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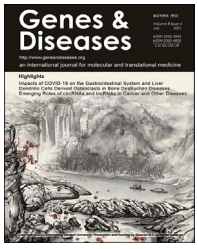

REVIEW ARTICLE

Emerging important roles of circRNAs in human cancer and other diseases

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Abstract CircRNAs are a large class of endogenous single-stranded RNA that is different from other linear RNA, which are produced by back-splicing and fusion of either exons, introns, or both exon-intron into covalently closed loops. CircRNAs are found in almost all living organisms and have emerged as potentially important players effecting on all life activities. It was characterized by stable structure, resistant to RNA degradation, highly abundance and conservation and tissue-specific expression. Early circRNAs were ignored as a by-product of meaningless abnormally cut RNA and had little biological function. Currently, circRNAs have become a research hotspot due to its special characteristics. CircRNAs could function as miRNA sponges, interfere with splicing and bind to protein to regulate the expression of parental genes and so on. In recent years, an increasing number of studies have revealed that circRNAs are closely related to a series of physiological and pathological processes. Additionally, circRNAs play an important role in the occurrence and development of a variety of diseases, suggesting circRNAs may be as novel indicators or biomarkers for cancer and other diseases with which they are associated. In this article, we review the biogenesis, biological functions of circRNAs and recent advances in circRNAs research in human diseases. Results will provide new insights on the roles and new ideas of circRNAs for the diagnosis and treatment of diseases and possible directions and approach for future circRNA applications.

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Introduction

CircRNAs are non-coding RNAs that have a special covalent loop structure with no 5′ caps or 3′ ploy (A), making them resistant to RNA exonucleases or RNaseR and more stable than linear RNAs.[1] CircRNAs were identified more than 40 years ago, which firstly were discovered as a viroid in plant in 1976 and were shown to encode subviral agents.[2] Later on, a handful of such circRNAs were found in yeast mitochondrial RNAs and hepatitis delta virus.[3,4] However, at that time, circRNAs have long been considered to be as by-products of pre-mRNAs rare mis-splicing. Thanks to the rapid development and breakthroughs of RNA sequencing and bioinformatics, the value of circRNAs in scientific field have been renewed starting about 7 years ago[5,6] and numerous circRNAs have been successfully identified in various cell lines and as well as in model organisms such as mice, rice, fly and worm.[7–9] Studies have revealed that circRNAs are abundantly and widely expressed in eukaryotes, and often show tissue/developmental stage-specific manners.[10–13] Furthermore, several researchers have confirmed that some circRNAs preferentially localize to exert their function in the cytoplasm, while the others circRNAs were localized in the nucleus.[14,15] Although their biological functions are still rudimentary, a select number of circRNAs are functioning as miRNA sponges, transcriptional regulators, protein translation, and so on. Growing evidence and existing reports has indicated the expression of circRNAs is usually abnormal in many diseases such as cancers.[16,17] In this review, we briefly review introduction the biogenesis, functions of circRNAs and emphasis on the currently progress of researches concerning circRNAs in different human diseases.

Categories and biogenesis of circRNAs

Understanding the structure features of circRNAs is critical for insight into their function. CircRNAs are produced from protein-coding genes in a non-canonical splicing event called back-splicing, in which a 5′ splice site (donor) attacks an upstream 3′ splice site (acceptor) generating a circular RNA molecule. Studies demonstrated that circularization and pre-mRNA splicing compete against each other via inhibiting the spliceosome by depleting components increases the ratio of circular to linear RNAs.[18] When pre-mRNA processing events are slowed down, nascent RNA can be directed to alternative pathways that facilitate back-splicing. Based on their composition by competition of RNA pairing across the flanking sequences,[19,20] circRNAs can be divided into four categories: exon-circRNAs (ecircRNAs), circular intron RNAs (ciRNAs), exon-intron circRNAs (EIciRNAs) and tRNA intronic circRNAs (tricRNAs)[21] (Fig. 1). Although the mechanisms of circRNA biogenesis are still unclear, there are three models of circRNAs biogenesis that we possible have an agreement including lariat-driven circularization, base-pairing-driven circularization, and RNA-binding proteins (RBP)-mediated circularization.[22] In lariat-driven circularization, a circRNA is formed by the joining of splice sites of the exons that are correlated with exon skipping during linear RNA formation, such as ecircRNAs and EIciRNAs.[23,24] Base-pairing-driven circularization is also known as the back splicing mechanism, which depends on inverse-repeating or complementary base-pairing sequences across different introns to generate circRNA including ciRNA and EIciRNAs.[13,25] Moreover, ciRNA is formed depending on a consensus motif containing an 11-nt C-rich element near the branch point and a 7-nt GU rich element near the 5′ splice site to escape disbranching. The other way that circRNA is derived from RBP-mediated circularization, which is the binding of RBP to the introns near splice sites to promote the circularization including the formation of ecircRNAs and EIciRNAs.[22,26] The pre-tRNAs is recognized and spliced by the tRNA splicing nuclease complex, and then release and ligate the end to form tRNA and tricRNA.[27]

