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European Journal of Medical Research (2025) 30:140
https://doi.org/10.1186/s40001-025-02382-0

European Journal
of Medical Research

REVIEW

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Multiple roles of circular RNAs in prostate cancer: from the biological basis to potential clinical applications

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Abstract

Prostate cancer is an important health concern affecting men. Circular RNAs (circRNAs) play an important molecular biological role in regulating gene expression due to their unique structure. Studies have revealed the involvement of circRNAs in many human diseases. In prostate cancer, circRNAs can act as oncogenes or tumour suppressor genes and affect cancer cell proliferation, invasion, resistance to chemotherapy and, consequently, disease progression. Accordingly, prostate cancer-related circRNAs are expected to serve as new targets in early clinical diagnosis and targeted therapy, but the various roles of circRNAs in prostate cancer have not been fully elucidated. This article reviews the molecular pathological roles of circRNA in prostate cancer and explores its prospects as a translational medicine in clinical treatment and prognostic evaluation.

Keywords Prostate cancer, Circular RNAs, Chemotherapy resistance, Radiotherapy resistance

Introduction

According to global cancer statistics, prostate cancer is now the second leading cause of cancer death in men after lung cancer. Globally, the numbers of new cases of prostate cancer and related deaths are expected to increase further over the next decade, with serious effects on men's health. Significant geographical differences in incidence have been observed, with the highest rates in North America, Europe and Australia [1]. Both the incidence and mortality of prostate cancer have increased globally over the past few decades. These increases are due mainly to global population aging, increased detection rates, changes in lifestyle and environmental factors [1, 2]. Clinically, prostate cancer can be staged as either localised or progressive. For localised prostate cancer, the main treatment strategies include ablative radiotherapy and radical prostatectomy. Patients with progressive advanced prostate cancer are treated mainly using comprehensive methods, such as androgen deprivation therapy (ADT, also known as endocrine therapy), radiotherapy, chemotherapy and cellular immunotherapy. Each of these treatments is associated with serious adverse effects, including but not limited to cytotoxicity, peripheral neuropathy, urinary incontinence and erectile dysfunction. These adverse effects seriously reduce the quality of life of patients and are not ideal for many patients with advanced prostate cancer. Genetic variations have an important impact on disease occurrence. These variations can change the action pathways of androgens and the metabolism of testosterone. However, the molecular pathological mechanism underlying the onset and progression of prostate cancer remains unclear. Further exploration of the molecular biological

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mechanism of the disease and the discovery of biomarkers for early diagnosis and treatment prognosis are needed to provide a basis for the subsequent development of treatment strategies with fewer adverse effects and improved efficacy.

Overview of circular RNA (circRNA)

A circRNA is a single, closed covalent ring formed by the selective cleavage of different linear transcripts by nucleases. This recently discovered type of non-coding RNA molecule is formed by connecting linear RNA end-to-end and thus lacks the 5′ cap structure and 3′ polyadenylated tail structure unique to linear RNA molecules [3]. CircRNAs were discovered in plant viruses using electron microscopy as early as the 1970s [4]. However, due to technical limitations at the time and insufficient understanding of the molecular structure, these molecules were considered to lack biological function. Accordingly, circRNAs were poorly understood and ignored for a long time. The recent development of RNA sequencing technology has enabled researchers to gain a better understanding of the biological role of circRNAs. These molecules are ubiquitous in mammalian cells and exist mainly in the cytoplasm. They exhibit high sequence conservation and tissue- and disease-specific expression patterns. Due to their closed-loop structure and ability to resist RNA exonucleases, they have great potential to become new biomarkers for a variety of diseases [5–9]. Abnormal expression of circRNAs has been identified in the molecular pathological progression of prostate cancer, and some circRNAs have provided substantial advantages in terms of the early diagnosis and pathological staging of prostate cancer and evaluation of its aggressiveness. However, the current understanding of the multiple roles of circRNAs in prostate cancer is incomplete, and many areas remain to be further explored and clarified [10].

