Review Article

The emerging prospects of circular RNA in tumor immunity

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Abstract: Circular RNA (circRNA), as a cluster of endogenous non-coding RNA (ncRNA) with tissue-specific expression in various eukaryotic species, may be involved in a variety of human physiological and pathological processes. With the continuous development of high-throughput sequencing in recent years, circRNA has been increasingly widely studied and become a hot spot in the field of tumor research. The immune system plays a crucial and complex role in tumor development. It is not only capable of inhibiting tumor progression, but it can also create conditions suitable for tumor development, thereby promoting tumor progression. Moreover, through ncRNA, tumor immunotherapy, as an essential means of tumor therapy, may regulate tumor immunity to achieve the purpose of treatment. This article reviews the role of circRNA in tumor immunity to supply a sufficient theoretical basis for tumor immunotherapy.

Keywords: circular RNA (circRNA); non-coding RNA (ncRNA); immune system; tumor immunity; tumor immunotherapy

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Introduction

More than 70% of genes in the human genome can be actively transcribed. However, only 1–2% of genes possess protein-coding ability, and most transcripts are non-coding RNA (ncRNA) (1). Circular RNA (circRNA) is a ncRNA commonly found in eukaryotes, which has abundance, stability, conservation, and a certain degree of tissue space specificity (2). circRNA has been found to be involved in the regulation of eukaryotic gene expression in various ways, including through binding to microRNA (miRNA) or RNA binding protein (RBP), interacting with transcription factors, encoding protein or polypeptide, and affecting pre-mRNA formation via competitive co-transcription (3-7). Moreover, the dysfunction of circRNA is associated with various diseases, including many types of tumors (8-13).

The importance of tumor immune response in tumor development is widely acknowledged (14). The earliest study on the response of the immune system to tumors used Coley's toxins to trigger an immune response and treat a variety of inoperable cancers (15). In recent years, research on tumor immunity has become increasingly intensive. The immune system carries out a dual role in the promotion and suppression of tumorigenesis and tumor development (16). At the same time, the role of linear ncRNAs, such as miRNAs and long non-coding RNAs (lncRNAs), in tumor immunity has become clearer (17). However, the functions of circRNA in tumor immunity need further investigation. Herein, we review the existing research on circRNA in tumor immunity, with a focus on the promising role of circRNA in the regulation of tumor immunity.

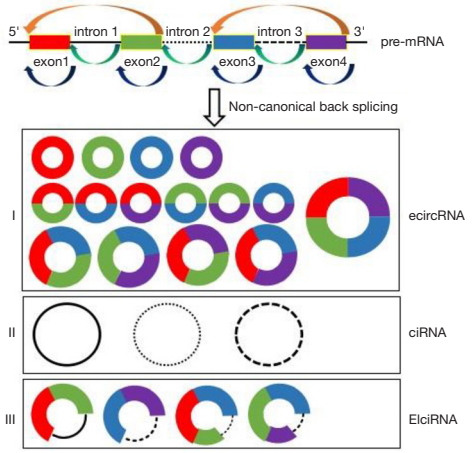

Figure 1 The formation and main categories of circRNA. ecircRNA, exonic circRNA; ciRNA, circular intronic RNA; EIciRNA, retained intron circRNA.

The formation and characteristics of circRNA

In recent years, circRNA, a naturally occurring non-coding RNA, has received widespread attention. circRNA does not have a 5' cap or a 3' tail but forms a covalently closed circular structure, making it resistant to ribonuclease digestion with higher stability than linear mRNA (18).

circRNA formation

Unlike the canonical splicing of linear mRNA, circRNA is produced by non-canonical forms of alternative splicing. Based on various biosynthesis models, circRNAs are divided into three main categories: exonic circRNA (ecircRNA) (2), retained intron circRNA (ElciRNA) (19), and circular intronic RNA (ciRNA) (3) (*Figure 1*). Of these categories, ecircRNA is the largest in number, accounting for more than 80% of identified circRNAs. There are two primary modes of ecircRNA formation: lariat-driven circularization and intron-pair-driven circularization (2). Wilusz *et al.* proposed that circRNA is predominantly produced during alternative back-splicing, in which the splice donor site of the primary transcript's downstream exon is connected to the splice acceptor site of the upstream exon in reverse order, forming a circular transcript. Moreover, exon circularization depends on the alternative pairing of flanking complementary intron sequences and inverted repeat Alu sequences, to enable the same gene locus to produce multiple circRNAs (20). Normally, introns between exons are spliced, but at some point, they are kept to form so-called retained-intron circRNAs (ElciRNAs) (5). Finally, in the nucleus of specific tissues, introns can independently circulate to form a circular intron RNA (ciRNA). ciRNA formation depends on a common motif containing a 7-nucleotide GU-rich element near the 5' splicing junction site and an 11-nucleotid C-rich element near the 3' splicing junction site, which allows the intron to avoid debranching and form a stable circRNA (3).

