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CircRNAs: functions and emerging roles in cancer and immunotherapy

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Abstract

Background Circular RNAs (circRNAs) are emerging as promising tools in cancer and immunotherapy, with unique characteristics that offer potential therapeutic applications.

Main body This review outlines the discovery, biogenesis, and mechanisms of circRNAs, emphasizing their roles in cancer and immune regulation. CircRNAs modulate immune responses by acting as miRNA sponges, binding RNA-binding proteins, or serving as translation templates. These interactions influence T cells, NK cells, macrophages, and immune checkpoints. The review also explores circRNAs' roles in different cancers, focusing on target identification, immune effects, and mechanisms of action. Additionally, it examines circRNA-based therapies, including vaccines, CAR-T cell therapy, and database applications.

Conclusion Despite their potential, technical hurdles must be overcome to advance circRNAs' clinical use in cancer immunotherapy. Future research should focus on addressing these challenges to fully realize the therapeutic potential of circRNAs.

Keywords CircRNAs, Cancer, Biomarkers, Immunotherapy, Tumor vaccines

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Background

Circular RNAs (circRNAs) are a class of non-coding RNAs characterized by their covalently closed loop structure [1]. Recent studies have revealed their pivotal roles in various biological processes [2–4]. These include regulation of gene expression, RNA splicing, and modulating the immune response [5]. Especially in the field of cancer, the functions of circRNAs as molecular sponges, translation templates, and scaffolds position them as key players in cancer biology [6–10]. Studies have shown that circRNAs play significant roles in tumorigenesis, tumor progression, and the regulation of the tumor microenvironment (TME) [11, 12].

Emerging evidence has also highlighted the potential of circRNAs as tumor biomarkers and therapeutic targets, especially in the realm of cancer immunotherapy [13–18]. CircRNAs have been shown to influence immune checkpoint regulation, particularly by modulating immune evasion mechanisms, such as the expression of programmed cell death ligand 1 (PD-L1) [19, 20]. The TME is a critical component of cancer biology, influencing tumor progression and immune evasion [21, 22]. CircRNAs have become a key regulatory factor within TME [23]. Studies have shown that they play a role in shaping the immune landscape and regulating the interactions between tumors and immune cells [24]. This highlights their potential in enhancing the efficacy of immune checkpoint inhibitors and in the development of novel tumor immunotherapies [15, 25–27].

Despite significant advancements in the field of circRNAs biology, their roles in cancer immunotherapy remain to be further explored. This review aims to provide a comprehensive discussion of the functions of circRNAs in cancer and to investigate their emerging roles in cancer immunotherapy. We will explore the potential of circRNAs as biomarkers for cancer diagnosis and prognosis, as well as their capacity to enhance the efficacy of immunotherapy. Furthermore, this review will address key biotechnological advancements and methodologies for translating circRNAs research into clinical applications, along with the challenges and opportunities associated with this translation process.

Main text

Discovery of circRNAs

In 1976, closed circular RNA structures were first observed in plant viroid, revealing a non-linear RNA configuration [28]. In 1979, electron microscopy confirmed the ubiquitous presence of circRNAs in the cytoplasm of HeLa cells [29]. In 1986, the circular RNA genome of hepatitis delta virus (HDV) was characterized, providing the first evidence of circRNAs in pathogenic animal viruses [30]. In 1991, the first human circRNA was identified from aberrant splicing of the tumor suppressor gene *DCC*, marking its discovery in higher organisms [31]. In 1993, the functional circRNA derived from the mouse *Sry* gene overturned the "splicing error" dogma [32]. In 2013, high-throughput sequencing uncovered over 25,000 circRNAs in human fibroblasts, demonstrating their prevalence and conservation. Genome-wide analyses further revealed that circRNAs are evolutionarily conserved and enriched near Alu elements, suggesting a regulatory mechanism shaped by natural selection [33]. In 2013, two pivotal Nature studies identified CDR1as (ciRS-7) as a miR-7 sponge, highlighting its role in cerebellar degeneration-related protein 1 transcript regulation [1, 34].

Biogenesis and mechanisms

CircRNAs are pivotal in gene regulation and cellular processes [35]. Clarifying their biogenesis and functional mechanisms is crucial for elucidating their roles in cancer and immunotherapy.

Biogenesis of CircRNAs

CircRNAs are generated through a unique form of alternative splicing known as back-splicing [36] (Fig. 1). Precursor messenger RNA (Pre-mRNA) undergoes back-splicing by connecting the 5' splice site of upstream exons to the 3' splice site of downstream exons, forming a circular RNA [37]. This back-splicing is associated with the transcription elongation rate (TER) of RNA Polymerase II (Pol II), where genes with a high TER are more likely to produce circRNAs [38]. Additionally, alternative splicing is also a key component of the biogenesis of circRNAs, as a single genetic locus can generate multiple distinct circRNAs through the variability of this process, specifically via different back-splicing events [39]. The abundance of circRNAs is regulated by various factors, including intron complementary sequences (ICS) and trans-acting factors [40]. ICS can promote the generation of circRNAs, while trans-acting factors such as splicing factors and RNA-binding proteins (RBPs) can regulate back-splicing through different mechanisms [41, 42]. The nuclear export of circRNAs is also an important component of their generation mechanism [43]. Previous studies have suggested that the nuclear export of circRNAs may be influenced by their length [44–46]. CircRNAs are predominantly localized in the cytoplasm [34]. Their nuclear export is orchestrated through a coordinated interaction between the transcription export complex and the exon junction complex, with a length-dependent mechanism [47]. Long circRNAs, approximately 1300 nucleotides in length, associate with the RNA helicase DDX39B, while shorter circRNAs, around 400 nucleotides, engage with the ATP-dependent RNA helicase DDX39A [44]. In terms

of stability, short circRNAs have a compact structure and exhibit strong resistance to degradation, whereas long circRNAs have a more complex structure and are more susceptible to enzymatic degradation [48–50]. Regarding their functions, short circRNAs are primarily utilized for precise regulation and vaccine development, while long circRNAs are employed for encoding large molecules and facilitating complex regulatory functions [51–53]. These RNA helicase complexes are subsequently recruited by the NTF2-related export protein 1 (NXT1) and the nuclear RNA export factor 1 (NXF1) heterodimer, which facilitates their translocation through the nuclear pore complex into the cytoplasm [54]. In summary, the generation of circRNAs is a complex process involving multiple molecular mechanisms and regulatory steps.

Functional mechanisms of CircRNAs

The discovery of circRNAs has unveiled a new layer of gene regulation, with their diverse functional mechanisms significantly impacting cellular processes and disease progression. In the following sections, we will discuss several major functional mechanisms of circRNAs (Table 1).