Following the transcription of precursor mRNA from the chromosome, various forms of cleavage are required to generate biologically active molecules. Linear RNA usually requires re-cleavage and docking of introns and exons, yielding three main types of circRNAs: exonic circular RNAs (ecRNAs), exon–intron circular RNAs (EIciRNAs), and circularised intron circular RNAs (ciRNAs). All three types are generated by reverse splicing of the precursor mRNA through unique lariat-driven circularisation and intron pairing-driven circularisation mechanisms [11, 12]. Lasso-driven circularisation refers to the covalent binding of the splicing donor to the splicing acceptor to produce an exon-containing, lasso-like structure that eventually forms an ecRNA [11, 12]. In intron pairing-driven circularisation, two exons are pulled together, usually by complementary base pairs at both ends of the middle intron, and the exons and introns are removed by the spliceosome and circularise to form ciRNA or EIciRNA [11, 12]. During intron pairing, RNA binding proteins (RBPs) promote or inhibit intron pairing, thereby regulating the biosynthesis of circRNA [13]. The biogenesis of circRNAs is also regulated by intron-specific sequence structures, multiple enzymes and transcription factors. CircRNAs are mainly present in the cytoplasm of cells, although a small amount is also present in the nucleus. Due to their closed loop structure, circRNAs are more stable than linear RNAs and are not easily degraded by RNase R [11]. They play roles in many biological processes, including the regulation of gene expression, the sponge effect of microRNAs, and the encoding of small proteins.

Research trends in circRNA in prostate cancer

Increasingly, studies have shown that the expression and roles of circRNA differ significantly between prostate cancer tissues and normal tissues [14, 15]. The differential expression of circRNA may be related to the occurrence, development and prognosis of the disease. Whereas the number of known protein-coding genes is fairly stable, functional circRNAs continue to be discovered. Researchers have verified the associations of many circRNAs with prostate cancer [16]. Advances in high-throughput sequencing and bioinformatics have promoted the discovery of circRNAs in prostate cancer. Many abnormally expressed circRNAs have been identified in prostate cancer cell lines and tissues. For example, hundreds of abnormally expressed circRNA molecules were identified through microarray analysis and chromatin immunoprecipitation assays [17]. Xia et al. used two differentially expressed circRNAs in combination with prostate-specific antigen (PSA) to evaluate patients' clinical phenotypes. The authors found that this approach to detection had better sensitivity and specificity than the current evaluation tool, which uses PSA alone [18]. High-throughput resequencing technology is a powerful means of screening new tumour-related circRNAs. Through high-throughput sequencing of circRNAs in prostate cancer cell lines, researchers have discovered hundreds or even thousands of differentially expressed circRNAs, some of which are even related to the mechanism regulating the biological phenotype of this malignancy [19, 20]. Bioinformatics tools provide a powerful means of exploring the biological effects indicated by these sequencing data [21]. In general, many circRNAs exhibit abnormal differential expression between prostate cancer tissues and normal tissues. In most studies involving prostate cancer tissues, the number of downregulated circRNAs is higher than the number of upregulated circRNAs.

Biological functions of circRNAs in prostate cancer

The increasing reports of newly discovered circRNAs have drawn attention to their biological functions. The expression and abundance of circRNAs vary greatly, although expression is usually stable and tissue-, timing- and disease-specific. Most circRNAs play a regulatory role at the post-transcriptional level, while a few play a role only at the transcriptional level. These molecules can regulate various cellular functions in the prostate cancer microenvironment. For example, high expression of circSMARCC1 is positively correlated with the colonisation of $CD68^+/CD163^+/CD206^+$ tumour-associated macrophages in the tumour microenvironment [22]. When overexpressed, circSMARCC1 regulates the expression of CC-chemokine ligand 20 (CCL20)/CC-chemokine receptor 6 (CCR6) target genes, promoting the expression of CD163 in tumour-associated macrophages. In turn, the macrophages are induced to infiltration into the tumour microenvironment and polarise to the M2 phenotype, leading to prostate cancer progression [22]. The rs11973492 locus of circHIBADH is a significant prostate cancer risk-associated variant that alters the secondary structure of its corresponding RNA chain, affecting its absorption and silencing of 21 RNA-splicing, pathway-rich RNA-binding proteins (RBPS) and thus promoting carcinogenesis [23]. These prostate cancer-related circRNAs are involved in a variety of pathological processes, including cell proliferation, apoptosis, invasion, metastasis, chemical resistance and radiation resistance [24]. The molecular pathological effects of circRNAs are summarised in Fig. 1.

