechanisms of controlled cell death.<sup>121</sup> Caspase protein is a key regulator of apoptosis pathways. circ\_KATNAL1 can regulate the activity of caspase through the

miR-145-3P/WISP1 pathway, thus regulating apoptosis.<sup>102</sup> Forkhead box transcription factor class O3 (FOXO3) is another key factor involved in the process of apoptosis.<sup>122</sup> Shen et al. have shown that circFoxo3 enhances Foxo3 expression through sponging miRNAs in PCa, promoting FoxO3-mediated apoptosis.<sup>106</sup> Similarly, Weng et al. found that circ-LARP4 inhibits cell migration of PCa by upregulating FOXO3A expression.<sup>105</sup> In addition, circ\_Foxo3 can also promote apoptosis in other cancers, such as breast cancer and bladder cancer.<sup>123,124</sup> However, circFoxo3 was found to act in a carcinogenic role in PCa through the circFoxo3/miR-29a-3P/SLC25A15 axis in another study.<sup>86</sup> Therefore, the role of circFOXO3 in PCa is still debatable. Moreover, Zhang et al. found that circ\_0057553 increases cell proliferation and inhibits cell apoptosis through miR-515-5P/YES1 signaling pathway.<sup>88</sup> Wang et al. confirmed that the circ\_ITCH/miR-17-5p/HOXB13 signaling pathway contributes to the apoptosis of PCa cells.<sup>97</sup> Furthermore, another study found that the expression of circ\_ITCH is decreased in PCa tissues, and upregulation of circ\_ITCH could promote apoptosis by targeting miR-197 ×<sup>96</sup>

**Table 2. Dysregulated circRNAs in PCa**

Name	CircBase ID	Expression change	Target	Gene	Function	Types of PCa tissues and PCa cell lines	Reference	Year
circSMARCA5	hsa_circ_0001445	up	-	-	promoted cell proliferation and inhibited cell apoptosis	21 pairs of PCa tissues and adjacent normal tissues; LNCaP, LNCaP-AI, 22RV1, DU145, PC-3, and WPMY-1 cell lines	Kong et al. <sup>72</sup>	2017
circRNA-MYLK	hsa_circ_0141940	up	miR-29a	-	promoted proliferation, invasion, and migration	17 pairs of PCa tissues and adjacent normal tissues; DU145, LNCaP, PC-3, PC-3MIE8, and WPMY-1 cell lines	Dai et al. <sup>73</sup>	2018
circ-102004	-	up	-	-	promoted cell proliferation, migration and invasion; decreased cell apoptosis	16 PCa samples and six normal prostate tissues; PC3 and 22RV1 cell lines	Si-Tu et al. <sup>74</sup>	2018
circCSNK1G3	hsa_circ_0001522	up	miR-181b/day	-	promoted cell proliferation	LNCaP, 22Rv1, PC-3, and V16A cell lines	Chen et al. <sup>32</sup>	2019
circABCC4	hsa_circ_0030586	up	miR-1182	FOXP4	promoted cell proliferation, migration, and invasion	47 pairs of PCa tissues and adjacent normal tissues; PC3 and DU145 cells	Huang et al. <sup>75</sup>	2019
circ0005276	hsa_circ_0005276	up	-	-	promoted cell proliferation and migration	90 pairs of PCa tissues and adjacent normal tissues; DU145, LNCaP, PC-3, VCaP, and RWPE-1 cell lines	Feng et al. <sup>76</sup>	2019
circAGO2	hsa_circ_0135889	up	-	-	promoted proliferation, invasion, and metastasis	PC-3 cell line	Cheng et al. <sup>77</sup>	2019
circHIPK3	hsa_circ_0000284	up	miR-193a-3p	MCL1	promoted cell proliferation, migration, and invasion	26 pairs of PCa tissues and adjacent normal tissues; LNCaP, PC3, DU145, 22Rv1, and RWPE-1 cell lines	Chen et al. <sup>78</sup>	2019
circHIPK3	hsa_circ_0,000284	up	miR-338-3p	ADAM17	promoted cell proliferation and invasion	60 pairs of PCa tissues and adjacent normal tissues; 22RV1, PC-3, DU145, LNCaP, and RWPE-1 cell lines	Cai et al. <sup>79</sup>	2019
circZNF609	hsa_circ_0000615	up	miR-186-5p	-	promoted cell proliferation and metastasis	25 pairs of PCa tissues and adjacent normal tissues; PC-3 and LNCaP cell lines	Jin et al. <sup>80</sup>	2019
circRNA-51217	-	up	miR-646	TGFβ1	promoted cell invasion	C4-2, PC3, DU145, LNCaP, and HEK293T cell lines	Xu et al. <sup>81</sup>	2020
circ_0044516	hsa_circ_0044516	up	miR-29a-5p	-	promoted cell proliferation and metastasis	blood samples from the six patients and six healthy persons; PC3, 2B4, LNCap, and 5637 cell lines	Li et al. <sup>68</sup>	2020
hsa_circ_0000735	hsa_circ_0000735	up	miR-7	-	promoted cell viability, migration, invasion; inhibited cell apoptosis and cell resistance to docetaxel	50 pairs of PCa tissues and adjacent normal tissues; PC3, DU145, PC-3/DTX, DU145/DTX, and RWPE-1 cell lines	Gao et al. <sup>82</sup>	2020