1) MiRNA sponge

The microRNA (miRNA) sponge of circRNAs is a well-validated mechanism supported by cross-cancer validation and clinical cohort studies, with high reproducibility and has progressed from preclinical research to early clinical stages [55, 56]. CircRNAs can bind to complementary miRNAs, thereby inhibiting the regulatory effects of miRNAs on target genes [57, 58]. The miRNA sponge describes the ability of circRNAs to absorb miRNAs due to the presence of multiple miRNA response elements, thereby relieving the repression of miRNAs on their target genes [59]. The core mechanism of this effect lies in the fact that circRNAs carry sequences complementary to specific miRNAs, forming stable RNA-miRNA complexes that are resistant to degradation [1, 34]. In this way, the miRNA sponge sequesters miRNAs from their original target genes, leading to the derepression of these target genes [60]. In short, circRNAs regulate the function of miRNAs through the sponge effect, thereby playing a crucial regulatory role within cells [61]. For instance, circRNA CDR1as contains over 70 binding sites for miR-7, making it a highly efficient miR-7 sponge [62]. By sequestering miR-7, CDR1as can relieve the repression of miR-7 target genes, such as the oncogene EGFR, thereby influencing cellular processes like proliferation and apoptosis [63]. Similarly, circHIPK3 has been shown to sponge multiple miRNAs, including miR-124, thereby modulating the expression of genes involved in cell cycle regulation and tumorigenesis [64]. The efficiency of circRNAs as miRNA sponges is influenced by several factors, including the number and affinity of miRNA-binding sites, the stability of the circRNAs, and the cellular context [65]. Moreover, the sponge effect can be both cell type-specific and developmentally regulated, highlighting the complexity and specificity of this mechanism (Fig. 2a) [66].

In summary, the miRNA sponge of circRNAs provides a novel gene regulation mechanism by sequestering miRNAs to derepress target genes. However, its efficiency is highly context-dependent, influenced by binding site affinity and cellular environment. This suggests limited generalizability across different cells and stages. Additionally, circRNAs' expression dynamics and potential functional redundancy imply a more nuanced impact. Future research should focus on clarifying these complexities to fully understand the role of circRNAs in immunotherapy.

2) RBP Interaction

(See figure on next page.)

Fig. 1 Mechanism of circRNAs biogenesis. This schematic illustrates the molecular mechanisms underlying the biogenesis of circRNAs from precursor mRNA (pre-mRNA). The synthesis of messenger RNA (mRNA) occurs through typical splicing, where introns are removed, and exons are ligated to form a linear mRNA transcript. CircRNAs are transcribed by RNA Pol II and formed through back-splicing of the pre-mRNA. In this process, the 3′ splice site of a downstream exon is joined to the 5′ splice site of an upstream exon, resulting in a covalently closed circular RNA. Exons, except for the first and last, can be incorporated into the circRNAs. This event is facilitated by specific trans-acting factors, such as RNA-binding proteins, and intronic complementary sequences that enhance the proximity between the 5′ and 3′ splice sites, thus driving the back-splicing reaction. Long circRNAs (~ 1300 nt) interact with the spliceosome RNA helicase DDX39B, while short circRNAs (~ 400 nt) associate with the ATP-dependent RNA helicase DDX39A. These complexes are then recruited by the NTF2-related export protein 1 (NXT1) and the nuclear RNA export factor 1 (NXF1) heterodimer, which facilitate their export through the nuclear pore complex (NPC) into the cytoplasm. This figure provides a comprehensive overview of the critical molecular steps involved in circRNAs generation and regulation. Alu: Short interspersed repeats with reverse complementary features, facilitating back-splicing by forming secondary structures. Exonic circRNAs: Composed of exon sequences, devoid of introns, formed through back-splicing, and primarily present in the cytoplasm. Intronic circRNAs: Composed of intron sequences, formed and located in the nucleus. Exonic-intronic circRNAs: Composed of both exon and intron sequences, retaining partial introns during formation

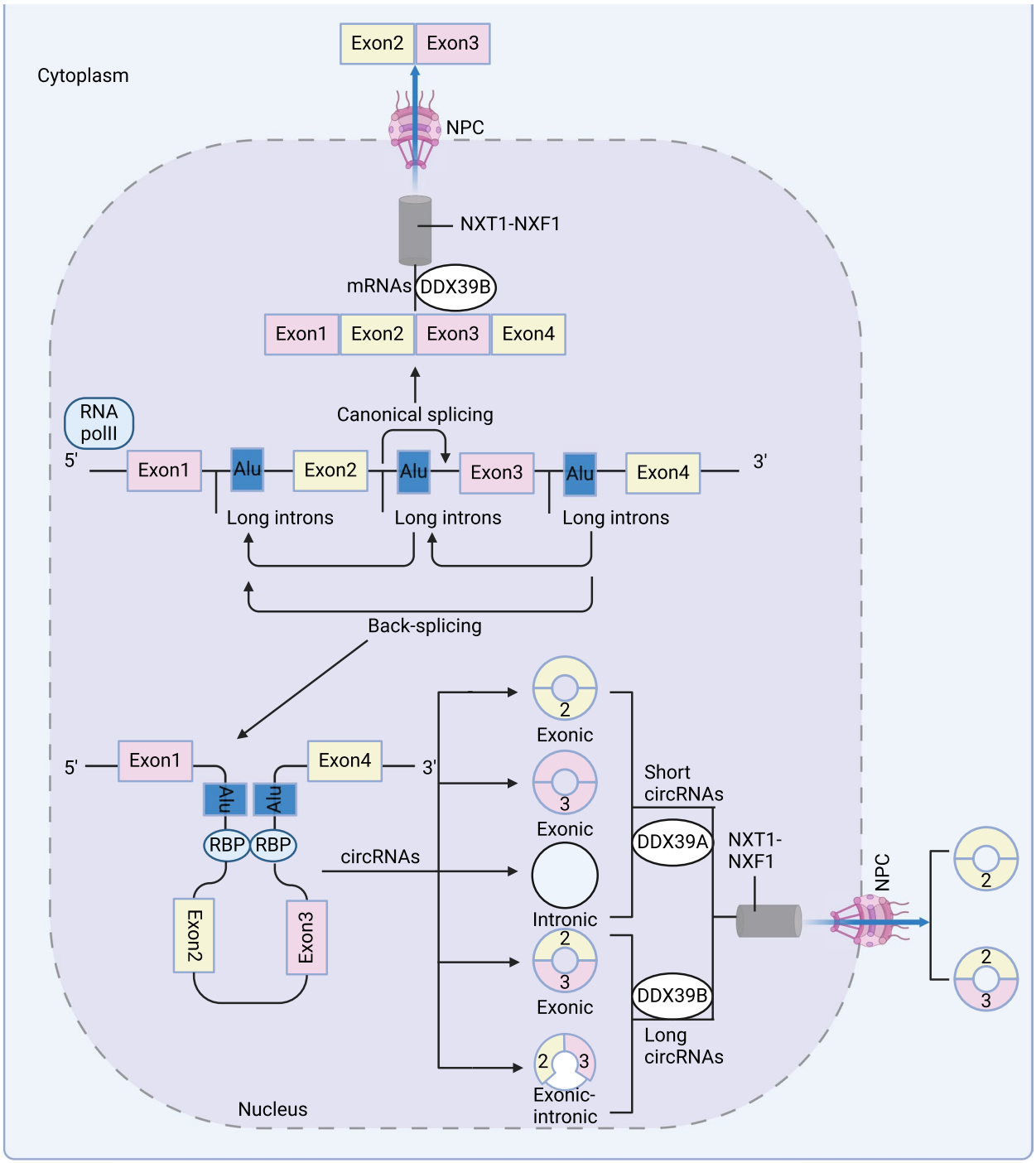

Fig. 1 (See legend on previous page.)