circRNA biosynthesis also depends on RNA-binding protein (RBP). Adenosine deaminase 1 (ADAR1), for example, cuts the formation of circRNA by binding the double-stranded RNA to the stem-loop structure (21). circRNA synthesis is inhibited by nuclear RNA helicase DHX9 through its explicit binding of the inverted repeat Alu sequence (IRAlus) (22). In contrast, circRNA formation is promoted by the splicing factors Quaking (QKI) (23) and Muscleblind (MBL) (7) as they bind to flanking introns of the circularized exons in their host gene mRNA precursors. The above studies show that RBP may play a vital role in the circularization of circRNA by inhibiting established splicing and bridging complementary sequences. However, the detailed mechanism of circRNA biogenesis needs further exploration.

Characteristics of circRNA

The prominent features of circRNA are as follows: (I) abundance: although the expression abundance of circRNA varies in different cells (24), the content of circRNA in some cells can be as high as ten fold more than its corresponding linear transcript (2). (II) Stability: the covalently closed loop structure of circRNA facilitates its resistance to exonuclease RNase R, meaning that circRNA is more stable than linear mRNA. Data has shown that in most species, the average half-life of circRNA exceeds 48 h, while the half-life of mRNA is about 10 h (25). (III) Conservation: most circRNAs have highly conserved sequences, meaning circRNAs are conserved among distinct species. For example, many circRNAs can be simultaneously detected in humans, mice, and even fruit flies (2,26). (IV) Distribution: most of the exon-derived circRNAs (ecircRNAs) are primarily located in cytoplasm and usually function as miRNA response elements (MRE) (27,28). A small number of intron-derived circRNAs, ciRNAs, and EIciRNAs, are located in the nucleus and may be involved in the regulation of gene expression at the transcriptional or post-transcriptional level (2,3). (V) Tissue and space specificity:

the expression level of circRNA in the mammalian brain, for example, is high, especially at the synaptic site, and circRNA is usually upregulated during neuronal differentiation (29).

The functions of circRNA

Based on the above characteristics of circRNAs, a growing body of evidence has revealed that circRNAs might take part in the regulation of eukaryotic gene expression by exerting a series of functions. Herein, we enumerated several prominent biological functions of circRNAs (*Figure 2*).

circRNA as miRNA sponge

Some circRNAs contain miRNA binding sites, which could serve as competitive endogenous RNA (ceRNA) to compete for miRNA binding sites to regulate miRNA activity negatively, thereby reducing the inhibitory effect of miRNA on its downstream target genes (30). One of the most typical examples is the antisense transcript of cerebellar degeneration-related protein-1 (*CDR1as*), also known as *ciRS*-7, which contains 74 selectively conserved miRNA binding sites and can serve as a molecular sponge for miR-7 (30). CDR1as can be cleaved in the nucleus by binding to miR-671 at the miR-7 target in an AGO2-dependent manner site, before miR-7 is transported to the subcellular site and released via the promotion of miR-671 (30). Studies have confirmed that ciRS-7 overexpression increases the expression of miRNA target genes, while knockdown of ciRS-7 has the opposite effect (30). Moreover, mouse testis-specific circRNA sex-determining region Y (*circSry*) has 16 miR-138 target sites and is associated with testicular development (30). circHIPK2 has been reported to be a molecular sponge for miR124-2HG, which regulates the activation of astrocytes through the synergistic effect of autophagy and endoplasmic reticulum (ER) stress (31). circBIRC6 regulates pluripotency and differentiation of human embryonic stem cells (hESCs) by binding to miR-34a and miR-145 (32). Other studies have found that circHIPK3 can function as a sponge for miR-124, which can upregulate the expression of the target genes IL6R and DXL2 of miR-124 through the ceRNA mechanism and promote cell proliferation in liver cancer (33). However, notably, the expression of most circRNAs in mammals is low, and the existence of multiple binding sites for the same miRNA is rare (34).