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Table 2. Continued

Name	CircBase ID	Expression change	Target	Gene	Function	Types of PCa tissues and PCa cell lines	Reference	Year
circ-ZNF609	hsa_circ_0000615	up	miR-501-3p	HK2	promoted cell proliferation, migration and glycolysis; inhibited cell apoptosis	30 pairs of PCa tissues and adjacent normal tissues; 22RV1, VCaP, DU145, LNCaP, and RWPE-1 cell lines	Du et al. <sup>83</sup>	2020
circ_CCNB2	hsa_circ_0035483	up	miR-30b-5p	KIF18A	promoted cell proliferation, migration and autophagy; inhibited apoptosis	25 pairs of PCa tissues and adjacent normal tissues; DU145, LNCaP, DU145/IR, and LNCaP/IR cell lines	Cai et al. <sup>84</sup>	2020
circMBOAT2	hsa_circ_0007334	up	miR-1271-5p	mTOR	promoted cell proliferation, migration, and invasion	50 pairs of PCa tissues and adjacent normal tissues; LNCaP, VCaP, PC3, DU145, C4-2B, and RWPE-1 cell lines	Shi et al. <sup>85</sup>	2020
circFOXO3	hsa_circ_0006404	up	miR-29a-3p	SLC25A15	promoted cell proliferation and inhibited cell apoptosis	53 pairs of PCa tissues and adjacent normal tissues; blood samples from the 26 patients and 19 healthy persons; LNCaP, 22Rv1, DU145, PC-3, and WPMY-1 cell lines	Kong et al. <sup>86</sup>	2020
circZMIZ1	hsa_circ_0005844	up	-	-	promoted cell proliferation	blood samples from the 14 patients and 14 healthy persons; DU145, C4-2, LNCaP, 22RV1, and RWPE-1 cell lines	Jiang et al. <sup>87</sup>	2020
circ_0057553	hsa_circ_0057553	up	miR-515-5p	YES1	promoted cell viability, migration, invasion, and glycolysis; inhibited cell apoptosis	37 pairs of PCa tissues and adjacent normal tissues; 22RV1, PC3, DU145, LNCaP, and RWPE-1 cell lines	Zhang et al. <sup>88</sup>	2020
circ_0088233	hsa_circ_0088233	up	miR-185-3p	E2F1 and WNT2B	promoted cell proliferation, migration, invasion, and inhibited apoptosis	46 pairs of PCa tissues and adjacent normal tissues; LNCaP, PC3, DU145, 22RV1, and RWPE-1 cell lines	Deng et al. <sup>63</sup>	2020
circ-0016068	hsa_circ_0016068	up	miR-330-3p	BMI-1	promoted cell proliferation, migration, and invasion	42 pairs of PCa tissues and adjacent normal tissues; VCaP, PC3, DU145, 22RV1, and RWPE-1 cell lines	Li et al. <sup>64</sup>	2020
circ_SLC19A1	hsa_circ_0062019	up	miR-497	SEPT2	promotes cell growth and invasion	PC3, 22Rv1, DU145, LNCaP, and WPMY-1 cell lines	Zheng et al. <sup>89</sup>	2020
circFMN2	hsa_circ_0005100	up	miR-1238	LHX2	promoted cell proliferation, migration, and invasion; inhibited apoptosis and EMT	90 pairs of PCa tissues and adjacent normal tissues; blood samples from the 30 patients and 30 healthy persons; VCaP, PC3, DU145, LNCaP, and RWPE-1 cell lines	Shang et al. <sup>67</sup>	2020
circHIPK3	hsa_circ_0000284	up	miR-338-3p	Cdc25B	promoted cell proliferation and inhibited apoptosis	45 PCa samples and 25 normal prostate tissues; LNCaP, DU145, PC3, 22RV1, and RWPE-1 cell lines	Liu et al. <sup>90</sup>	2020