Cell proliferation

Continuous tumour cell proliferation requires the continuous activation of many signalling pathways. The PI3K/Akt signalling pathway is one of the main pathways related to cell proliferation. In prostate cancer, proliferation, metastasis and recurrence are often related to the continuous activation of this pathway [25]. Studies have found that changes in the PI3K/Akt pathway occur in approximately 42% of localised prostate tumours and almost 100% of metastatic prostate tumours [26]. CircSMARCC1 was shown to be significantly upregulated in prostate cancer cells, plasma and tissues [22]. Its expression promotes tumour proliferation and metastasis both in vivo and in vitro [22]. CircSMARCC1 regulates the expression of CCL20 by absorbing miR-1322 and activates the PI3K–Akt signalling pathway, thus affecting prostate cancer cell proliferation [22]. The protein kinase mammalian target of rapamycin (mTOR) is an important downstream target of the PI3K/Akt pathway. Both circMBOAT2 and circITCH functionally regulate the PI3K/AKT/mTOR pathway to affect prostate cancer cell proliferation and metastasis [10, 24, 27]. Phosphatase and tensin homolog (PTEN) is a key negative regulator in the PI3K/Akt pathway, and mutations in the gene encoding PTEN can significantly increase the risk of primary prostate cancer [28]. Low PTEN expression has been reported in prostate cancer tissues, and hsa_circ_0007494 can act