circRNA as RBP sponge

Studies have shown that circRNAs can bind to RBPs such as QKI, AGO, and MBL, to play an essential role in tumor progression as RBP sponges (35,36). CircRNA can bind to QKI protein in EMT and participate in the regulation of tumor metastasis (23). QKI-5, as a widely studied RBP, is considered as a novel tumor suppressor in many cancers, including lung and prostate cancer (37,38). The abnormal overexpression of AGO proteins has also been found in cancers and is closely related to the development of cancers that depend on miRNA-dependent or non-dependent pathways (39). These studies show that circRNA may interact with RBP and play an essential role in tumorigenesis and tumor development. Besides, circ-Foxo3 binds to cyclin-dependent kinase 2 (CDK2) and p21 to form a Foxo3-p21-CDK2 ternary complex that inhibits CDK2 function and blocks the cell cycle process, thereby participating in the regulation of cancer development (40). circPABPN1 has also been reported to inhibit the binding of HuR to PABPN1 mRNA by binding to HuR, which provides the first example of the competition between circRNA and its homologous mRNA for RBP (41).

circRNA can regulate transcription and splicing

Although most circRNA is found in the cytoplasm, EIciRNA and ciRNA retained in the nucleus may be involved in transcriptional regulation. Studies have revealed that by knocking out several EIciRNAs, the transcription of their parent genes can be reduced. EIciRNA can interact with U1 small nuclear ribonucleoprotein (U1snRNP), and the EIciRNA-U1 snRNP complex interacts with RNA polymerase II (Pol II) on the promoter of its parent gene to enhance gene expression. Blocking this RNA-RNA interaction disrupts the interaction between EIciRNA and Pol II and later reduces the transcription of its parent gene. For example, circEIF3J and circPAIP2 interact with U1 snRNP and Pol II to enhance the transcription of their parent genes (5). circSEP3 is a retaining nuclear circRNA derived from exon 6 of SEPALLATA3 (*SEP3*) in Arabidopsis thaliana, which regulates the splicing of linear transcripts. circSEP3 tightly binds to its homologous DNA locus to form a RNA, DNA hybrid, while linear RNA with the same sequence binds weakly to the DNA. Studies have shown that the formation of the circRNA mentioned above, DNA complex, forced the transcription to suspend,