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Table 2. Continued

Name	CircBase ID	Expression change	Target	Gene	Function	Types of PCa tissues and PCa cell lines	Reference	Year
circSMARCA5	hsa_circ_0071043	up	miR-432	PDCD10	accelerated the proliferation, metastasis, and glycolysis of cells	30 pairs of PCa tissues and adjacent normal tissues; DU145, 22RV1, and RWPE-1 cell lines	Dong et al. <sup>91</sup>	2020
circSLC19A1	hsa_circ_0062019	up	miR-326	MAPK1	promoted the proliferation, migration, and invasion of PCa cells	48 pairs of PCa tissues and adjacent normal tissues; DU145, PC3, LNCaP, 22RV1, and RWPE-1 cell lines	Huang <sup>92</sup>	2020
circ_0062020	hsa_circ_0062020	up	miR-615-5p	-	promoted cell proliferation, migration, and invasion; inhibited apoptosis and radiosensitivity	30 radiosensitive PCa samples, 30 radioresistant PCa samples and 30 normal prostate tissues; DU145, LNCaP, and WPMY-1 cell lines	Li et al. <sup>93</sup>	2020
circRNA17	hsa_circ_0001427	down	miR-181c-5p	ARv7	inhibited cell enzalutamide resistance and invasion	26 PCa samples and 13 normal prostate tissues; C4-2, CWR22Rv1, and 293T cell lines	Wu et al. <sup>94</sup>	2019
circSMAD2	hsa_circ_0047603	down	miR-9	STAT and MEK/ERK pathways	inhibited cell proliferation and migration; blocked EMT process	20 pairs of PCa tissues and adjacent normal tissues; LNCaP and PC3 cell lines	Han et al. <sup>95</sup>	2019
circ_ITCH	hsa_circ_0001141	down	miR-197	-	inhibited cell proliferation and promoted cell apoptosis	DU 145, 22RV1, VCaP, PC-3, and RWPE-1 cell lines	Yuan et al. <sup>96</sup>	2019
hsa_circ_0001206	hsa_circ_0001206	down	miR-1285-5p	Smad4	inhibited cell proliferation, migration, and invasion	50 pairs of PCa tissues and adjacent normal tissues; DU145, PC-3, LNCaP, and RWPE-1 cell lines	Song et al. <sup>66</sup>	2019
circ_ITCH	hsa_circ_0001141	down	miR-17-5p	HOXB13	suppressed cell growth, invasion and metastasis; induced cell apoptosis	52 pairs of PCa tissues and adjacent normal tissues; C4-2, LNCaP, DU145, 22RV1, PC-3, VcaP, and RWPE-1 cell lines	Wang et al. <sup>97</sup>	2019
circUCK2	hsa_circ_001357	down	miR-767-5p	TET1	inhibited cell proliferation and invasion	C4-2 cell line	Xiang et al. <sup>98</sup>	2019
hsa_circ_0004870	hsa_circ_0004870	down	miR-145	RBM39	-	LNCaP cell line	Greene et al. <sup>69</sup>	2019
circAMOTL1L	hsa_circ_000350	down	miR-193a-5p	PCDHA8	inhibited cell migration and invasion	62 PCa samples, and 35 normal prostate tissues; Du145, LNCaP, PC3, and RWPE-1 cell lines	Yang et al. <sup>65</sup>	2019
circDDX17	hsa_circ_0063308	down	miR-346	LHPP	inhibited cell proliferation, invasion, and EMT	20 pairs of PCa tissues and adjacent normal tissues; 22RV1 and PC-3 cell lines	Lin et al. <sup>99</sup>	2020
circCRKL	hsa_circ_0001206	down	miR-141	KLF5	repressed cell cycle, migration, and invasion, and boosted apoptosis	45 pairs of PCa tissues and adjacent normal tissues; LNCaP, DU145, C4-2, 22RV1, and RWPE-1 cell lines	Nan et al. <sup>100</sup>	2020

(Continued on next page)



Table 2. Continued

Name	CircBase ID	Expression change	Target	Gene	Function	Types of PCa tissues and PCa cell lines	Reference	Year
hsa_circ_0007494	hsa_circ_0007494	down	miR-616	PTEN	inhibited cell proliferation, migration, and invasion	49 pairs of PCa tissues and adjacent normal tissues; C4-2, PC3, 22Rv1, DU145, LNCaP, and RWPE-1 cell lines	Zhang et al. <sup>101</sup>	2020
circ_KATNAL1	hsa_circ_0008068	down	miR-145-3p	WISP1	inhibited cell proliferation and invasion; promoted cell apoptosis	22Rv1, DU145, LNCaP, PC3, and WPMY-1 cell lines	Zheng et al. <sup>102</sup>	2020
circ-ITCH	hsa_circ_0001141	down	miR-17	Wnt/ $\beta$ -catenin and PI3K/AKT/mTOR pathways	inhibited cell proliferation, migration, and invasion	10 pairs of PCa tissues and adjacent normal tissues; LNCaP, PC-3, and RWPE-1 cell lines	Li et al. <sup>103</sup>	2020
circ-MTO1	hsa_circ_0076979	down	miR-17-5p	–	inhibited cell proliferation and invasion	298 pairs of PCa tissues and adjacent normal tissues; DU145, PC-3, VCaP, and RWPE-1 cell lines	Hu et al. <sup>104</sup>	2020
circ-LARP4	hsa_circ_0026224	down	–	FOXO3A	inhibited cell migration and invasion	55 pairs of PCa tissues and adjacent normal tissues; 22RV1, DU145, LNCaP, and P69 cell lines	Weng et al. <sup>105</sup>	2020
circFoxo3	hsa_circ_0006404	down	–	FOXO3	inhibited cell survival, migration, invasion, and chemoresistance to docetaxel	22 low-grade PCa samples, 24 high-grade PCa samples, and 18 normal prostate tissues; VCaP, LNCaP, Du145, PC3, and PWPE1 cell lines	Shen et al. <sup>106</sup>	2020

### Invasion, migration, and metastasis

Tumor cells invade and migrate into lymphatic vessels and blood vessels, eventually resulting in metastasis to distant organs.<sup>125</sup> Some circRNAs can promote the invasion, migration, and metastasis of PCa. Argonaute 2 (AGO2) is a component of the mammalian AGO protein family, which is widely expressed and involved in posttranscriptional gene silencing.<sup>126</sup> AGO2 has been verified as having expression levels that are aberrant in various types of cancers, including gastric cancer,<sup>127</sup> colorectal cancer,<sup>128</sup> and neuroblastoma,<sup>129</sup> meanwhile AGO2 regulates proliferation, migration, and invasion.<sup>130</sup> Chen et al. reported that circAGO2 interacts physically with human antigen R (HuR) protein, inhibits AGO2/miRNA-mediated gene silencing, and promotes tumor genesis and aggression.<sup>77</sup> TGF $\beta$ 1 plays a crucial role in the migration and invasion of many types of tumors.<sup>131</sup> TGF $\beta$ 1 has been reported to induce PCa cell invasion *in vitro* by Smad and non-Smad signaling.<sup>132–134</sup> A study indicated that circRNA-51217 can sponge miRNA-646 to increase TGF $\beta$ 1 expression and thereby induces TGF $\beta$ 1/P-SMAD signaling to increase PCa cell invasion.<sup>81</sup> Feng et al. revealed that the hsa\_circ-0005276/FUS axis promotes the proliferation, migration, and epithelial-mesenchymal transition (EMT) of PCa cells by upregulating XIAP.<sup>76</sup> Similarly, Jin et al. proposed that circZNF609 promotes invasion and metastasis of PCa cells by downregulating

miR-186-5p.<sup>80</sup> Li et al. found that circ\_0044516 promotes tumor invasion and metastasis through interaction with miR-29a-5P.<sup>68</sup>