Biological functions of circRNAs

CircRNAs act as miRNA and protein (RBP) sponges

Accumulating studies has shown that circRNAs can bind miRNAs as the competitive endogenous RNA (ceRNA) affecting miRNA activities to bind its target mRNA, resulting in the increased expression of targets[9,14] (Fig. 2A). This regulatory mechanism has become most common manner for cricRNAs. An illustrative example is that circRNA named CDR1as sponge for miR-7, which has been experimentally verified to act as a miR-7 sponge over 70 conserved miR-7 binding sites associating with Argonaute (AGO) proteins by a miR-7-dependent manner.[14] Another typically example is that a highly expressed Circsry in mouse testis possessing 16 binding sites for miR-138.[1] This is firstly demonstrated circRNAs act as miRNA sponges. In addition to above two circRNAs, more and more studies have confirmed that circRNAs can function as a ceRNA preventing their combinations or interactions with target mRNAs.[28] Liu et al revealed that circCER regulated MMP13 expression by sponging miR-136 in human cartilage degradation.[29] Chen and his group found that circFGFR2 could regulate skeletal muscle proliferation and differentiation in fibroblast cell lines of chicken embryo via sponging miR-133a-5p and miR-29b-1-5p.[30]

In addition, circRNAs may be used as protein or RBP sponges to interact with proteins to regulate their function (Fig. 2B). A convincing example is circFoxo3, which interacts with p21 and CDK2 to form a complex of the ternary complex circFoxo3-p21-CDK2 giving rise to block cell cycle progression.[31] CircMBL is also the best example, which sequesters muscleblind (MBL) protein and prevents it from binding to other targets.[25] In a recent research of Qin et al they reported that hsa_circ_0001649 harbor six potential protein binding sites for U2 auxiliary factor 65 kDa subunit (U2AF65), 5 potential protein binding sites for eukaryotic initiation factor 4A-III, and one potential protein binding site for regulator of nonsense transcripts1.[32] However, functions of hsa_circ_0001649 interacting with these proteins is still unknown and further studies should be investigated.

CircRNAs can be translated into proteins or peptides

As a conventional viewpoint, circRNAs are generally believed having no ability to encode proteins due to lacking