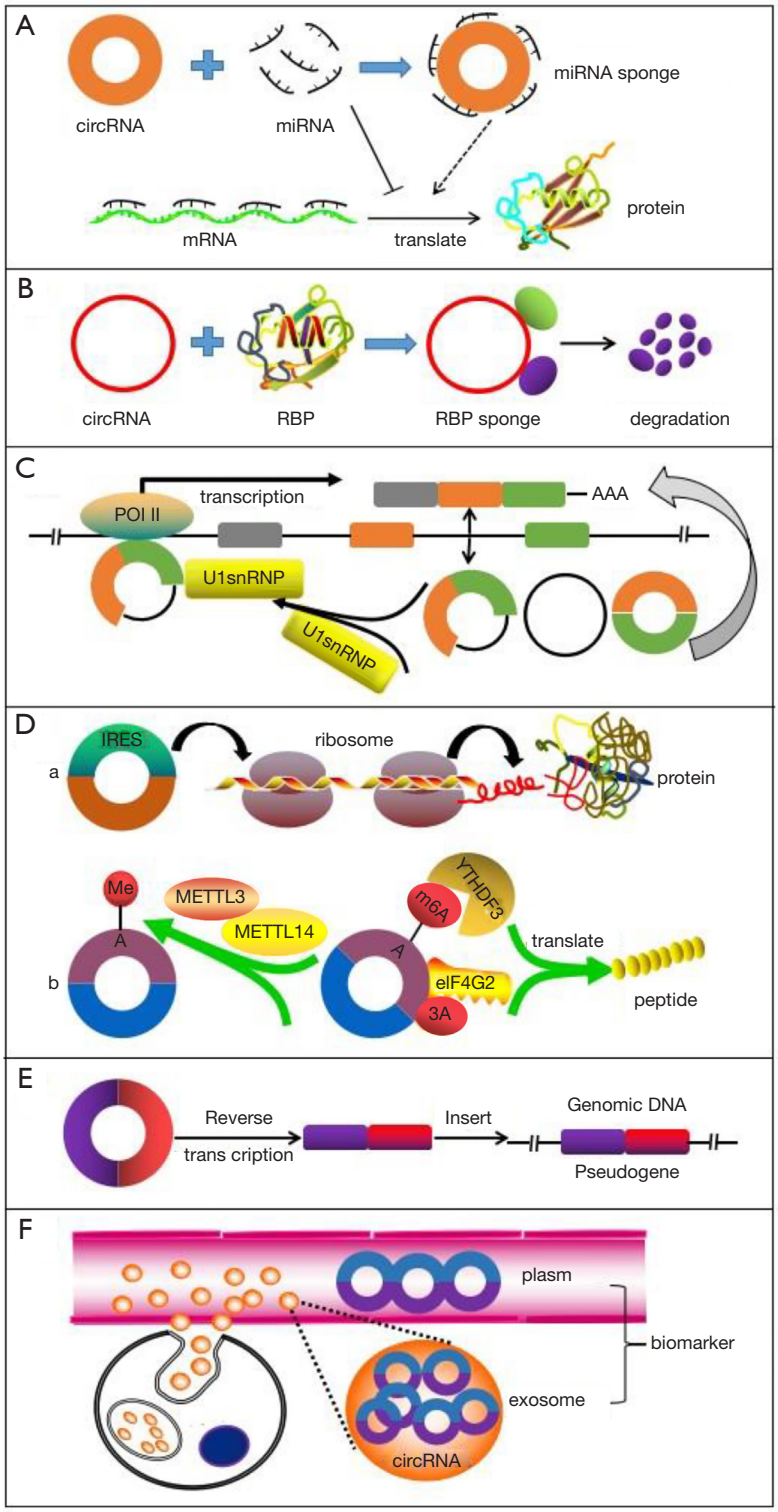

Figure 2 The reported functions of circular RNA. (A) Acting as miRNA sponge; (B) acting as RBP sponge; (C) the regulation of transcription and splicing; (D) translate protein; (E) circRNA-derived pseudogenes; (F) acting as potential biomarkers. miRNA, microRNA; RBP, RNA binding protein.

resulting in the enhanced splicing efficiency of SEP3 exon-skipped mRNA (42).

Also, ci-ankrd52 belonging to ciRNA participates in prolonging the Pol II mechanism and positively regulates Pol II transcription by accumulating up to its transcription site. The knockout of ci-ankrd52 reduces the expression of its parent gene (3). These studies taken altogether show that some nuclear-localized circRNAs can regulate gene expression at the transcription and splicing levels.

circRNA can translate proteins

Although most circRNAs are ncRNAs, some circRNAs containing internal ribosome entry site elements (IRES) (43-49) or prokaryotic ribosome binding sites (50) are able to encode proteins that differ from their corresponding canonical transcripts. There is a circRNA database named circRNADb containing 32,914 human ecircRNAs, which provides detailed information about circRNA, including genomic sequences, ORFs, and IRES, to predict the translatability of certain circRNAs (51). circZNF609 was found to be translated and function to control myoblast proliferation during muscle differentiation (52). The ribosomal footprint from the fly's head also showed that a group of circRNAs are related to translated ribosomes, and circMbl can produce proteins (6). It is worth noting that IRES is embedded in circMbl and circZNF609 to allow cap-independent translation. Since the ribosome-associated circRNA uses the same start codon as its host mRNA, this circRNA-derived polypeptide may have a similar function to the mRNA-encoded protein or serve as a main negative competitor (52,53).

In addition to IRES, N6-methyladenosine (m6A) modification can also drive circRNA translation. m6A modification has been reported to be the most abundant base modification of RNA and can promote translation of circRNA from reporter genes and endogenous gene loci. circRNA has been identified as being rich in m6A consensus motifs, and a single m6A site is enough to drive translation initiation. The m6A-driven translation is started by eIF4G2 and m6A reader YTHDF3, enhanced by the methyltransferase METTL3/14, inhibited by the demethylase FTO, and upregulated during heat shock (54). Also, m6A-driven translation of circRNA is widespread, and many endogenous circRNAs have translation potential, which indicates the role circRNA-derived proteins potentially hold in cellular stress responses. Cell starvation, for example, leads to enhanced translation of circMbl (53), and the translation of GFP in m6A-rich circRNA plasmids can be promoted by heat shock (54). However, only a small part of circRNA is associated with polysomes, and the cap-independent initiation efficiency is low. Therefore, the products of circRNA translation may be limited (2,34,54,55).