The interactions between circRNAs and RBPs represent a partially validated mechanism with clear mechanisms but are limited by tissue specificity. They show moderate reproducibility and remain in the basic research stage [67–69]. The interactions between circRNAs and RBPs are essential for various cellular processes, including RNA stability, localization, and translational regulation [70, 71]. RBPs bind to circRNAs by recognizing specific sequences or structural elements within them, thereby modulating their function and stability [40]. Specifically, RBPs can stabilize circRNAs by protecting them from nucleolytic degradation [72]. For example, HuR binds to

Table 1 Assessment of evidence quality, reproducibility, and research stage of circRNAs functional mechanisms

Functional mechanism	Evidence quality	Reproducibility	Research stage	Examples
miRNA Sponge	High (validated across cancers and clinical cohorts)	High (consistent across multiple studies)	Preclinical (in vivo models) to early clinical (patient cohort studies)	CDR1as and miR-7 (refs.[62, 63]) circHIPK3 and miR-124 (ref. [64])
RBP interaction	Moderate (validated in specific tissues, limited by context)	Moderate (variable across studies)	Basic research (primarily in vitro, some early in vivo)	circPABPN1 and HuR (ref.[73]) circSMARCA5 and QKI (ref.[75])
Protein scaffolding	Moderate (specific interactions validated, limited by model specificity)	Low (limited independent studies)	Basic research (primarily in vitro, some early in vivo)	circFoxo3 and p21 or CDK2 (refs.[76, 77])
Translation template	Low (preliminary validation, lacks multi-model support)	Low (rarely reproduced independently)	Basic research (primarily in vitro)	circZNF609 and IRES (refs. [79, 87]) circMbl and Mbl (ref.[86])

The evaluation of evidence quality, reproducibility, and research stage provides a systematic classification for mechanisms such as miRNA sponge, RBP interaction, translation template, and protein scaffolding. Evidence quality is determined based on the rigor of experimental design (e.g., multi-method validation), credibility of data sources, mechanistic specificity, and biological significance. Reproducibility is assessed by result consistency, methodological standardization, and data transparency, with high-quality reproducibility requiring multi-laboratory validation and open data access. Research stage is categorized into basic research, preclinical research, and clinical research phases. This framework ensures the scientific rigor and systematic evaluation of these mechanisms

Definitions of evidence quality: ①*High*: Validated by ≥3 independent methods; includes in vitro and animal model validation but lacks clinical data. ② *Medium*: Validated by in vitro or animal model studies, but lacks clinical data. ③*Low*: Based solely on bioinformatics prediction or data from a single sample set

AU-rich elements in circPABPN1, enhancing its stability [73]. RBPs also influence circRNAs' localization [70], as seen with Quaking (QKI) promoting nuclear retention of circRNAs like circSMARCA5, which is crucial for gene expression regulation in neural cells [74]. Furthermore, RBPs can regulate circRNA biogenesis by facilitating or inhibiting back-splicing [70]. QKI, for instance, binds to intronic regions flanking circRNA-forming exons, promoting the back-splicing process and increasing circRNAs' abundance (Fig. 2b) [75]. These multifaceted interactions highlight the dynamic roles of RBPs in modulating circRNAs' function and stability.

To enhance the understanding of RBP-circRNA interactions, future studies should address tissue-specific variability and improve reproducibility by standardizing experimental conditions. The development of high-throughput screening methods to map RBP-binding sites on circRNAs could further elucidate their regulatory roles.

3) Protein scaffolding

CircRNAs can act as protein scaffolds, facilitating the assembly of protein complexes to regulate cellular processes [40]. Protein scaffolding represents a mechanism with moderate validation, as specific interactions have been validated but are limited by model specificity, showing low reproducibility due to limited independent studies, and remains in the basic research stage. CircRNAs like circFoxo3 can bind multiple proteins, such as p21 and CDK2, to form complexes that primarily modulate the G1 phase of the cell cycle [76, 77]. By acting as scaffolds, circRNAs enhance the efficiency of protein–protein interactions, influencing pathways such as apoptosis and stress response (Fig. 2c) [78]. The specificity of these interactions depends on the structural features of circRNAs, which provide stable binding platforms [53]. However, the context-dependent nature of these interactions and the limited number of validated examples necessitate further investigation to establish their broader relevance.

4) Translation template

The translation template function of circRNAs represents a speculative mechanism with preliminary functional validation but lacks support from multiple models, showing low reproducibility and remaining at the proof-of-concept stage [79–82]. Recent studies have revealed that some circRNAs can serve as templates for translation [83, 84]. This discovery has expanded our understanding of the functional diversity of circRNAs. Unlike linear mRNAs, circRNAs lack a polyA tail and a cap structure, which are typically required for translation initiation [85]. However, certain circRNAs can recruit the translation machinery through alternative mechanisms [79, 86]. For example, circZNF609 has been shown to harbor an Internal Ribosome Entry Site (IRES) element that allows it to be translated into a functional protein [87]. This protein has been implicated in muscle development and regeneration, highlighting the potential for circRNAs to encode functional peptides [79]. Similarly, circMbl has been shown to encode a protein that can regulate the splicing of its