There is increasing evidence that circRNAs can also act as inhibitors of PCa invasion or metastasis. EMT is closely related to tumor metastasis.<sup>135</sup> E-cadherin and N-cadherin are important proteins in the EMT process and are considered as markers of EMT.<sup>136</sup> Han et al. proved that overexpression of circSMAD2 can upregulate E-cadherin and downregulate N-cadherin by sponging miR-9, thus inhibiting the EMT process of PCa.<sup>95</sup> In addition, Lin et al. proposed that circDDX17 could inhibit proliferation, invasion, and EMT of PCa through the circDDX17/miR-346/LHPP signaling pathway.<sup>99</sup> Similarly, circAMOTL1L can upregulate the expression of E-cadherin by targeting the miR-193A-5P/PCDHA8 axis to prevent the metastasis of PCa.<sup>65</sup> In fact, the inhibition of EMT in PCa cells by p53 is also achieved through the circAMOTL1L/miR-193a-5P/PCDHA8 signaling pathway.<sup>65</sup>

### Chemotherapy resistance

Most PCa cells are sensitive to androgen castration therapy (ADT), which makes ADT a first-line treatment for patients with advanced PCa.<sup>137</sup> However, some studies have shown that ADT only slightly

improves the survival rate of patients, and one-third of patients will relapse and eventually develop castration-resistant PCa (CRPC).<sup>138</sup> Chemotherapy drug resistance is a troublesome problem in the therapy of CRPC. Tumor response to various chemotherapies is a complex process involving multiple circRNAs.

Docetaxel (DTX)-based chemotherapy is the standard first-line treatment for CRPC patients and can prolong the survival time of patients.<sup>139</sup> However, repeated DTX treatment will produce DTX resistance and reduce the therapeutic effect.<sup>140</sup> Understanding the underlying mechanisms of DTX resistance is critical to improve the prognosis of patients with CRPC. miR-7 plays a crucial role in the chemical resistance of various tumors, such as small-cell lung cancer,<sup>141</sup> glioblastoma,<sup>142</sup> and hepatocellular carcinoma.<sup>143</sup> Gao et al. found that hsa\_circ\_0000735 is upregulated in DTX-resistant PCa tissues and cells, and inhibition of the expression of hsa\_circ\_0000735 could improve the sensitivity of PCa to DTX by sponging miR-7.<sup>82</sup> In another study, circFoxo3 was demonstrated to be low expressed in PCa tissues, and circFoxo3 could improve the sensitivity of PCa to DTX.<sup>106</sup>

Although CRPC is resistant to ADT, it still relies on androgen through the androgen receptor (AR) pathway.<sup>144</sup> Enzalutamide, as a new oral drug targeting androgen receptor signaling pathway, can competitively inhibit the binding of AR.<sup>145</sup> It is a first-line drug for patients with CRPC who have not received chemotherapy.<sup>146</sup> Its affinity to androgen receptors is five to eight times higher than that of previous antiandrogen drugs such as bicalutamide.<sup>147</sup> However, about 20%–40% of patients will show inherent resistance to enzalutamide, and patients with initial objective response will eventually develop secondary drug resistance.<sup>148</sup> Androgen receptor splicing variants (AR-Vs) in tumor cells of CRPC patients are associated with resistance to both abiraterone and enzalutamide.<sup>149,150</sup> In a study, the researchers found that upregulating the expression of circRNA17 can inhibit the growth and invasion of enzalutamide-resistant cells, and confirmed that the circRNA17/miR-181c-5p/ARv7 signaling pathway plays a crucial role in the process of enzalutamide resistance.<sup>94</sup> In addition, the expression level of circRNA17 is positively correlated with that of miR-181c-5p, indicating that circRNA17 functions as a reservoir or a stabilizing factor for miR-181c-5p, rather than sponging the miRNAs.<sup>94</sup> Greene et al. reported that the circRNA expression profile is associated with enzalutamide-resistant PCa. Compared with the control, there are 278 upregulated circRNAs and 588 downregulated circRNAs in enzalutamide-resistant cell lines.<sup>69</sup>

### Radiotherapy resistance

Radiation therapy has made exciting breakthroughs in the metastasis of PCa and postoperative repairing.<sup>151–153</sup> However, a large proportion of PCa patients receiving radiotherapy relapse, which may be due to the development of radiation resistance.<sup>154</sup> Understanding the anti-radiation mechanism of PCa is helpful to confront recurrent PCa and block its metastasis. Several studies have shown that circRNAs are connected with the regulation of radiosensitivity of

many cancers.<sup>155–157</sup> Cai et al. discovered that circ\_CCNB2 is over-expressed in radiation-resistant PCa tissues and cells, and inhibition of circ\_CCNB2 expression could increase the radiosensitivity of PCa through the miR-30b-5P/KIF18A axis.<sup>84</sup> Therefore, inhibition of circ\_CCNB2 can improve the radiotherapy efficacy of patients with recurrent PCa. In another study, circ-ZNF609 was abnormally up-regulated in PCa tissues and cells. circ-ZNF609 accelerates glycolysis through miR-501-3P/HK2 axis, promoting the progression of PCa cells and radiation therapy resistance.<sup>83</sup> It has also been reported that circ\_0062020 can inhibit radiotherapy sensitivity through circ\_0062020/miR-615-5P/TRIP13 signaling pathway.<sup>93</sup> In general, the association between circRNA imbalance and the development of radioresistance of PCa remains to be further studied.