circRNA-derived pseudogenes

Pseudogenes typically originate from the process by which linear mRNAs are integrated into their host genome. Dozens of circRNA-derived pseudogenes have been found in the genomes of humans and mice (56,57). Among them, dozens of pseudogenes derived from circRFWD2 were found in mice, and high-density long terminal repeats (LTR) were found in the flanking regions, indicating that the retrotransposition process of circRFWD2 and LTR are related. Moreover, the insertion of reverse-transcribed circRNA may potentially disrupt the integrity of the host genome. For example, the circSATB1-derived pseudolocus overlaps with CCCTC binding factor (CTCF) and Rad21 binding sites in several mouse cell lines. This CTCF binding is specific in the circSATB1-derived pseudogene region, but is not specific in its original SATB1 region (58).

circRNA as potential biomarkers

As mentioned above, circRNA is abundant and conserved among species. At the same time, it is stably expressed in saliva, blood, exosomes, and shows tissue/developmental stage specificity, which makes it a potential biomarker (58-60). Besides, circRNA is more straightforward to detect than the small number of miRNAs. A variety of circRNAs have been considered as potential biomarkers. In laryngeal squamous cell carcinoma (LSCC), for example, circ_100855 is significantly upregulated, while circ_104912 is significantly downregulated. Their expression is significantly related to tumor stage and cervical lymph node metastasis, suggesting that they could be used as potential new biomarkers in LSCC tumorigenesis (61). Other studies have found that circBRAF can be used as a biomarker to predict the pathological grade and prognosis of glioma patients (62). In bladder cancer, circTCF25 overexpression may promote proliferation and migration and could serve as a novel potential marker (63). Recent studies have shown that mature cancer-related chromosomal translocations produce fusion circRNAs (*f-circRNAs*), which are produced by transcriptional exons of different genes affected by translocations. When f-circRNA is combined with other

carcinogenic stimulants, it can take on a decisive role in promoting leukemia progression (64). f-circM9 and f-circPR are a fusion of the *PML/RARa* and *MLL* genes. Knocking out f-circM9 and f-circPR can lead to apoptosis of tumor cells and increase their sensitivity to drugs such as arsenic, which indicates that f-circM9 and f-circPR play a carcinogenic role in hematological malignancies (64). Other studies have found that the circRNA content in human platelets is 17- to 188-fold that of nucleated tissues, mainly because circRNA is more stable than linear mRNA and is not easily degraded (65). Also, circRNA can also be used as ceRNA in the regulation of miRNA on platelets (66). In summary, circRNA can be used as a potential biomarker for the diagnosis, treatment, and prognosis of cancer patients.

circRNA in tumor immunity

Based on the above, circRNAs have many biological functions and play a critical regulatory role in tumorigenesis and development. The immune system plays a dual role in tumor occurrence and development. On the one hand, the immune system can resist tumorigenesis through innate and acquired immunity; on the other hand, tumor cells can escape the recognition and attack by the immune system through the formation of a specialized immune suppressive microenvironment or other mechanisms to generate immune escape. The tumor immune suppressive microenvironment comprises immunosuppressive molecules, matrix components, and immune suppressor cells. These immune suppressor cells include tumor-associated macrophages (TAMs), regulatory T cells (Tregs), and myeloid-derived suppressor cells (MDSCs). An intricate interplay between immune suppressor cells occurs throughout tumor progression. MDSCs, as one example, interfere with the body's innate immunity by interacting with natural killer (NK) cells and NKT cells; concurrently, they transform macrophages into M2 macrophages with immunosuppressive effects to regulate anti-tumor immunity (67). Given the complex role of the body's immune system in cancer, and the scarcity of research on tumor immune regulation by circRNA, we systematically summarize the functions of circRNA in tumor immunoregulation under four headings below (*Figure 3*).

Function as a miRNA sponge to regulate tumor immunity

CircRNA has been reported to regulate tumor immunity via the circRNA-miRNA-mRNA axis (17). For instance, circRNA hsa_circ_0020397 has been revealed to sponge miR-138 and inhibit miR-138 activity, resulting in its downstream target gene telomerase reverse transcriptase (*TERT*) and programmed death-ligand 1 (*PD-L1*) enhanced expression in colorectal cancer (CRC) cells. After this, the highly expressed PD-L1 binds to PD-1 in CRC, causing T cell inactivation and tumor immune escape (68). Hsa_circ_0000654 was also identified as an oncogenic circRNA in esophageal squamous cell carcinoma (ESCC) through sponging miR-149-5p and the subsequent indirect activation of the IL-6/STAT3 signaling pathway, which has been widely certificated to be involved in tumor immune processes (69). Moreover, the well-known circRNA, ciRS-7, could accelerate ESCC progression by sponging miR-876-5p to enhance the tumor antigen melanoma-associated antigens-A (MAGE-A) family expression (70).