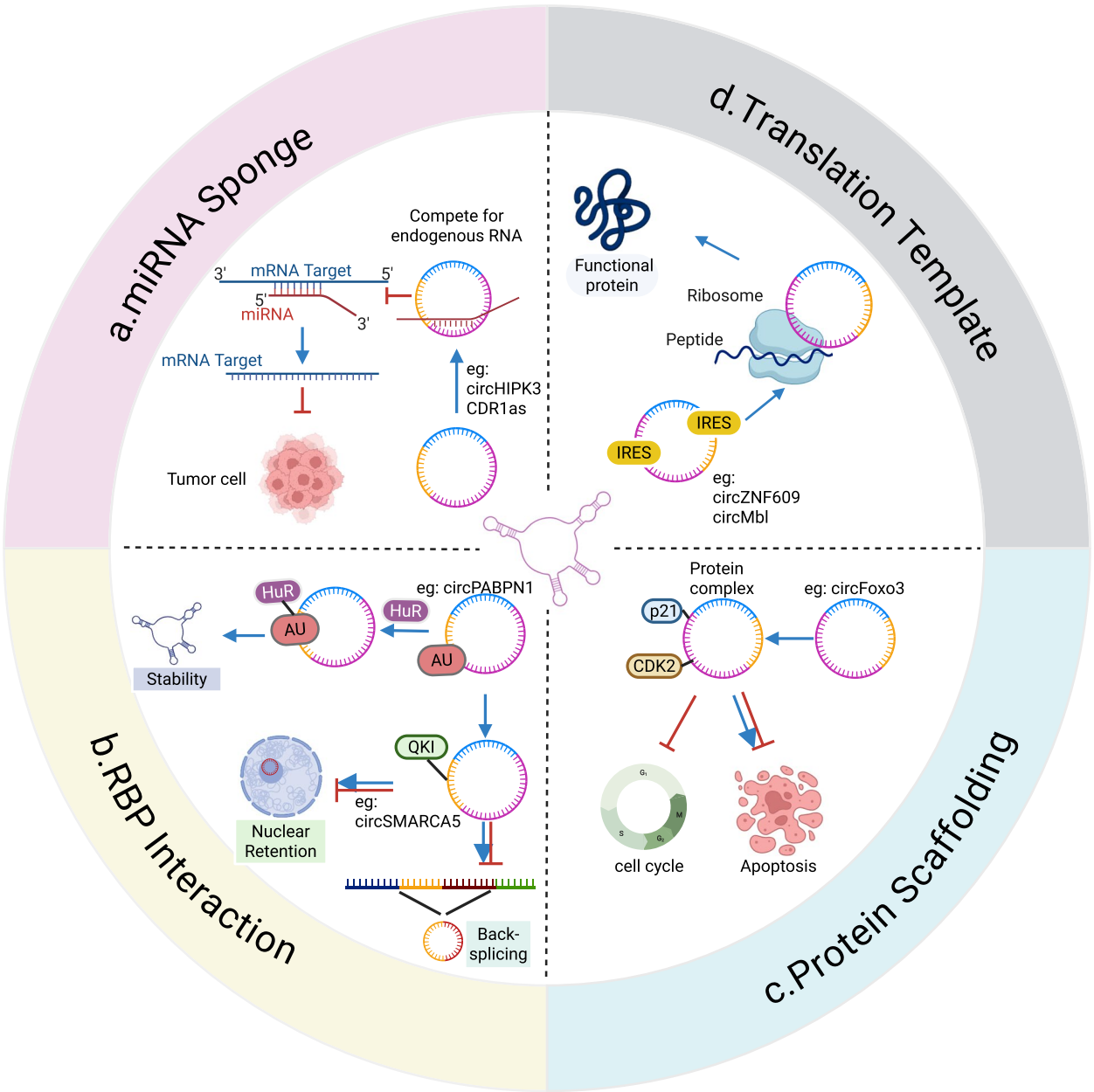

Fig. 2 Functions of circRNAs in immunotherapy. **a** As miRNA Sponge: CircRNAs can bind to specific miRNAs and act as "sponges" to sequester miRNAs, thereby inhibiting the miRNA-mediated suppression of target genes, which in turn suppresses tumor growth. **b** RBP Interaction: RBPs interact with specific sequences or structural elements (e.g., AU-rich elements or QKI) of circRNAs to regulate their stability, nuclear retention, and back-splicing. **c** CircRNAs, such as circFoxo3, can bind to multiple proteins, including p21 and CDK2, forming complexes that inhibit G1 phase progression in the cell cycle or regulate apoptosis. **d** Translation Template: CircRNAs, such as circZNF609, contain IRES elements, thereby encoding functional proteins

own host gene, Mbl, thereby creating a feedback loop in gene regulation (Fig. 2d) [86].

These findings suggest that circRNAs can encode functional peptides, adding complexity to their regulatory roles. However, the low reproducibility and limited model systems underscore the need for rigorous validation and standardized assays to confirm translational capabilities.

In summary, circRNAs exhibit diverse functional mechanisms. While the miRNA sponge is well-validated and clinically relevant, RBP interaction and protein scaffolding remain tissue-specific and less reproducible.