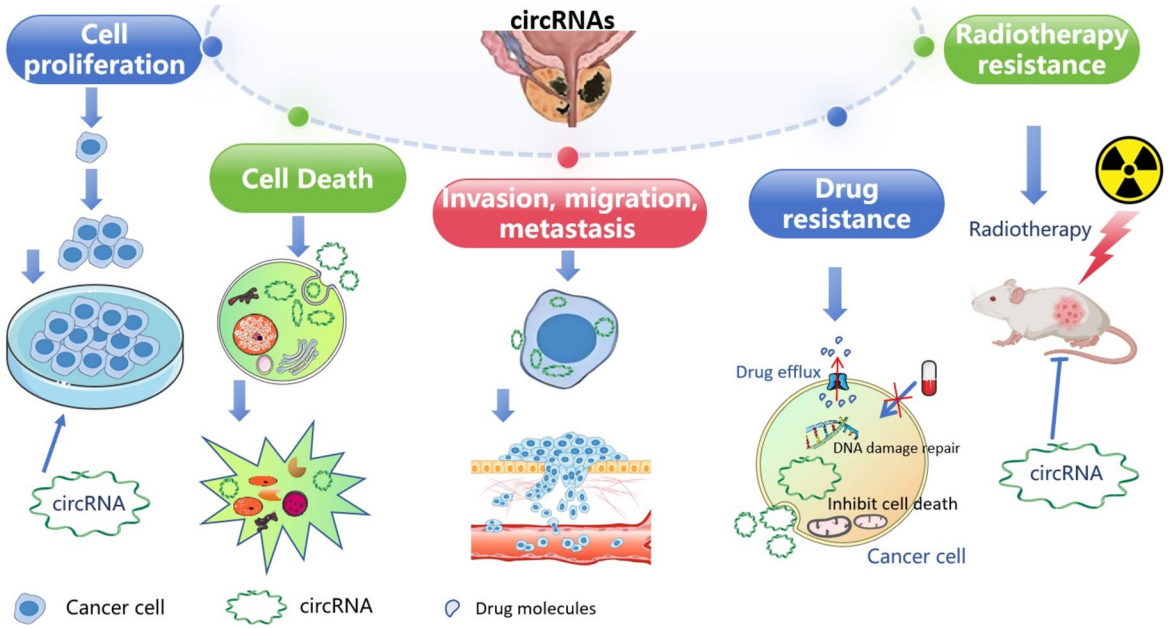

Fig. 1 Molecular pathological roles of circular RNAs in prostate cancer

as a tumour suppressor by upregulating PTEN to inhibit prostate cancer cell proliferation [28]. As the regulatory roles of circRNA in prostate cancer progression often exhibit a network rather than linear pattern, the associated regulatory signalling pathways are often complex and diverse. For example, circABCC4, circHIPK3 and circ_SLC19A1 can all promote prostate cancer cell proliferation and invasion via the regulatory networks of competing endogenous RNAs (ceRNAs) [29, 30]. In addition, circ-102004 was shown to inhibit prostate cancer cell proliferation and migration. CircDHRS3 is expressed at low levels in prostate cancer clinical samples and cell lines [31]. Overexpression of circDHRS3 can inhibit the growth of prostate cancer cells[32]. Furthermore, circZMIZ1 and circROBO1 can promote the proliferation of prostate cancer cells [33, 34]. In addition, the dysregulation of cell cycle regulators contributes to unrestricted tumour cell growth and proliferation. CDC25B activates the cyclin-dependent kinase (CDK) complex and plays an important role in cell cycle control. For example, circHIPK3 promotes the G2/M transition in the cell cycle and induces prostate cancer cell proliferation by sponging miR-338-3p and increasing CDC25B expression, thereby playing a carcinogenic role in prostate cancer [35]. Another study confirmed that circHIPK3 can enhance prostate cancer cell proliferation through the cirHIPK3/miRNA-338-3P/ADAM17 axis, thereby promoting the occurrence of malignant prostate cancer cell phenotypes [36]. Kong et al. also found that circSMARCA5 promotes the cell cycle, inhibits apoptosis, and acts as an oncogene in prostate cancer [37]. CircSMARCA5 was also shown to promote prostate cancer cell glycolysis and proliferation through the circSMARCA5/miR-432/PDCD10 regulatory axis to accelerate the progression of prostate cancer [37].

Cell death

Apoptosis and autophagy are the main mechanisms controlling cell death. Caspase proteins are key regulators of the apoptosis pathway. Circ_KATNAL1 can regulate caspase activity and, subsequently, apoptosis through the miR-145-3P/WISP1 pathway [38]. In prostate cancer tissues, circTFDP2 expression was found to be upregulated and positively correlated with the Gleason score [39]. Regarding the molecular biological mechanism, circTFDP2 interacts with the DNA binding domain of the protein poly (ADP-ribose) polymerase 1 (PARP1), preventing it from performing active caspase-3-dependent cleavage; this ultimately reduces DNA damage in prostate cancer cells and inhibits their apoptosis [39]. Prostate cancer cells can also release circTFDP2 molecules through exosomes, exacerbating the tumour microenvironment and promoting prostate cancer progression [39]. However, the roles of individual circRNAs in prostate cancer cell apoptosis remain controversial. Expression of the gene encoding FOXO3 (forkhead box transcription factor O3 class) can promote apoptosis in a variety of cancer cells. Both circFoxo3 and circ-LARP4 were reported to promote prostate cancer cell apoptosis by upregulating FOXO3 [10, 40]. However, circFoxo3 may play a carcinogenic role in prostate cancer through the circFoxo3/miR-29a-3P/SLC25A15 axis [41]. CircDDIT4 is formed by the reverse splicing of the 5′ splice acceptor site in mRNA exon 2 of the linear DDIT4 transcript and the 3′-untranslated region (UTR) followed by circularisation [42]. Analysis of clinical prostate cancer tissues revealed low circDDIT4 expression. The 3′-UTR of this circRNA can competitively bind to ELAV-like RNA binding protein 1 (ELAVL1/HuR) to regulate its expression, which in turn reduces anoctamin 7 (ANO7) expression [42]. Usually, ANO7 is highly expressed in prostate cancer; thus, circDDIT4 acts as an ELAVL1 protein sponge to promote prostate cancer cell apoptosis [42]. Zhang et al. found that circ_0057553 was significantly upregulated in prostate cancer tissues and cells [43]. Knockdown of circ_0057553 inhibits cell viability and promotes prostate cancer cell apoptosis. Circ_ITCH expression is reduced in prostate cancer tissues, and upregulation of this circRNA can target miR-197/miR-17-5p to promote apoptosis [44, 45]. At high doses, dihydrotestosterone can inhibit the circRNA–BCL2 axis, resulting in autophagic cell death and inhibiting the growth of enzalutamide-resistant, castration-resistant prostate cancer (CRPC) cells [46].