As is widely understood, the tumor inflammatory microenvironment plays a crucial role in tumor immunity. In the inflammatory microenvironment of tumors, continuous inflammatory reactions result in abnormal activation of the nuclear factor kappa B (NF-κB) pathway and the promotion of tumor development (71). Some studies have shown that certain circRNAs could indirectly affect the NF-κB pathway to regulate tumor immunity. For example, ciRS-7 was found to trigger the migration and invasion of ESCC cells via miR-7/KLF4 and NF-κB signals (72). Moreover, ciRS-7 could also function as a miR-7 sponge and then reactivate the HOXB13-mediated NF-κB pathway, inducing malignant progression of ESCC (11). Also, circRNA-000911 plays an anti-oncogenic role in breast cancer through sponging miR-449a to activate the Notch1 and NF-κB signaling pathways (73). By sponging miR-615-5p and miR-6753-5p, circPUM1 upregulated the expression of NF-κB and MMP2 to exert its carcinogenic effects in epithelial ovarian cancer (EOC) cells (74). We have summarized the function of circRNA as a miRNA sponge to regulate tumor immunity in *Table 1*.

Function as RBP sponge to regulate tumor immunity

Unlike the points dicussed above, the regulation of circRNA as an RBP sponge in tumor immunity has rarely been reported. circAmotl1 has been shown to interact with Stat3 and Dnmt3a, which are both the target gene of miR-17-5p. Dnmt3a inhibits miR-17-5p expression through methylation of the miR-17 promoter, and the decreased miR-17-5p induces enhanced Stat3 level in tumor immunity regulation (17,75). Besides, circFoxo3 could bind to