### Mechanisms of circRNAs in PCa

circRNAs mainly play regulatory roles in the pathological process of PCa by acting as miRNA sponges. Some studies have also found that circRNAs in PCa can bind to proteins to play regulatory roles. It should be noted that circRNAs can be translated into polypeptides, but the existence of this kind of mechanism has not been found in studies related to PCa.

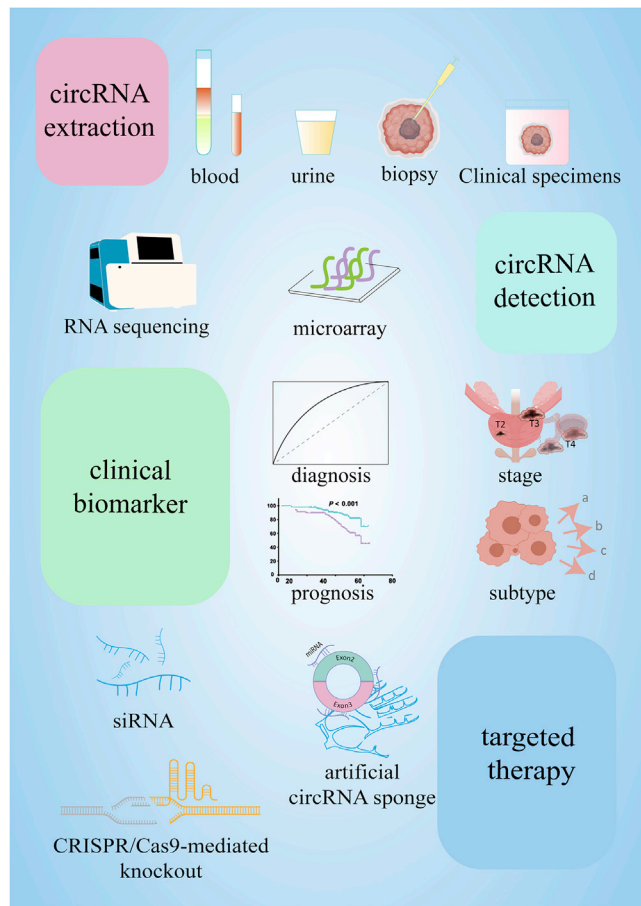
The ceRNA hypothesis indicates that circRNAs can compete with mRNA for binding to miRNAs, thus positively regulating target genes of miRNAs.<sup>8</sup> For example, circHIPK3 acts as a molecular sponge for miR-193a-3P in PCa. Since miR-193A-3P usually inhibits MCL1 expression by targeting its 3' UTR, circHIPK3 ultimately upregulates the expression of MCL1 in PCa.<sup>78</sup> However, there are a few reports that circRNAs binding with miRNAs can enhance the inhibition of miRNA on downstream target genes. For example, Wu et al. revealed that circRNA17 inhibits the expression of ARv7 by sponging to miR-181c-5.<sup>94</sup> Similarly, it has been reported that circ\_KATNAL1 binding with miR-145-3p inhibits the expression of downstream target gene WISP1.<sup>102</sup> The specific mechanism of this phenomenon remains to be further studied.

circRNAs play crucial roles in regulating gene expression at the transcriptional level by interacting with RBPs. Feng et al. found that the RNA-binding protein FUS interacts with circ0005276 to promote XIAP expression, thus promoting the occurrence and development of PCa.<sup>76</sup> In another study, circAGO2 inhibits AGO2/miRNA-mediated gene silencing by binding to HuR, thereby promoting tumorigenesis and invasiveness in the PCa.<sup>77</sup>

### CLINICAL SIGNIFICANCE OF circRNAs IN PCa

Localized PCa shows a relatively long-term survival, but metastatic PCa remains largely incurable even after intensive multimodal therapy.<sup>158</sup> Therefore, early diagnosis, prognosis judgment, and the development of new therapies are of great significance for PCa.

Since its introduction in 1987 as a serum tumor marker, PSA has been the standard biomarker used to screen, diagnose, and monitor PCa.<sup>159</sup> However, the application of PSA was thought to offer a small benefit for reducing PCa morbidity, but with flaws of overdiagnosis and



**Figure 3. The clinical significance of circRNAs in PCa**

circRNAs could be detected from various clinical samples using RNA-seq or microarray. Besides, circRNAs can be used as diagnosis or prognosis biomarkers, and circRNAs are also promising therapeutic targets.

overtreatment.<sup>160–162</sup> Moreover, the level of PSA could be affected by multiple factors, such as trauma, prostatitis, and age.<sup>163,164</sup> Prostate biopsy is the gold standard method to confirm the presence of cancer, but this technique is invasive and has some complications, such as infection and bleeding.<sup>165</sup> circRNAs show great potential in the diagnosis and prognosis as biomarkers of PCa. First of all, as unique endogenous non-coding RNAs, circRNAs are highly conserved and widely expressed in a variety of tissues.<sup>166</sup> Second, circRNA has a covalent closed-loop structure and high stability against RNA exonuclease degradation.<sup>21</sup> Finally, in addition to physical tissues, PCa-related circRNAs can also be detected in the human bodily fluids, such as blood and urine.<sup>167,168</sup> More and more circRNAs have been identified as diagnosis and prognosis biomarkers of PCa (Figure 3).