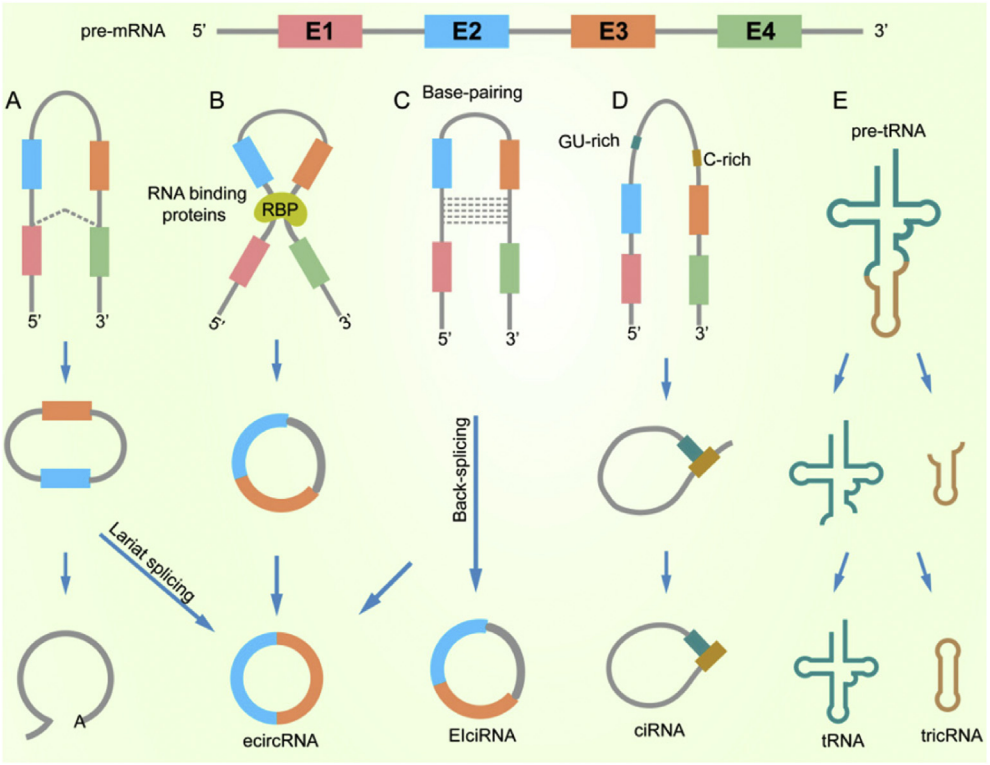

Figure 1 CircRNA biogenesis mechanisms.

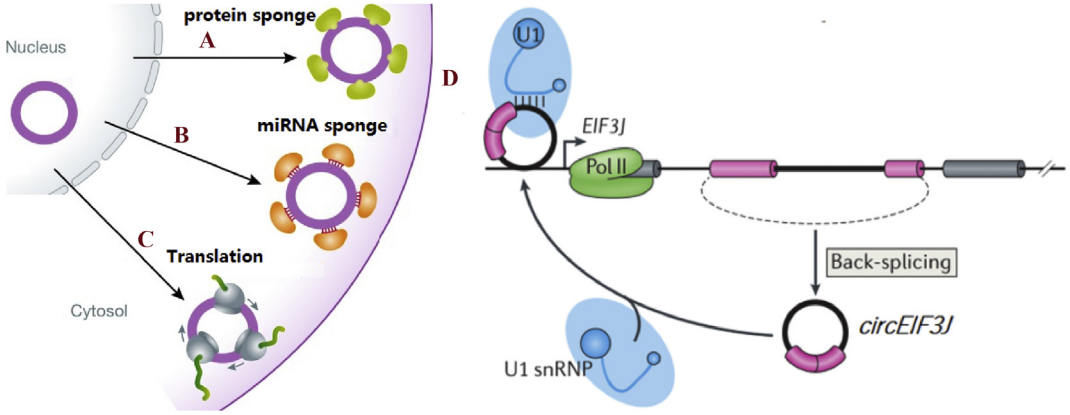

Figure 2 Functions of circRNAs. **(A)** miRNA sponge; **(B)** protein sponge; **(C)** translation and **(D)** parental gene regulation.

5′ and 3′ ends. Emerging evidence indicated that circRNAs function is as a template for translation or synthesis of proteins or peptides (Fig. 2C). For example, a study confirmed that a circRNA with 220 nts length from the rice yellow mottle virus can encode a highly basic, 16-kDa protein.[33] Zhong's group reported that not only proteins can be translated from circRNAs but it can also perform its potential function. They demonstrated that circ-ZNF609 could translate proteins in murine myoblasts when driven by internal ribosome entry site (IRES), which functions in myogenesis.[34] From a research by Yang et al showed that N^6-methyladenosine (m^6A) is sufficient to drive translation initiation of protein from circRNAs in human cells.[35] Subsequently, further studies confirmed the prevalence of m^6A in circRNAs.[36] More recently, Yang et al revealed that circFBXW7 can directly encode protein FBXW7-185aa, which could regulate the stability of c-Myc leading to repress the progress of malignant glioma.[37]