Invasion, migration and metastasis

In metastasis, tumour cells leave the primary site, invade nearby lymphatic vessels and blood vessels to enter the circulatory system and eventually form tumours in distant organs. In prostate cancer, some circRNAs can promote this type of pathological progression. Argonaute 2 (AGO2), a member of the human AGO protein family, affects the biogenesis of multiple non-coding RNAs and regulates tumour cell proliferation, migration and invasion [44]. CircAGO2 can bind to ELAV1/HuR to inhibit AGO2/miRNA-mediated gene silencing, leading to the exacerbation of cancerous phenotypes, such as tumour cell invasiveness [47]. Transforming growth factor beta 1 (TGFβ1) is a crucial factor that regulates tumour cell migration and invasion. This cytokine can induce prostate cancer cell invasion mainly through the SMAD and non-SMAD signalling pathways. Studies have shown that circ-51217 can activate the TGFβ1/P-SMAD signalling pathway by adsorbing miRNA-646 to increase TGFβ1 expression, thus enhancing prostate cancer cells invasiveness [47]. In addition, hsa-circ-0005276, circZNF609 and

circ_0044516 all promote the invasion and metastasis of prostate cancer cells by binding to their respective specific miRNAs [48–51].

Increasing evidence shows that circRNAs can also inhibit prostate cancer invasion or metastasis. For example, miR-421 is a downstream target of circDHRS3 [32], which regulates the expression of the target gene *MEIS2* through the circDHRS3/miR-421/MEIS2 axis, thereby inhibiting prostate cancer cell proliferation and metastasis [32]. In vivo studies have confirmed that high circDHRS3 expression can inhibit prostate cancer metastasis to the bone and lung [32]. Circ_0006156 is expressed at low levels in prostate cancer tissues and cells. When overexpressed, circ_0006156 can bind to S100 calcium binding protein A9 (S100A9) and block its ubiquitination, significantly inhibiting the migration and invasion of prostate cancer cells [52]. Tumour cell metastasis is closely related to epithelial–mesenchymal transformation (EMT), of which E-cadherin is an important signature protein [53]. An *AMOTL1*-derived circRNA (circAMOTL1L) was shown to be downregulated in human prostate cancer; increasing its expression upregulated the expression of E-cadherin and inhibited the migration and invasion of prostate cancer cells [54]. Lin et al. found substantially reduced circDDX17 expression in prostate cancer tissue samples via bioinformatics analysis and showed that significant inhibition of circDDX17 induced cell colonisation ability, invasiveness and EMT in vitro [55]. He et al. observed lower circRNA_100395 expression in prostate cancer tissues than in adjacent normal tissues, and reported that expression of this circRNA in clinical pathological tissues was negatively correlated with tumour size, Gleason score, tumour stage and lymph node metastasis [56]. Overexpressed circRNA_100395 could also inhibit proliferation, alter the cell cycle, reduce migration and invasiveness and inhibit EMT in prostate cancer cells [56]. Similarly, circAMOTL1L could prevent prostate cancer metastasis by upregulating E-cadherin expression via the miR-193a-5p/PCDHA8 axis [54].

Bone metastasis is a main malignant feature of advanced prostate cancer. Multiple circRNAs with regulatory roles in this process have been discovered. Most circRNAs that promote or inhibit bone metastasis of cancer cells act as miRNA sponges [57]. However, a few circRNAs form complexes with other molecules to block the N6-methyladenine (m6A) methylation of translation initiation factors, inactivate downstream signalling pathways by regulating epigenomic factors and help to inhibit bone metastasis of cancer cells [58, 59].