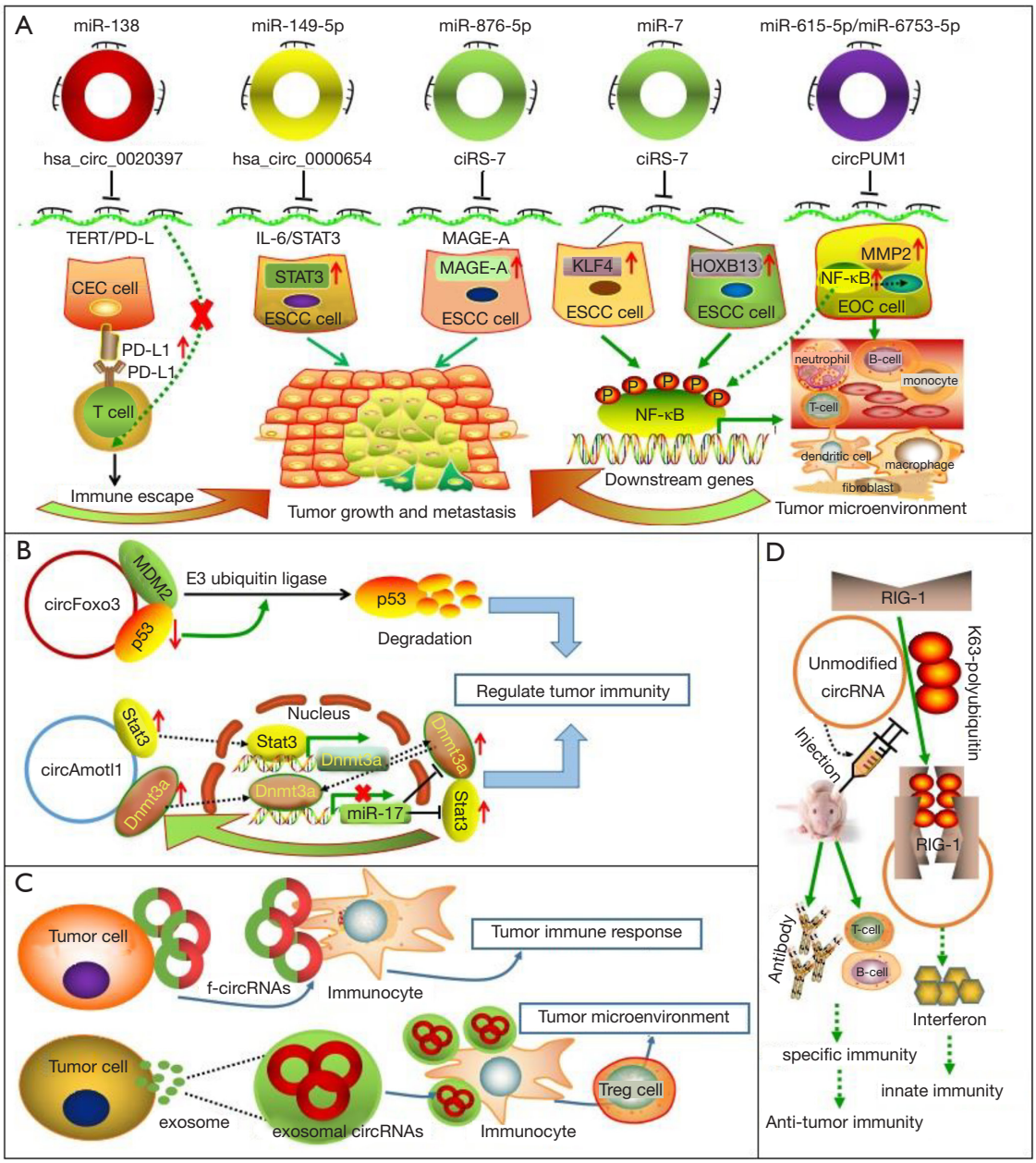

Figure 3 The emerging roles of circular RNA found in tumor immunoregulation. (A) Function as a miRNA sponge to regulate tumor immunity, such as hsa_circ_0020397 sponging miR-138 in CRC cells, hsa_circ_0000654 sponging miR-149-5p in ESCC cells, ciRS-7 sponging miR-876-5p in ESCC cells, ciRS-7 sponging miR-7 in ESCC cells, circRNA-000911 sponging miR-449a in breast cancer cells, and circPUM1 sponging miR-615-5p and miR-6753-5p in EOC cells; (B) function as an RBP sponge to regulate tumor immunity, such as circFoxo3 interacting with MDM2 and p53 in breast cancer cells, and circAmotl1 is interacting with Stat3 and Dnmt3a in a mouse model; (C) f-circRNAs, have been reported to function as tumor antigens recognized by immunocytes in mice tumor model studies, and exosomal circRNAs as tumor antigens in the modulation of intercellular connection and the tumor microenvironment in cancer cells; (D) function as vaccine adjuvants to induce anti-tumor immunity, such as the unmodified foreign circRNAs, have been reported to be potent adjuvants to induce antigen-specific T cell activation, antibody production, and anti-tumor immunity in a mouse model. ESCC, esophageal squamous cell carcinoma; EOC, epithelial ovarian cancer.

Table 1 The circRNAs as a miRNA sponge related to tumor immunity

CircRNA name	Tumor type	Target gene	Function overview
hsa_circ_0020397	Colorectal cancer (LoVo, HCT116, SW480, SW620 cell lines)	*TERT, PD-L1*	hsa_circ_0020397 regulates the cell viability, apoptosis, and invasion of colorectal cancer by sponging miR-138 to target TERT and PD-L1
hsa_circ_0000654	Esophageal squamous cell carcinoma (TE-1, KYSE410, TE-13, ECA109, KYSE450 cell lines)	*IL-6, STAT3*	hsa_circ_0000654 promotes esophageal squamous cell carcinoma progression by regulating the miR-149-5p/IL-6/STAT3 pathway
ciRS-7	Esophageal squamous cell carcinoma (Eca109, TE1, TE13, KYSE30 cell lines)	*MAGE-A*	ciRS-7 accelerates ESCC progression through sponging miR-876-5p to enhance MAGE-A family expression
ciRS-7	Esophageal squamous cell carcinoma (KYSE150, KYSE140, KYSE70, Eca9706, EC18, TE13 cell lines)	*KLF4, NF-κB*	ciRS-7 triggers the migration and invasion of esophageal squamous cell carcinoma via miR-7/KLF4 and NF-κB signals
ciRS-7	Esophageal squamous cell carcinoma (Eca109, KYSE510, KYSE410, KYSE150 cell lines)	*HOXB13, NF-κB*	ciRS-7 promotes growth and metastasis of esophageal squamous cell carcinoma via regulation of miR-7/HOXB13/NF-κB signals
circRNA_000911	Breast cancer (MCF-7, MDA-MB-231, MDA-MB-468, MDA-MB-453, SKBR-3, T47D cell lines)	*Notch1, NF-κB*	circRNA-000911 plays an anti-oncogenic role in breast cancer through sponging miR-449a to activate Notch1 and NF-κB signaling pathway
circPUM1	Ovarian cancer (A2780, CAOV3, HMrSV5 cell lines)	*NF-κB, MMP2*	circPUM1 upregulated the expression of NF-κB and MMP2 by sponging miR-615-5p and miR-6753-5p to exert its carcinogenic effects in ovarian cancer

TERT, telomerase reverse transcriptase; PD-L1, programmed death-ligand 1; MAGE-A, melanoma-associated antigens-A; NF-κB, nuclear factor kappa B; MMP2, matrix metalloproteinase 2.