CircRNAs regulate the expression of parental gene

Recent advances have revealed that circRNAs could regulate the expression of parental genes. Researcher has reported that knockdown of circRNAs decrease the transcription of their host genes. As described in early 2013 from *Molecular Cell* published a study, they reported that three circRNAs (ci-ankrd52, ci-mcm5 and ci-sirt7) from

intron can also function as positive regulators of their parental gene transcription by interacting with RNA polymerase II (Pol II) and knockdown of their led to the reduced expression of their parental genes.[38] In addition, circRNAs can interact with U1 small nuclear ribonucleoproteins (U1snRNP) to regulate the translations of the transcript from its parental gene by binding to RNA Pol II complex (Fig. 2D). For instance, both circEIF3J and circPAIP2 can bind to U1snRNP and RNA Pol II in a *cis*-acting form to elevate their parental gene transcription.[39] In addition, a study showed that circPABPN1 positive regulates PABPN1 mRNA to inhibit the target HuR protein, and subsequently suppress the translation of its parental gene.[40] Due to the unique structure and high stability, circRNAs may exert a series of biological functions through different mechanisms. In addition to above defined functions, other functions of circRNAs are summarized in Table 1. However, more detailed studies are needed to explore and determine the functions of circRNAs in future.

CircRNAs and cancer or tumor

A vast number of evidence has uncovered a potential role of circRNAs which involved in a variety of human diseases, especially in the occurrence and development of cancer. It is also increasingly understood that circRNAs functions associating with cancer are being recognized. Cancerogenesis involves a number of causal molecular alterations, including genetic mutations and changes of gene expression states. Here, we focus mainly on the recent progress of circRNAs in different cancers.

CircRNAs and breast cancer

Breast cancer (BC) is one of the most ordinary malignant tumors with the highest and increasing morbidity and mortality affects more than 10% of females over 100 countries.[48] According to the latest data from Global Cancer Statistics 2018, there are over 2 million females who are newly diagnosed with BC. It is well acknowledged that circRNAs were often unconventionally expressed in BC, which may have potential functions. Currently, many BC-related circRNAs had been identified. Related studies have suggested that circ_0067934 functions as an oncogene in BC by targeting Mcl-1.[49] Study showed that circ_0067934 expression was significantly higher in BC tissues compared with that in adjacent non-tumor samples. After knockdown of circ_0067934 *in vitro*, cell proliferation in BC was inhibited, thereby effecting cell cycle in BC. Results implied that Mcl-1 was down-regulated via the knockdown of circ_0067934 in BC. The expression levels of hsa-circRNA-0005795 and hsa-circRNA-0088088 were significantly different both in serum exosomes and tissues and might function as ceRNA and play vital roles in BC development suggesting circRNAs hold significant diagnostic value for the prediction of BC by examining the expression of the circRNAs in serum exosomes between BC patients with healthy donors.[50] Hsa_circ_0008039 can be used as a sponge of miR-432-5p to promote proliferation and invasion of the BC cells.[51] More recently, Li et al investigated the differentially expressed (DE) profiles of circRNAs between plasma of patients with BC and normal human. Among DE circRNAs, hsa_circ_0069094, hsa_circ_0079876, hsa_circ_0017650, and hsa_circ_0017536 showed significant differences in expression levels between plasma of patients with BC and normal human.[52] Results will provide new directions for the prediction, diagnosis and treatment for BC.

Table 1 Putative functions of circRNAs.

Putative function	Representative circRNA	Reference
Alternative splicing	circSEP3	[41]
Retrotransposition	circRFWD2	[42]
RNA maturation	circANRIL	[43]
Protein scaffold	circFoxo3	[44]
Protein localization	circAGO2	[45]
Modulate immune response	circRasGEF1B	[46]
Histone modification	circANRIL	[47]