Resistance to chemotherapy and radiotherapy

ADT is currently the first-line treatment for patients with advanced prostate cancer. However, studies have shown that although most prostate cancer cells are sensitive to androgens, the vast majority of patients receiving ADT will eventually progress to CRPC. This is likely to be due to the persistence of AR signalling in prostate cancer cells, despite circulating androgen depletion and androgen receptor (AR) blockade. Therefore, ADT has a limited effect on patient survival rate [60]. Chemotherapeutic resistance is the main obstacle in the treatment of CRPC. Patients with CRPC often develop resistance to docetaxel (DTX) after repeated treatment cycles, reducing the treatment effect. Studies have found that multiple circRNAs are involved in the molecular mechanism of DTX resistance [61, 62]. For example, DTX therapy can increase the expression of hsa_circ_0000735 in prostate cancer tissues and cells; therefore, inhibition of hsa_circ_0000735 can significantly increase the sensitivity of prostate cancer to DTX therapy. In addition, circFoxo3 is underexpressed in prostate cancer, and its overexpression can also increase the sensitivity of prostate cancer cells to DTX [10, 40]. CRPC remains dependent on androgens via the AR pathway [63]. Enzalutamide is a first-line treatment for patients with CRPC who have not received chemotherapy. This drug competitively inhibits AR binding and thus targets the AR signalling pathway. However, approximately 20–40% of patients develop intrinsic resistance to enzalutamide [63]. In tumour cells from patients with CRPC, AR splicing variants (AR-Vs) are associated with resistance to enzalutamide [64, 65]. Studies have found that circRNA17 and hsa_circ_0001610 can affect the resistance of prostate cancer to enzalutamide by stabilising the levels of miRNAs that target AR-Vs and PTK6, respectively [66, 67].

In a circRNA expression profile of enzalutamide-resistant cell lines, 278 circRNAs were upregulated and 588 circRNAs were downregulated [68]; In addition, 2,127 downregulated circRNAs were found in androgen-independent cell lines, while 2,236 downregulated and abnormally expressed circRNAs were derived from multiple drug resistance-related parental genes in prostate cancer cell lines [69]. Knocking down circROBO1 significantly increases the sensitivity of prostate cancer cells to enzalutamide treatment. Regarding cellular mechanisms, inhibiting the function of circROBO1 can slow glycolysis in prostate cancer cells, inhibiting their growth and helping to overcome resistance to enzalutamide [33]. This suggests that circROBO1 promotes prostate cancer growth and enzalutamide resistance by accelerating glycolysis. Interestingly, Li et al. recently found that the splice variant hsa_circ_0085121 (circRNF19A), expressed by *RNF19A*, can encode the novel protein circRNF19A-490aa; in prostate cancer cells, this protein can promote malignant behaviour and drug resistance by interacting with the oncoproteins HSP90AA1 and HNRNPF to

activate the downstream Akt/mTOR pathway and accelerate the alternative splicing of AR-V7, respectively [70].