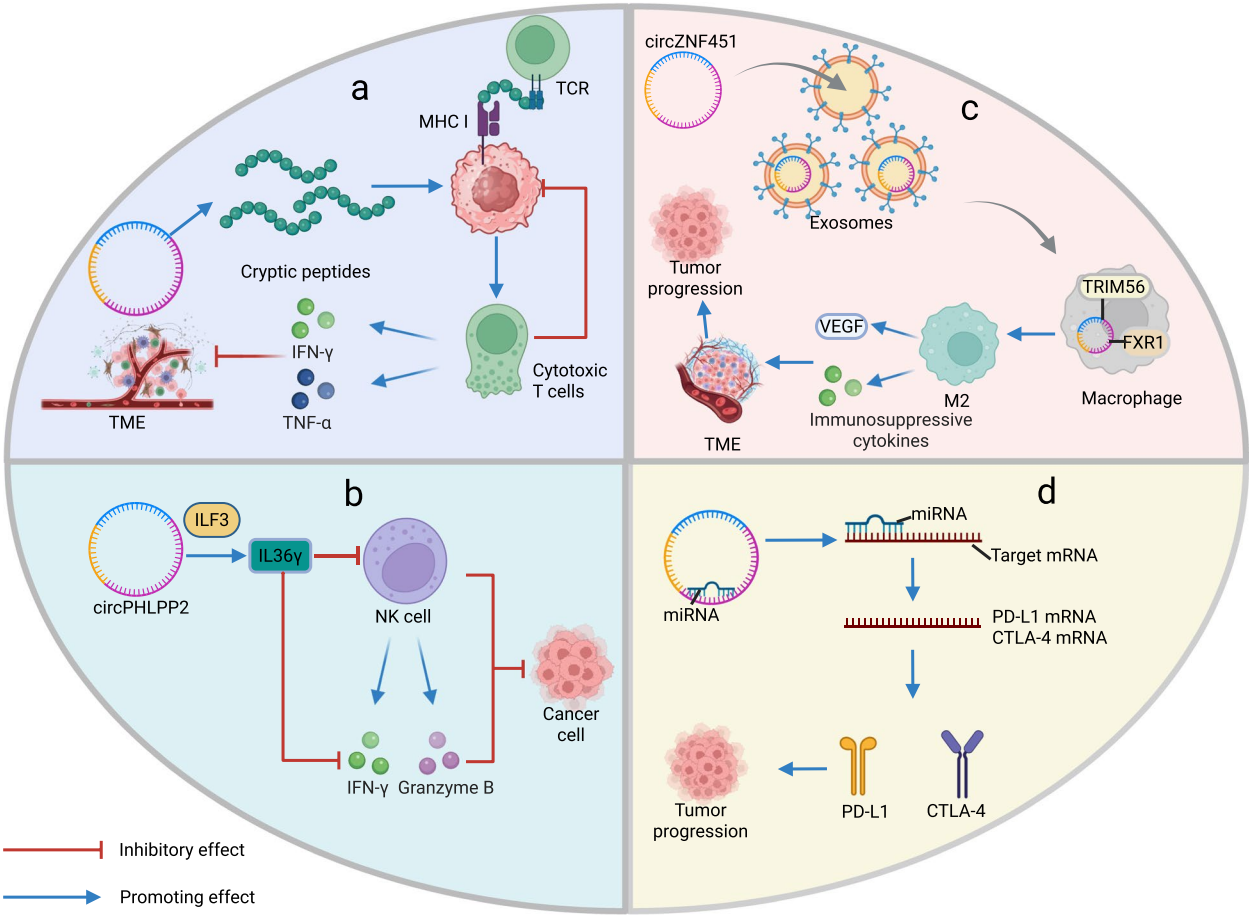

Fig. 3 CircRNAs in immune modulation. **a** circRNA-encoded cryptic peptides are presented on the surface of tumor cells via MHC class I molecules, where they are recognized by CD8 + T cells. This recognition activates CD8 + T cells, promoting their differentiation into cytotoxic effector T cells, which specifically kill tumor cells and release cytokines (such as IFN-γ and TNF-α) to enhance the immune response, forming a synergistic anti-tumor effect. **b** circPHLPP2 binds to ILF3, promoting IL36γ transcription and secretion, which inhibits NK cell infiltration and reduces granzyme B and IFN-γ production, thereby decreasing NK cell numbers and function, ultimately promoting tumor growth. **c** circZNF451, delivered to macrophages via exosomes, interacts with TRIM56 and FXR1 to promote M2 macrophage polarization, leading to the secretion of immunosuppressive cytokines and growth factors (VEGF), establishing an immunosuppressive TME that impairs immune cell function, thereby facilitating tumor growth and immune evasion. **d** circRNAs act as miRNA sponges, competitively binding miRNAs to prevent their inhibitory effects on PD-L1 and CTLA-4 mRNA, thereby upregulating PD-L1 and CTLA-4 expression and promoting tumor growth

Translation templating is highly speculative, with limited evidence. Future research must critically address these disparities to elucidate circRNAs' true regulatory potential and overcome the challenges of translating these mechanisms into therapeutic applications (Fig. 2).

CircRNAs in immune modulation

Regulating immune cell functions

CircRNAs regulate immune cell function through various mechanisms, such as influencing T cells, NK cells, and macrophage polarization, thereby collectively shaping the tumor immune microenvironment and affecting the efficacy of cancer immunotherapy (Fig. 3).

1) Regulation of T cell

Research has found that certain circRNAs can influence T cell differentiation, promoting their transition into effector T cells and enhancing anti-tumor immunity [88]. For example, certain circRNAs can encode cryptic peptides, which are translated within tumor cells, degraded into smaller fragments by the proteasome, and presented on the cell surface via MHC class I molecules [89]. These presented peptides are recognized by CD8 + T cells, triggering T cell receptor (TCR)-mediated signaling pathways that promote T cell proliferation and differentiation into cytotoxic effector T cells [90]. These activated CD8 + T cells acquire cytotoxic functions,

specifically recognizing and killing tumor cells expressing the peptides [91]. They also secrete cytokines (such as IFN-γ and TNF-α), which further enhance the immune response by recruiting other immune cells into the TME, thereby creating a synergistic antitumor effect (Fig. 3a) [91]. In lung adenocarcinoma (LUAD), circMAPK1 binds to IGF2BP1 and induces its interaction with the 3′UTR of CCL5 mRNA, thereby stabilizing CCL5 mRNA [92]. IGF2BP1, an RBP, stabilizes mRNA via m^6A modification, and this process is further enhanced by its interaction with circMAPK1 [93]. The stabilization of CCL5 mRNA by circMAPK1 significantly increases the translational efficiency of CCL5, leading to its upregulation [92]. As a chemokine, CCL5 attracts $CD8^+$ T cells into the TME, thereby enhancing antitumor immune responses [94].

2) Regulation of NK cell

CircRNAs play a critical role in the regulation of NK cells. For example, in colorectal cancer (CRC), circPHLPP2 binds to ILF3 to promote IL36γ transcription [95]. The increased secretion of IL36γ inhibits NK cell infiltration and reduces the production of granzyme B and IFN-γ by NK cells [96]. This mechanism decreases the number and function of NK cells in the TME, weakens NK cell-mediated antitumor immunity, and thereby promotes tumor growth (Fig. 3b) [97].

3) Polarization of macrophages

CircRNAs play a crucial role in regulating the polarization of macrophages, which is essential for immune responses within the TME and the success of immunotherapeutic strategies [98]. The TME is composed of various components, including tumor cells, stromal cells, immune cells, and the extracellular matrix. It creates an immunosuppressive environment that hampers the function of immune cells, facilitating tumor growth and immune evasion [99]. The study by Gao et al. revealed that circZNF451 is transferred to macrophages via exosomes and interacts with the proteins TRIM56 and FXR1; this interaction promotes the polarization of macrophages toward the tumor-promoting M2 phenotype [14]. M2-polarized macrophages secrete immunosuppressive cytokines and growth factors, contributing to the establishment of an immunosuppressive TME [100]. This immunosuppressive environment impairs the function of immune cells, thereby facilitating tumor growth and immune evasion (Fig. 3c) [101].

4) Regulation of immune checkpoints

CircRNAs can also improve the efficacy of immunotherapeutic agents (such as PD-1/PD-L1 inhibitors) by regulating the expression of immune checkpoint molecules [102]. In head and neck squamous cell carcinoma (HNSCC), circ_0000052 competes with PD-L1 mRNA for binding to miR-382-3p, effectively sequestering miR-382-3p and thereby preventing its inhibitory effect on PD-L1 [103]. The overexpression of PD-L1 enhances the ability of cancer cells to evade immune surveillance, leading to increased invasiveness and metastatic potential of HNSCC cells [104]. Moreover, circRNAs can regulate the expression of CTLA-4 through direct or indirect mechanisms [105]. Specifically, certain circRNAs act as molecular sponges, binding to miRNAs that target CTLA-4 mRNA. This interaction prevents the miRNAs from degrading CTLA-4 mRNA, thereby increasing the levels of CTLA-4 protein [13]. The upregulation of CTLA-4 enhances immune suppression, contributing to immune evasion and tumor progression (Fig. 3d) [106].

In conclusion, circRNAs exhibit multifaceted roles in immune modulation within the TME. While they can enhance anti-tumor immunity by promoting T cell activation and NK cell function, they also contribute to immune evasion through the upregulation of immune checkpoints like PD-L1 and CTLA-4. Additionally, circRNAs influence macrophage polarization, shaping an immunosuppressive environment that facilitates tumor progression. Future research should critically explore the dual nature of circRNAs, elucidating their mechanisms to identify potential therapeutic targets that can optimize cancer immunotherapy outcomes while mitigating immune escape.