#### circRNAs and clinicopathologic characteristics in PCa

Many circRNAs have been validated to be related or unrelated to some clinicopathological parameters of PCa patients (Table 3).

Xia et al. found that circ\_SLC19A1 is related to the patient's age, Gleason score, plasma PSA level, and tumor invasion, while circ\_0057558 is only related to Gleason score.<sup>59</sup> A study found that circAR3 is significantly upregulated in the serum of PCa patients. Except for Gleason score, circAR3 is also related to lymph node metastasis (LNM), but not serum PSA levels or tumor invasion.<sup>169</sup> Moreover, the expression of circAMOTL1L is significantly lower in PCa tissues than in normal prostate tissue, and its expression is related to Gleason score and serum PSA level.<sup>65</sup> circFOXO3 can be detected in PCa tissues and serum, and it is irrelevant to the patient's age or PSA level, but is related to the Gleason score.<sup>86</sup> Wang et al. found that circ\_ITCH is downregulated in PCa tissues and closely related to Gleason score, serum PSA level, T stage, and OS rate, but not related to age, LNM, and number of tumor.<sup>97</sup> Besides, Huang et al. studied the circ\_ITCH and had some different findings. They found that circ\_ITCH is downregulated and closely related to T stage, LNM, surgical margin, disease-free survival (DFS), and OS, but has nothing to do with Gleason score and serum PSA level. In fact, circ\_ITCH is the only circRNA related to surgical margins in PCa-related studies and is the circRNA related to the largest number of clinicopathological parameters in the currently available research.<sup>170</sup> circ\_HIPK3 is one of the most studied circRNAs in PCa. Cai et al. found that it is upregulated in PCa tissues and has relationships with T stage, LNM, and distant metastasis (DM).<sup>79</sup> A study carried out by Chen et al. showed circ\_HIPK3 is upregulated in PCa tissues and related to T stage.<sup>78</sup> Moreover, Liu et al. revealed that circ\_HIPK3 is upregulated in PCa tissues and has a relationship with Gleason score.<sup>90</sup>

Summarizing the current research data, common PCa parameters associated with circRNAs include Gleason score, serum PSA level, tumor T stage, LNM, DM, OS, and DFS. Other parameters include age, tumor size, surgical margin, and invasion. circRNAs related to the tumor number of PCa have not been found.

#### circRNAs as diagnostic biomarkers for PCa

Several studies have explored the promising value of circRNA being a diagnostic biomarker for PCa. There are 15, eight, and five circRNAs that are related to T stage, LNM, and DM, respectively (Table 3). For diagnosis, receiver operating characteristic (ROC) curves were applied to evaluate the clinical diagnostic value of circRNAs. Xia et al. studied the circ\_0062019 and circ\_0057558 and the area under the ROC curve (AUC) of these two circRNA. This study revealed that the AUC of circ\_0062019 is 0.828 with 95% confidence interval (CI) from 0.764 to 0.893, and the sensitivity and specificity are 80.0% and 74.6%, respectively. Correspondingly, the AUC of circ\_0057558 is 0.729 with 95% CI from 0.651 to 0.807, and the sensitivity and specificity are 74.1% and 63.4%, respectively. Moreover, when the two differential circRNAs are combined, the AUC is better (0.861) than PSA alone (0.854).<sup>59</sup> Huang et al. verified that the AUC of circ\_ITCH is 0.812, and the sensitivity and specificity are 88.3% and 61.7%, respectively.<sup>170</sup> Therefore, circRNAs are potential diagnostic biomarkers for PCa, and the combination of multiple circRNAs often contributes to better diagnostic value.

**Table 3. Relationship between circRNAs level and clinicopathologic characteristics in PCa**

circRNA name	CircBase ID	Host gene	Cutoff value	Internal reference	Dysregulation	Number of patients
circ_SLC19A1	hsa_circ_0062019	SLC19A1	–	18S rRNA	upregulated	173
circ_0057558	hsa_circ_0057558	SLC19A1	–	18S rRNA	upregulated	173
circAR3	–	AR	–	GAPDH	upregulated	91
circAMOTL1L	hsa_circ_000350	PCHAD8	–	GAPDH	Downregulated	97
circFOXO3	hsa_circ_0006404	FOXO3	MEL	β-actin	upregulated	53
circABCC4	hsa_circ_0030586	ABCC4	–	GAPDH & U6	upregulated	47
circ_ITCH	–	ITCH	MEL	GAPDH & U6	downregulated	52
circ-MTO1	hsa_circ_0076979	MTO1	MEL	GAPDH	downregulated	298
hsa_circ_0001206	hsa_circ_0001206	CRKL	–	β-actin	downregulated	50
hsa_circ_0009061	hsa_circ_0009061	KDM1A	–	β-actin	downregulated	50
circRNA17	hsa_circ_0001427	PDLIM5	–	GAPDH	downregulated	39
circHIPK3	hsa_circ_0000284	HIPK3	–	GAPDH or U6	upregulated	26
circ_ITCH	–	ITCH	MEL	GAPDH	downregulated	324
circ_0088233	hsa_circ_0088233	PAPPA	–	GAPDH	upregulated	46
circMBOAT2	hsa_circ_0007334	MBOAT2	–	GAPDH	upregulated	112
circ-0016068	hsa_circ_0016068	BTG2	MEL	GAPDH	upregulated	42
circFMN2	hsa_circ_0005100	FMN2	MEL	18S rRNA	upregulated	88
circ_HIPK3	–	HIPK3	–	–	upregulated	45
hsa_circ_0007494	hsa_circ_0007494	ROCK2	–	GAPDH	downregulated	49
circ-LARP4	–	LARP4	–	GAPDH	downregulated	55
hsa_circ_0000735	hsa_circ_0000735	P2RX1	MEL	GAPDH	upregulated	50