Radiation therapy provides good control of localised progressive prostate cancers and metastases and can achieve a radical cure in some patients. However, many prostate cancer patients who receive radiotherapy still experience recurrence and progression, which may be due to the development of cellular radioresistance [71, 72]. Understanding the mechanisms by which radiation resistance occurs could help to combat prostate cancer recurrence and metastasis. Some studies have shown that circRNAs help to regulate radiosensitivity in many cancers. For example, circ-ABCC4 is enriched and significantly elevated in prostate cancer tissue specimens and cells [73]. Depletion of circ-ABCC4 was shown to inhibit prostate cancer cell proliferation, invasion and radioresistance and to trigger apoptosis. Circ-ABCC4 silencing was also shown to exacerbate the radiation-induced inhibition of xenograft tumour growth. MiR-1253 is a downstream target regulated by circ-ABCC4. A decrease in the abundance of miR-1253 can partially reverse the anticancer effect mediated by circ-ABCC4 depletion in prostate cancer cells. Furthermore, miR-1253 targets SOX4 mRNA to reduce the malignancy of prostate cancer cells. Circ-ABCC4 can increase the abundance of SOX4 by absorbing miR-1253 to alter the radioresistance of prostate cancer cells and inhibit apoptosis, thereby promoting malignancy [73]. A circRNA encoded by *Cyclin B2* (circ_CCNB2) is highly overexpressed in irradiation-resistant prostate cancer tissues and cells. Functionally, circ_CCNB2 can inhibit autophagy in prostate cancer cells by regulating genes targeted by the miR-30b-5p/KIF18A axis, thereby improving the sensitivity of radioresistant prostate cancer to radiotherapy [74]. Li et al. observed the upregulation of both circ_0062020 and thyroid hormone receptor-interacting protein 13 (TRIP13) and the downregulation of miR-615-5p in prostate cancer tissues and cells [75]. Subsequent molecular mechanism studies found that circ_0062020 induced radioresistance in prostate cancer cells by regulating the miR-615-5p/TRIP13 axis [75]. In addition, cell glycolysis is involved in prostate cancer radioresistance. Du et al. found that silencing circ-ZNF609 could inhibit glycolysis and promote apoptosis in prostate cancer cells through the miR-501-3p/HK2 axis, thereby improving sensitivity to radiotherapy [76]. Radiotherapy (RT) toxicity in patients with prostate cancer is associated with single-nucleotide polymorphisms (SNPs) in *KDM3B*; among these SNPs, rs17599026 is located in a motif that is important for the expression of a circRNA that absorbs miRNA to regulate *KDM3B* expression [77]. In a mouse model with heterozygous deletion of the *kdm3b* gene, it was found that lower *kdm3b* expression was associated with changes in the urination pattern after bladder irradiation, a side effect related to the degree of tissue inflammation in patients. This finding suggests that SNPs in *KDM3B* can affect gene self-expression by regulating non-coding RNA expression, leading to radiation toxicity due to tissue inflammation at the molecular and physiological levels. Testicular nuclear receptor 4 (TR4) may play a key role in the progression of prostate cancer. However, its ability to alter prostate cancer radiosensitivity and the underlying molecular mechanism remain unclear. Recent studies have found that TR4 affects radiosensitivity by targeting the action modes of circRNAs. Specifically, TR4 can increase the expression of the RNA binding protein QKI via transcription; QKI promotes the increased expression of circZEB1, which adsorbs miR-141-3p to reduce its inhibitory effect on the expression of the host gene *ZEB1* [78]. Preclinical studies conducted in mouse models further demonstrated that TR4 could alter prostate cancer radiosensitivity and regulate disease progression through the QKI/circZEB1/miR-141-3p/ZEB1 signalling pathway.

Clinical significance and future prospects of circRNAs in prostate cancer

Improving the therapeutic efficacy of prostate cancer will involve two approaches: developing predictive biomarkers for early diagnosis, and discovering new targets that can improve the prognosis of treatment-resistant prostate cancer. Serum PSA has been the standard biomarker for prostate cancer screening, diagnosis and monitoring since 1987. However, its use is considered to only slightly reduce the incidence of prostate cancer, and the specificity of the so-called 'grey area' of PSA levels (2.0–10.0 ng/mL) is low (25–40%), resulting in a substantial number of unnecessary benign biopsies and the detection of clinically indolent disease [79]. In addition, the practical application of the PSA level is limited by its susceptibility to many factors, such as trauma, prostatitis and age; therefore, it cannot be used as a specific cancer marker. Prostate biopsy is an invasive procedure with multiple complications, such as infection and bleeding, and is not conducive to widespread disease screening [80]. Bioinformatics analyses of circRNA expression and clinical pathological data in online tumour databases have identified multiple circRNA molecules potentially associated with disease risk and prognostic value [81], suggesting that these molecules could be highly useful biomarkers for prostate cancer diagnosis and prognosis. First, circRNAs are unique, endogenous, highly conserved non-coding RNAs that are widely expressed in a variety of tissues. Second, the structural advantage of the covalently closed loop of the circRNA structure allows it to resist RNA exonuclease degradation, causing it to be more stable than linear nucleic acid molecules. Moreover, circRNAs

vary widely in molecular size, and after secretion by various cells of the body, the molecules can distribute widely in peripheral circulating tissues, such as bodily fluids [82]. For example, RNA sequencing can be used to identify potential cancer-associated circRNAs in extracellular vesicles from the urine of patients with high-grade prostate cancer and prostate hyperplasia, with the aim of identifying a urine extracellular vesicle circRNA classifier for detecting high-grade prostate cancer. Such an approach is repeatable, non-invasive and can be implemented in a clinical prostate cancer screening workflow [79].