CircRNAs in specific cancers

We have systematically investigated the mechanisms and clinical applications of circRNAs in various cancers, including lung cancer (LC), hepatocellular carcinoma (HCC), pancreatic ductal adenocarcinoma (PDAC), CRC, breast cancer (BC), gastric cancer (GC), nasopharyngeal carcinoma (NPC), esophageal cancer (EC) and bladder urothelial carcinoma (BLCA) (Table 2). The selection of these cancers is based on the following considerations: First, these cancers have high incidence and mortality rates globally, posing significant threats to public health. For example, LC, HCC, BC, and CRC are major causes of cancer-related deaths [107, 108]. Second, significant progress has been made in the study of circRNAs in these tumors, revealing their important roles in tumor occurrence, development, metastasis, and immune regulation, which provides a theoretical basis for the development of new diagnostic and therapeutic strategies. In addition, we have cited over seventy high-impact articles published within the past 5 years to elucidate the specific

Table 2 CircRNA targets in cancer: evidence, mechanisms, and immune regulation

Cancer types	CircRNA targets	Levels of evidence		Mechanistic classes	Immune effects	Ref
LC	Circ6834	Preclinical		miRNA sponge	Tumor suppression; destabilizes ANKHD1, affects immune microenvironment	[7]
	CircHIPK3	Preclinical		miRNA sponge RBP interaction	Indirect immune impact via TAM infiltration	[64]
HCC	CircARNT2		Preclinical	miRNA sponge	Inhibits HCC cisplatin sensitivity; impacts immune microenvironment	[113]
	CircMAP3K4		Preclinical	Translation template	Prevents HCC apoptosis; promotes immune evasion	[114]
PDAC	CircZNF91	Preclinical		RBP interaction	Promotes chemoresistance in PDAC cells; impacts immune microenvironment	[120]
	Circ0000284	Preclinical		miRNA sponge	Promotes PDAC progression; alters immune surveillance	[121]
CRC	CircLPAR1	Preclinical		miRNA sponge	Promotes CRC progression; may relate to immune evasion	[128]
	CircPPP1R12A	Preclinical		Translation template		[129]
BC	CircZCCHC2	Preclinical		miRNA sponge	Promotes TNBC progression; may involve immune evasion	[134]
	CircHIF1A	Preclinical		RBP interaction	Promotes TNBC progression; may involve immune evasion	[135]
GC	CircPDIA4	Preclinical		RBP interaction	Promotes GC progression; may influence immune microenvironment	[140]
	CircNFATC3	Preclinical		RBP interaction	Promotes GC progression; may influence immune microenvironment	[141]
NPC	CircIPO7	Preclinical		RBP interaction	Enhances NPC metastasis/chemoresistance; may affect immune microenvironment	[146]
	CircCENPM	Preclinical		miRNA sponge	Promotes NPC metastasis/stemness; may alter immune evasion	[147]
EC	CircARAP2	Preclinical		miRNA sponge	Promotes ESCC progression; may affect immune microenvironment	[156]
	Circ0014879	Preclinical		miRNA sponge	Affects ESCC radiosensitivity; potential immune-related mechanisms	[157]
BLCA	CircSTX6	Preclinical		miRNA sponge RBP interaction	Promoting immune evasion and chemoresistance in BLCA	[159]
	CircXRN2	Preclinical		RBP interaction	Inhibits BLCA progression; potential immune impact	[160]

mechanisms of circRNAs in these cancers. Lastly, the selected tumor types are diverse and representative, covering various tissue origins and pathological types, which helps to comprehensively display the mechanisms of circRNAs in different TMEs and their potential applications in immune regulation and immunotherapy.

CircRNAs and lung cancer

Given the high mortality and significant treatment challenges associated with LC, circRNAs such as circ6834 and circHIPK3 have been identified as key regulators of tumor progression and immune responses in preclinical studies [2, 4, 7, 25, 64, 109–112]. Circ6834 primarily functions as a miRNA sponge, destabilizing ANKHD1 to suppress tumor progression and potentially influencing the immune microenvironment, although the precise effects on immune cell infiltration are still under investigation [7]. CircHIPK3, acting as both a miRNA sponge and an RBP binder, indirectly impacts the immune response by modulating tumor-associated macrophage(TAM) infiltration [64]. These findings underscore the diverse roles of circRNAs in lung cancer and highlight their potential for therapeutic development and biomarker discovery.

CircRNAs and hepatocellular carcinoma

Given the high incidence and poor prognosis associated with HCC, circRNAs such as circARNT2 and circMAP3K4 have been identified as key regulators in preclinical studies [19, 113–119]. CircARNT2 functions as a miRNA sponge, inhibiting the sensitivity of HCC cells to cisplatin [113]. Meanwhile, circMAP3K4 serves as a translation template, encoding a novel peptide that prevents apoptosis in HCC cells [114]. These findings highlight the diverse roles of circRNAs in HCC, suggesting their potential as therapeutic targets.

CircRNAs and pancreatic ductal adenocarcinoma

Given the aggressive nature and poor survival rates associated with PDAC, circRNAs such as circZNF91 and circ_0000284 have been identified as key regulators in preclinical studies [120–127]. CircZNF91 functions as an RBP binder, promoting chemoresistance in PDAC cells

[120]. Meanwhile, circ_0000284 acts as a miRNA sponge, facilitating proliferation, metastasis, and angiogenesis in PDAC cells [121]. These findings underscore the potential of circRNAs as therapeutic targets in PDAC, offering a novel approach to overcoming chemoresistance and inhibiting tumor progression.

CircRNAs and colorectal cancer

Given the high incidence and poor prognosis associated with CRC, circRNAs such as circLPAR1 and circPPP1R12A have been identified as significant regulators in preclinical studies [128–133]. CircLPAR1 functions as a miRNA sponge, promoting proliferation and metastasis of CRC cells by sequestering tumor-suppressive miRNAs [128]. Meanwhile, circPPP1R12A serves as a translation template, encoding a novel protein that further drives CRC progression. These findings highlight the potential of circRNAs as therapeutic targets in CRC [129]. However, the specific downstream pathways and potential interactions with the TME remain to be fully elucidated, suggesting a need for more comprehensive studies to fully understand their roles and therapeutic potential.

CircRNAs and breast cancer

Given the high mortality and treatment resistance associated with BC, particularly in the aggressive triple-negative subtype (TNBC), circRNAs such as circZCCHC2 and circHIF1A have been identified as significant regulators in preclinical studies [88, 134–139]. CircZCCHC2 functions as a miRNA sponge [134], while circHIF1A acts as an RBP binder regulated by FUS, modulating NFIB expression and translocation [135]. These findings highlight the potential of circRNAs as therapeutic targets in TNBC. However, the specific mechanisms by which these circRNAs interact with other cellular components and their broader impact on tumor biology remain to be fully elucidated, suggesting a need for further investigation to fully harness their therapeutic potential.

CircRNAs and gastric cancer

In GC, a highly prevalent and aggressive malignancy, circRNAs such as CircPDIA4 and CircNFATC3 have been identified as significant regulators in preclinical studies [23, 140–144]. CircPDIA4 promotes GC progression by enhancing ERK1/2 activation and oncogenic circRNA biogenesis [140]. CircNFATC3 also drives GC proliferation by binding to IGF2BP3 and stabilizing CCND1 mRNA [141]. These findings highlight the potential of circRNAs as therapeutic targets in GC. However, the detailed mechanisms and clinical applicability require further investigation.

CircRNAs and nasopharyngeal carcinoma

NPC is a highly aggressive cancer with limited treatment options, making it crucial to explore new therapeutic targets [145]. In preclinical studies, circRNAs such as CircIPO7 and CircCENPM have been identified as significant regulators in NPC [146–151]. CircIPO7 functions as an RBP binder, enhancing YBX1 nuclear localization to promote metastasis and cisplatin chemoresistance in NPC [146]. Meanwhile, CircCENPM acts as a miRNA sponge, enhancing BMI1 expression to promote metastasis and stemness in NPC [147]. These findings highlight the potential of circRNAs as therapeutic targets in NPC. However, further studies are needed to fully understand their mechanisms and clinical applicability.