MDM2 and p53, resulting in p53 ubiquitination and later degradation, which has been widely reported to regulate tumor immunity and progression (17,76,77). Although there is not enough research on circRNA as an RBP sponge to participate in tumor immunity so far, the above cases suggest that circRNA can regulate tumor immunity by interacting with some immune-related proteins like Stat3 and p53.

Function as tumor antigens to regulate tumor immunity

It was reported that the transfection of exogenous circRNAs into mammalian cells could effectively induce innate immunity and resist viral infection (78). Moreover, another study showed that endogenous circRNAs are prone to form 16-26bp imperfect RNA duplexes and serve as inhibitors of the double-stranded RNA (*dsRNA*)-activated protein kinases (PKRs) associated with innate immunity (79). During tumorigenesis, cancer-associated chromosomal translocations may produce some novel aberrant fusion circRNAs, that are f-circRNAs, which may be conveyed to immunocytes and then induce tumor immune response (59).

Besides, some exosomal circRNAs may also function as tumor antigens to regulate tumor immunity. For instance, there was a study that revealed that compared with the cellular circRNAs, the expression profile of exosomal circRNAs was more abundant based on RNA-Seq data in three KRAS mutant CRC cell lines (80). Exosomes, as a medium of cell communication, could be easily detected in serum and body fluids, representing a potential tumor biomarker (81). Together with the expression enrichment of circRNAs in exosomes, the exosomal circRNAs play a potential role in the modulation of intercellular connection and tumor microenvironment (17,82). Furthermore, exosomal circRNAs were found to modulate the homeostasis and function of regulatory T (Treg) cells (83).

Function as vaccine adjuvants to induce anti-tumor immunity

Tumor vaccines activate tumor-specific immune responses through tumor-associated antigens to kill and clear

tumor cells, which have been widely applied for cancer immunotherapy (84). As a critical part of many tumor vaccines, adjuvants can increase the intensity, breadth, quality, and longevity of the immune response to tumor antigens (85). A recent study demonstrated that unmodified foreign circRNAs could act as potent adjuvants to induce antigen-specific T and B cell activation, antibody production, and anti-tumor immunity. In contrast, m6A modification of the circRNAs recognized as "self" may inhibit innate immunity and adjuvant activity via m6A reader YTHDF2 (86). This study supplies a powerful insight for breakthroughs regarding circRNAs in tumor immunotherapy.

Discussion

This review summarizes the formation mechanism, key features, biological functions, and research advances in tumor immunity of circRNAs. Although circRNAs were initially considered as a by-product of mis-splicing, with the development of high-throughput sequencing in recent years, more and more circRNAs have been discovered and characterized. circRNA can function as a miRNA and RBP sponge, and its inherent closed-loop structure makes it relatively stable in tissue and blood, making it more likely to be a biomarker for tumor diagnosis, treatment, and prognosis. Although most circRNAs are non-coding RNAs, some circRNAs have been found to encode proteins and may perform specific biological functions. Moreover, some circRNAs take part in tumor immunity regulation and may serve as potential molecular targets for tumor immunotherapy.

Currently, tumor immunotherapy plays an increasingly crucial role in cancer treatment. However, non-coding RNA, especially circRNA. is still not commonly applied in tumor immunotherapy. Given the increasingly improved status of circRNA in tumors, the in-depth exploration of the regulatory effect of circRNA on tumor immunity can not only unearth more novel tumor biomarkers and benefits for tumor diagnosis, treatment, and prognosis, but it could also dig out new immunotherapy targets, providing more effective methods for the prevention and treatment of various tumors in the future.

Overall, this review supplies a new perspective on the molecular mechanism and clinical application of circRNAs in the field of tumor immunity. It has specific scientific significance for attracting more scholars to explore the biological potential of circRNAs further.

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Footnote

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at http://dx.doi.org/10.21037/atm-19-4751). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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