Intramolecular and intermolecular RNA interactions are essential for cancer cell survival and function. In eukaryotic cells, nonsense-mediated mRNA decay (NMD) is an important mRNA quality control mechanism that participates in the fine regulation of gene expression by targeting specific natural mRNAs [83]. CircRNAs can bind to the 3′ UTR of the target mRNA and guide its exon junction complex (EJC) to the vicinity of the 3′ UTR to trigger EJC-dependent NMD [83]. This circRNA-induced NMD mechanism enables cells to rapidly degrade target mRNAs and dynamically regulate gene expression. These findings not only have expanded our understanding of the functions of circRNAs but also suggest strategies for the development of new tumour treatment options. For example, designing circRNAs that specifically bind to mRNAs expressed at excessively high levels in drug-resistant prostate cancers could reduce and inhibit the expression of the targeted pathogenic genes [83]. This potential circRNA-based therapeutic strategy would have advantages, such as high stability and low side effects, and it provides a new direction for the development of RNA biology and therapeutics.

Despite great progress in elucidating the roles of circRNA in prostate cancer, many exploratory and verification efforts are needed before selecting circRNA markers with practical clinical application value. First, the analysis and detection of circular RNA remains substantially limited. Current sequencing technology cannot guarantee that all present circular RNA molecules are detected, and uniform, certified standard operating procedures for evaluating the sensitivity and specificity of prostate cancer diagnostics are lacking. Furthermore, it is impossible to standardise the control of all variables that may affect circular RNA detection [84]. It also remains challenging to safely and effectively deliver oligonucleotides to cancer tissues and cells. Although some chemical modifications can further increase the stability of circRNAs and their affinity for their targets, an optimal delivery system that would allow circRNAs to exert their biological effects in vivo is lacking, meaning that the theoretical biological effects cannot be fully achieved. At present, the development of this type of delivery system faces many challenges. However, advances in nanotechnology and advanced computing methods have enabled rapid development of the RNA vector field, and this will enable the use of circRNA in targeted prostate cancer therapies.

Conclusion

In summary, prostate cancer is a complex disease involving multiple molecular pathological mechanisms, and its aetiology remains unclear. The biological effects of circRNAs are extensive. In prostate cancer, circRNAs affect various pathological characteristics of cancer cells, such as proliferation, migration, invasion, cell death, and chemotherapy and radiotherapy tolerance. Further elucidation of the mechanisms of action of circRNAs in these processes will be crucial for understanding the occurrence of prostate cancer and for discovering potential targets with early diagnostic and therapeutic value. Structurally, circRNAs are highly conserved, stable, specific and detectable, which will assist the development of these molecules into promising clinical biomarkers for prostate cancer. As more biological effects of circRNAs are revealed, these molecules are expected to be useful as biological markers of prostate cancer in future disease screening and prognosis assessment strategies.

Acknowledgements
Professional English language editing support was provided by AsiaEdit (asiaedit.com).

Author contributions
Conceived and designed the study: Xianping Zheng and Shoutian Sun. Performed the study: Xianping Zheng, Ling Song and Ce Cao. Wrote the paper: Xianping Zheng and Shoutian Sun. All authors read and approved the final manuscript.

Availability of data and materials
Not applicable.

Declarations

Ethics approval and consent to participate
All procedures performed in this study were in accordance with the ethical standards of the responsible committee on human experimentation and with the Declaration of Helsinki of 1964 and later versions.

Consent for publication
Not applicable.

Competing interests
The authors declare that they have no competing interests.

Received: 3 January 2025 Accepted: 13 February 2025
Published online: 27 February 2025

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