CircRNAs and esophageal cancer

EC is a major malignancy with a poor prognosis [152]. CircRNAs have emerged as potential regulators in EC progression and treatment response [153–155]. One important subtype of EC, esophageal squamous cell carcinoma (ESCC), has been particularly studied in relation to circRNA functions. For instance, circARAP2 promotes ESCC progression by acting as a miRNA sponge [156], while circ0014879 affects ESCC radiosensitivity through similar mechanisms [157]. These findings highlight the potential of circRNAs as therapeutic targets, though clinical validation is still needed. Future research should further explore the specific mechanisms of circRNAs in EC, particularly their roles via RBPs and as translation templates, to better understand their impact on tumor progression.

CircRNAs and bladder urothelial carcinoma

BLCA is selected due to its high incidence and mortality [158]. In BLCA, circRNAs such as circSTX6 and circXRN2 have been identified in preclinical studies [159–166]. These circRNAs function as miRNA sponges or RBPs binders [159]. CircXRN2 inhibits the progression of BLCA by promoting immune evasion and chemoresistance [160]. However, further clinical validation is needed to confirm their therapeutic potential.

CircRNAs and other cancers

CircRNAs have also garnered significant attention in various other cancers [167], such as glioblastoma [168], cervical cancer [169], ovarian cancer [170], head and HNSCC [171], neuroblastoma [172] and glioma [173]. However, the research on circRNA in these malignancies is currently largely confined to its role as a miRNA sponge, while other potential mechanisms and specific molecular regulatory mechanisms remain to be fully elucidated.

In conclusion, while circRNAs show promise as therapeutic targets and biomarkers in various cancers, current research is predominantly preclinical and often limited to miRNA sponge functions. Further investigation is needed to elucidate their diverse mechanisms, interactions with the TME, and clinical applicability. Addressing these gaps will be crucial for translating circRNA findings into effective diagnostic and therapeutic strategies.

Emerging therapeutic technologies

Among the emerging therapeutic technologies, circRNAs have demonstrated significant potential due to their unique properties and versatile applications in cancer treatment [174, 175]. Subsequently, we will rank and deliberate on these technologies based on their clinical application potential, innovativeness and advancement, research maturity, as well as practical needs and urgency.

CAR-T cell therapy

Chimeric antigen receptor T-cell (CAR-T cell) therapy, with its direct clinical application potential and innovative and cutting-edge nature, has emerged as one of the most promising technologies in cancer immunotherapy. Although its research maturity still needs improvement, it is significant in meeting the practical needs and urgency of cancer treatment [174, 175]. Recent studies have highlighted several key advancements and challenges in CAR-T therapy. For instance, the integration of circRNA technology has shown promise in enhancing CAR-T cell stability and efficacy, as demonstrated in a study focusing on DLL3-targeted CAR-T cells for small cell lung cancer (SCLC). This approach leverages the enhanced stability and prolonged protein expression of circRNA compared to traditional mRNA, potentially mitigating issues such as T-cell exhaustion and improving therapeutic outcomes [175]. Another study explored the potential of circRNA-based CAR-T therapy to enhance specificity and minimize off-target effects, thereby improving therapeutic durability. These advancements underscore the potential of circRNA to address critical gaps in current CAR-T cell therapeutic strategies [174].

However, CAR-T cell therapy still faces significant challenges. Technical limitations, such as T-cell exhaustion and limited penetration of solid tumors, continue to restrict the broad application of CAR-T therapies. Scaling up production is also a major hurdle, with complex genetic engineering and cell manufacturing processes leading to high costs and difficulties in standardization. Regulatory barriers are substantial, particularly concerning the long-term safety and potential risks associated with genetic modifications. Finally, there is a significant gap in human validation, with the need for more extensive clinical trials to verify efficacy and safety across diverse patient populations. Future research must focus on addressing these key issues to translate the potential of circRNA-enhanced CAR-T therapies into tangible clinical benefits, thereby advancing the next generation of personalized cancer treatments.

CircRNAs as vaccine platforms

Cancer vaccines are a novel immunotherapy for tumor treatment, demonstrating immense potential [176, 177]. Cancer vaccines stimulate tumor-specific immunity by introducing tumor antigens, eliciting immune responses mediated by T cells and B cells, and activating specific anti-tumor immunity [178, 179]. Notably, circRNAs as vaccine platforms have demonstrated substantial clinical potential in cancer immunotherapy, emerging as a research hotspot due to their innovation and advancement. Despite the need for further maturation, circRNA vaccines are significant in addressing the urgent clinical needs for cancer treatment [180–182].

Among the various cancer immunotherapies, RNA-based cancer vaccines hold the most promising potential due to their rapid antigen expression, strong immune activation, and the absence of genomic integration risks [183–187]. However, linear RNA vaccines face challenges such as rapid degradation and limited stability. CircRNA vaccines, due to their circular structure, are more stable and resistant to nuclease degradation, maintaining their activity for a longer period and enhancing immune durability [188, 189]. Wan et al.'s study shows that circRNA vaccines are more stable than linear mRNA vaccines, enabling sustained expression of therapeutic proteins or peptides and extending antigen presentation duration [190]. Li et al.'s study finds that the circRNAOVA-luc vaccine successfully induced anti-tumor immune responses in a mouse melanoma model and significantly inhibited tumor progression [191]. The study by Amaya et al. demonstrates that circRNA vaccines can effectively activate dendritic cells, thereby stimulating a robust antigen-specific CD8 T cell response in lymph nodes and tissues [192]. CircRNA-LNP vaccines demonstrate considerable promise for clinical translation, serving as both primary therapies and adjuvant treatments for a range of malignancies. The HLA-I binding concealed antigen peptide is derived from oncology-specific circular RNA, with its non-classical translation resulting in circFAM53B. The hidden peptide effectively stimulates immature CD4 and CD8 T cells in an exclusive manner related to the antigen, thereby enhancing anti-tumor immunity [191]. Studies conducted in vivo indicate that in mice with breast carcinoma or melanoma, the infiltration of cytotoxic T cells targeting tumor antigens is enhanced by a vaccine

comprising cancer-specific circRNAs or their translated peptides, resulting in effective tumor management [88]. In addition, the study by Ren et al. found that circRNAs generate neoantigens through atypical translation pathways, effectively activating immune responses. These neoantigens present unique epitopes on tumor cells, opening new targets for vaccine development [193].

However, the technology faces several challenges. First, technical limitations are significant. Although circRNA vaccines are more stable than traditional linear RNA vaccines, their delivery efficiency and cellular uptake still require optimization. Second, large-scale production is challenging. The complex preparation process of circRNAs, high costs, and stringent quality control needed to ensure stability and functionality pose difficulties. Additionally, regulatory hurdles are substantial. The long-term safety and potential risks of circRNA vaccines need rigorous preclinical and clinical assessments. Finally, there is a significant gap in human validation. Current research is primarily focused on animal models and in vitro experiments, necessitating more clinical trials to verify efficacy and safety across different tumor types. Future research must focus on addressing these key issues to facilitate the clinical translation and widespread application of circRNA vaccines.