Age	Tumor size	Gleason score	PSA	T stage	LNM	Number of tumors	DM	Invasion	Surgical margin	DFS	OS	Reference	Year
Yes	–	yes	yes	–	–	–	–	yes	–	–	–	Xia et al. <sup>59</sup>	2018
No	–	yes	no	–	–	–	–	no	–	–	–	Xia et al. <sup>59</sup>	2018
–	–	yes	no	–	yes	–	–	no	–	–	–	Luo et al. <sup>169</sup>	2019
No	–	yes	yes	–	–	–	–	–	–	–	–	Yang et al. <sup>65</sup>	2019
No	–	yes	no	–	–	–	–	–	–	–	–	Kong et al. <sup>86</sup>	2020
No	–	–	–	yes	yes	–	yes	–	–	–	yes	Huang et al. <sup>75</sup>	2019
No	–	yes	yes	yes	no	no	–	–	–	–	yes	Wang et al. <sup>97</sup>	2019
No	–	no	no	yes	yes	–	–	–	no	yes	yes	Hu et al. <sup>104</sup>	2020
No	–	yes	no	yes	no	–	–	–	–	–	–	Song et al. <sup>66</sup>	2019
No	–	no	no	yes	no	–	–	–	–	–	–	Song et al. <sup>66</sup>	2019
–	–	yes	–	–	–	–	–	–	–	–	–	Wu et al. <sup>94</sup>	2019
–	–	–	–	yes	–	–	–	–	–	–	–	Chen et al. <sup>78</sup>	2019
No	–	no	no	yes	yes	–	–	–	yes	yes	yes	Huang et al. <sup>170</sup>	2019
No	–	–	–	yes	–	–	–	–	–	–	–	Deng et al. <sup>63</sup>	2020
No	–	yes	no	yes	no	–	–	–	–	yes	–	Shi et al. <sup>85</sup>	2020
No	–	yes	–	yes	yes	–	–	–	–	–	yes	Li et al. <sup>64</sup>	2020
No	–	–	–	yes	yes	–	yes	–	–	–	–	Shang et al. <sup>67</sup>	2020
No	–	yes	–	–	no	–	no	–	–	–	–	Liu et al. <sup>90</sup>	2020
No	yes	no	–	yes	no	–	yes	–	–	–	–	Zhang et al. <sup>101</sup>	2020
–	–	–	–	–	–	–	–	–	–	–	yes	Weng et al. <sup>105</sup>	2020
–	–	–	–	–	–	–	–	–	–	–	yes	Gao et al. <sup>82</sup>	2020

MEL, median expression level.

**Table 4. circRNAs as prognostic biomarkers for PCa**

circRNA	Cutoff value	Number of circRNA expression		p value	HR	95% CI		Follow-up (months)	Prognosis	Reference	Year
		Low	High			Lower	Higher				
circMBOAT2	MEL	25	25	0.024	0.33 (KMA)	0.13	0.86	96	DFS	Shi et al. <sup>85</sup>	2020
	MEL	31	31	0.037	0.39 (KMA)	0.1	0.98	96	DFS		
circ_ITCH	MEL	162	162	<0.001	0.476 (MCRA)	0.329	0.690	–	DFS	Huang et al. <sup>170</sup>	2019
circMTO1	MEL	149	149	0.005	0.541 (UCRA)	0.351	0.832	48	DFS	Hu et al. <sup>104</sup>	2019
circ_0000735	MEL	25	25	0.02	–	–	–	–	OS	Gao et al. <sup>82</sup>	2020
circ_0016068	MEL	21	21	0.036	–	–	–	–	OS	Li et al. <sup>64</sup>	2020
circLARP4	–	55	55	0.009	–	–	–	–	OS	Weng et al. <sup>105</sup>	2020
circABCC4	–	23	24	<0.05	–	–	–	–	OS	Huang et al. <sup>75</sup>	2019
circ_ITCH	MEL	162	162	0.001	0.415 (MCRA)	0.245	0.703	–	OS	Huang et al. <sup>170</sup>	2019
circ_ITCH	MEL	26	26	<0.01	–	–	–	–	OS	Wang et al. <sup>97</sup>	2019
circMTO1	MEL	149	149	0.016	0.444 (UCRA)	0.229	0.860	48	OS	Hu et al. <sup>104</sup>	2019

HR, hazard ratio; KMA, Kaplan-Meier analysis; MCRA, multivariate Cox regression analysis; UCRA, univariate Cox regression analysis.