Tumor CircRNA databases

The integration of comprehensive circRNA datasets is crucial for advancing downstream research in tumor biology, immunotherapy, and personalized medicine. Such databases provide a centralized repository of information that facilitates the identification of novel biomarkers, elucidates the mechanisms underlying cancer progression, and supports the development of targeted therapies. In this context, two databases, MiOncoCirc and TCCIA, have emerged as particularly significant resources.

MiOncoCirc is the first database primarily composed of circRNAs directly detected in tumor tissues. MiOncoCirc technology employs high-throughput sequencing and sophisticated bioinformatics analysis to effectively identify and quantify circRNAs in cancer samples. This advanced technology not only improves the sensitivity and specificity of circRNAs detection but also enables researchers to investigate the expression patterns and functional roles of circRNAs across various cancer types in greater depth. MiOncoCirc technology establishes a foundation for discovering new biomarkers, elucidating the mechanisms of cancer progression, and developing personalized treatment strategies, signaling a promising future for circRNAs research in tumor biology [194].

Our group previously constructed TCCIA, the first database that combines circRNA profiles, immunotherapy response data, and clinical outcomes across multiple cancer types. TCCIA provides researchers with a well-structured database that integrates various datasets related to circRNAs and their involvement in cancer immunotherapy mechanisms. By compiling information on circRNAs expression profiles, functional roles, and interactions within the TME, TCCIA enables researchers to gain a deeper understanding of how these molecules influence immune responses to tumors.This resource not only helps identify circRNAs that may serve as biomarkers for patient stratification but also highlights potential circRNAs therapeutic targets. The methodologies employed in the development of TCCIA ensure that the database is both comprehensive and user-friendly, allowing researchers to easily navigate extensive datasets and extract meaningful insights. By fostering collaboration and knowledge sharing, TCCIA is poised to accelerate discoveries in circRNAs research, ultimately enhancing the effectiveness of cancer immunotherapies [195].

Despite the substantial potential of circRNA databases in tumor research, several challenges remain. First, technical limitations are significant, as the precision of detection technologies and the complexity of circRNA structures restrict the accuracy and comprehensiveness of the databases. Current sequencing methods may fail to capture all circRNA variants completely, resulting in incomplete data. Second, scaling up the production and maintenance of comprehensive circRNA databases is challenging, requiring substantial computational resources and bioinformatics expertise. The complexity of data integration from multiple sources and the need for continuous updates pose difficulties for scalability. Additionally, regulatory hurdles are substantial, as ensuring the reliability and validity of database data is crucial for clinical applications. Rigorous regulatory approval processes are needed to validate the quality and consistency of data. Finally, there is a significant gap in human validation. Although circRNA databases provide valuable insights, translating these findings into clinical benefits requires more clinical trials to confirm the efficacy and safety of circRNA-based diagnostics and therapeutics across diverse patient populations. Future research must focus on addressing these key issues to facilitate the clinical translation and widespread application of circRNA databases.

In summary, circRNA technologies in CAR-T therapy, vaccine platforms, and databases hold promise for cancer treatment but face distinct challenges. Future research must address technical limitations, scalability issues, regulatory hurdles, and human validation gaps to fully realize their potential in oncology.

Conclusions

This article systematically reviews the role of circRNAs in tumor immune regulation and their potential for clinical application. CircRNAs modulate the functions of immune cells and immune checkpoints through various mechanisms, such as acting as miRNA sponges, interacting with RBPs, and serving as translation templates, thereby demonstrating significant potential in cancer therapy. However, the clinical application of circRNAs faces numerous challenges. First, the biogenesis and degradation mechanisms of circRNAs are not fully understood, which limits our in-depth comprehension of their stability and functional regulation in vivo. Second, the efficiency and specificity of circRNA delivery systems are insufficient, making it difficult to ensure precise targeting of tumor cells. Moreover, the immunogenicity of circRNAs and their potential off-target effects may cause adverse reactions, affecting the safety of treatment. In terms of clinical translation, the transition of circRNA therapy from the laboratory to the clinic requires substantial validation, especially in clinical trials with higher levels of evidence, where their efficacy and stability still need further confirmation. These technical and clinical barriers indicate that despite the broad prospects of circRNA therapy, its widespread application still requires overcoming many challenges.

Future research should focus on optimizing circRNA delivery systems to enhance their targeting and stability, while also delving deeper into their biological mechanisms to reduce immunogenicity and off-target effects. In terms of therapeutic approaches, the combination of circRNA vaccines and CAR-T cell therapy may be an important trend for the future. Although CAR-T cell therapy has achieved significant progress, its application in solid tumors still faces challenges, and circRNA technology is expected to provide new solutions. In contrast, circRNA vaccines are still in the early stages of exploration and require more clinical trials to verify their safety and efficacy. In terms of resource allocation, priority should be given to optimizing mature technologies (such as CAR-T cell therapy) while actively exploring the potential of emerging technologies (such as circRNA vaccines) to promote the widespread application of circRNA therapy in cancer immunotherapy.

Abbreviations

CircRNAs	Circular RNAs
RBPs	RNA-binding proteins
miRNA	MicroRNA
PD-L1	Programmed cell death-ligand 1
CDR1as	Cerebellar degeneration-related protein 1 transcript
TME	Tumor microenvironment
Pre-mRNA	Precursor messenger RNA
mRNA	Messenger RNA
TER	Transcription elongation rate
Pol II	Polymerase II
ICS	Intron complementary sequences
NXT1	NTF2-related export protein 1
NXF1	Nuclear RNA export factor 1
PMN-MDSCs	Polymorphonuclear myeloid-derived suppressor cells
FATP2	Fatty acid transport protein 2
RIPK3	Receptor interacting protein kinase 3
NPC	Nuclear pore complex
QKI	Quaking
IRES	Internal Ribosome Entry Site
HEp-2	Human epidermoid carcinoma 2
TAM	Tumor-associated macrophage
HNSCC	Head and neck squamous cell carcinoma
HCC	Hepatocellular carcinoma
NPC	Nasopharyngeal carcinoma
EC	Esophageal cancer
ESCC	Esophageal squamous cell carcinoma
BC	Breast cancer
TNBC	Triple-negative breast cancer
LC	Lung cancer
LUAD	Lung adenocarcinoma
NSCLC	Non-small cell lung cancer
PDAC	Pancreatic ductal adenocarcinoma
GC	Gastric cancer
BLCA	Bladder urothelial carcinoma
CeRNAs	Competitive endogenous RNAs
CAR	Chimeric antigen receptor
CAR-T cell	Chimeric antigen receptor T-cell

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Authors' contribution

YW conceived the review. YW wrote the manuscript and drafted the figures and tables. YC and XL edited and supervised the review. JZ, SW, HM, SJ, HW and GU critically reviewed and edited the manuscript. All authors read and approved the final Manuscript.

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Data availability

No datasets were generated or analyzed during the current study.

Declarations

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