#### circRNAs as prognostic biomarkers for PCa

circRNA levels can be used to predict patient survival parameters (Table 4). Univariate or multivariate Cox regression analysis is often used to explore the relationship between circRNA and PCa prognosis. Here, we summarize the results found by the researchers up to now. For prognosis, there are six and three circRNAs that are related to OS and DFS, respectively. Among them, two downregulated circRNAs (circ\_MTO1 and circ\_ITCH) as well as one upregulated circRNA (circMBOAT2) are related to poor DFS.<sup>85,104,170</sup> Besides, three downregulated circRNAs (circ\_ITCH, circ-MTO1, circ-LARP4) as well as three upregulated circRNAs (circABCC4, circ-0016068, circ\_0000735) are related to poor OS.<sup>75,82,97,104,105,170</sup> The above circRNAs can be detected in PCa tissues. Wang et al. first constructed an eight-circRNA risk score model, which could reliably predict the biochemical recurrence of PCa patients. The AUC for the model (AUC = 0.799) was better than the AUC of clinical factors (AUC of PSA = 0.557, AUC of Gleason score = 0.626, and AUC of pathological stage = 0.569).<sup>171</sup>

#### circRNAs as therapeutic targets for PCa

Considering the important roles of circRNAs in tumorigenesis and development of PCa, circRNAs definitely could be the potential therapeutic targets. Novel therapies will be based on the individual changes of circRNAs in PCa, bringing the tumor therapy into the era of precision therapy. So far, two strategies have been proposed to treat tumors by targeting circRNAs. The first is to restore the function of circRNAs with tumor suppressor activities to modulate native disease-linked circRNAs, while the second is to block the actions of non-coding RNAs with oncogenic function.<sup>172</sup> In general, the study of circRNAs as potential therapeutic targets has attracted extensive attention in oncology.

#### CHALLENGES AND FUTURE PERSPECTIVE

Currently, there is a better understanding about the role of circRNAs in PCa, but they are still a long way from clinical application. First of all, the correct analysis and detection is the primary condition for the use of circRNAs as biomarkers. However, the detection techniques for circRNAs still have limitations, especially in terms of sensitivity and specificity. Future studies must document the standard operating procedures to analyze all variables that may affect circRNA detection, such as sample processing, RNA isolation protocol, and data normalization strategies.<sup>173,174</sup> To avoid these potential errors, basic and applied researchers need to collaborate with clinicians to translate circRNA research findings to clinical applications. Laboratory scientists are the link between the basic science and clinical applications. During the phases of clinical validation based on retrospective or prospective studies, the primary task of the laboratory scientist is to monitor the quality of the measurements and make a practice-oriented evaluation of the data.

In addition, safe and effective delivery of the oligonucleotides into the cancer tissue remains a challenge. Although modifications could increase the stability and affinity to targets, most of the oligonucleotide therapies need additional optimal delivery systems to achieve the desired biological effects.<sup>175</sup> To improve delivery efficiency, viral and non-viral vectors have been developed. The virus-based delivery system has high transduction efficiency and can effectively deliver genetic material to target cells. However, viral vectors have some disadvantages, such as immunogenic/inflammatory responses, low loading capacity, and quality control. Compared with viral vectors, non-viral delivery systems are relatively safe, and can effectively avoid the problems faced by viral vectors through rational design and appropriate modifications. Therefore, non-viral delivery systems have emerged as promising intracellular biomolecule carriers. RNA nanoparticles

are representative of the non-viral vectors. RNA nanoparticles are modular, so functional modules composed of RNA can self-assemble into the multifunctional architectures. There are two main approaches for RNA nanoparticle construction. The first approach is the sequence-dependent self-folding of RNA nanostructures based on computational algorithms and secondary or tertiary structure prediction.<sup>176,177</sup> The second approach is to assemble RNA nanoparticles using the naturally occurring RNA motifs as core building blocks, such as three-way junction, four-way junction, and kissing loops.<sup>178–180</sup> In short, the field of RNA vectors has developed rapidly over the last decade, which will facilitate the application of circRNAs in targeted therapy.

## CONCLUSION

PCa is a complex disease, and its specific pathogenesis is still unclear. Elucidating circRNA biology has been crucial to understanding tumorigenesis over the past decade. As outlined in this review, the functions of circRNAs are involved in various physiological and pathological processes, such as cell proliferation, migration, invasion, apoptosis, chemotherapy resistance, and radiotherapy resistance. It has been reported that circRNAs are significantly correlated with many clinicopathological features of PCa and survival parameters of PCa patients, which make them potential diagnostic and prognostic biomarkers of PCa. The characteristics of circRNAs, such as conservation, stability, specificity, and detectability, make them potential diagnostic and prognostic biomarkers for PCa. In addition, circRNAs play important regulatory roles in the carcinogenesis and progression of PCa and are potential targets for the treatment of PCa.

In summary, the use of circRNAs in the diagnosis and treatment of PCa is promising and attractive. However, further studies are needed before circRNAs can be incorporated into clinical practice.

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## AUTHOR CONTRIBUTIONS

K.T., Y.T., and X.L. designed the study. X.L., T.Y., Y.H., and Y.T. collected data. Z.Y., Z.C., D.X., H.L., E.P., and X.Y. analyzed the data. Y.T. and X.L. made the figures and tables. K.T., Y.T., and X.L. drafted the article. All authors revised the paper and approved the final version of the manuscript, and agreed to be accountable for all aspects of the work.

## DECLARATION OF INTERESTS

The authors declare no competing interests.

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