Hepatocellular carcinoma

Hepatocellular carcinoma (HCC) is the third leading cause of cancer-related deaths and accounts for 90% of primary liver carcinomas in the word.[53] It is estimated that HCC has high morbidity and mortality rates in humans, which give rise to over over 750,000 deaths each year.[54] A recent study suggests that circRNAs are important for the initiation, migration, and invasion of HCC. Liu et al[55] confirmed that circRNA-5692 overexpression effectively attenuated the malignant behaviors of HCC. Furthermore, circRNA-5692 sponge oncogenic miR-328-5p to enhance tumor suppressor DAB2IP expression, decreasing the malignant behaviors of HCC *in vitro* and *in vivo*. The investigations by Zhan et al showed that hsa_circRNA_103809 could promote HCC development via regulation axis of miR-377-3p/FGFR1/ERK.[56] Studies by Su et al[57] revealed that CDR1as could promote HCC progression by sponging miR-1270, which is directly transferred from HCC cells to surrounding normal cells via exosomes to further mediate the biological functions of surrounding cells. Zhang et al[58] found that circTRIM33-12 is down-regulated in HCC which promoted HCC progression including cell proliferation, invasion, and immune evasion. According to Han's researches, they reported that circMTO1 repressed HCC progression through sponging miR-9.[59] Therefore, the implication is that circMTO1 may become new targets in treating HCC.

Gastric cancer

Gastric cancer (GC), alias stomach adenocarcinoma, is one of the most frequent cancers and poses a serious threat to human life and leading causes of cancer-induced death worldwide, with geographically high morbidity in East Asia.[60] In 2018, there are estimated 1,033,701 new cases of GC and 782,685 cases of GC-related death, which ranks the fifth and third in cancer incidence rates and mortality rates, respectively.[61] Sun et al uncovered a regulatory network of circCOL6A3/miR-3064e5p/COL6A3 mRNA, which

regulated malignant behaviors of GC cells by sequestration of miR-3064e-5p and dis-inhibition of COL6A3.[62] CircRNA_100269 is down-regulated in GC and further inhibits cell growth in GC by targeting miR-630.[63] Other study showed that overexpressed circRNA_001569 promoted cell viability of GC via suppressing the expression of miR-145, which was mediated by NR4A2.[64] Wei et al analyzed 30 patients and found that hsa_circRNA_102958 exhibited highly expression in GC tissues compared with paired adjacent normal tissues. A Clinic Pathological and experiment analysis showed that hsa_circRNA_102958 level in GC tissues was positively associated with TNM stage ($P = 0.032$). The area under the ROC curve was 0.74.[65] Hsa_circ_0042881, derived from exons 2—8 of tumor-suppressive gene *NF1*, serves as a novel oncogenic circRNA through functioning as miR-16 sponge in GC.[66] For example, hsa_circ_0000096 regulates the proliferation and migration of GC cells by modulating the gene expression of cyclin D1, CDK-6, MMP-2, MMP-9, and E-cadherin.[67] These discoveries will provide new therapeutic strategies for the prevention and treatment of GC in future. In a recent research reported that cir-cYAP1 was down-regulated in GC, and acted as a tumor suppressor by sponging miR-367-5p to further repress expression of target p27, thereby result in inhibition of GC cell proliferation and invasion.[68]

Lung cancer

Lung cancer (LC) is a global problem of cancer-associated deaths with high incidence and mortality for both sexes. A total of 85% of LC cases are diagnosed as non-small-cell lung cancer (NSCLC).[69] With ongoing environmental degradation and pollution, the morbidity and mortality rate of NSCLC is increasing.[70] Recently, circRNAs were reported to be closely associated with NSCLC. From the investigation by Zhao et al found that hsa_circ_404833 sponges miR-149-5p and inhibits cell motility, resulting in the acquired gefitinib resistance in LC.[71] A research group used human circRNAs microarray analysis technology to screen circRNAs expression profiles in NSCLC oncogenesis. They identified a total of 957 abnormally expressed circRNAs in NSCLC tissue compared with normal tissue.[72] Further experiment revealed that hsa_circ_0007385 was significantly up regulated in NSCLC tissue and cells. Moreover, the knockdown of hsa_circ_0007385 could significantly suppress the proliferation, migration and invasion of NSCLC cells. Dai et al analyzed the expression of circ0006916 and its parental gene *HOMER1* in normal and LC bronchial epithelial cells and in LC tissues in relation to prognosis.[73] Subsequently, the author also further examined the effect of circ0006916 on cell proliferation and demonstrated an important role for circ0006916 in anti-BPDE-induced carcinogenesis. CircRNA-100876 was found to up-regulate in NSCLC and closely associated with tumor staging and lymph node metastasis, and could serve as a potential prognostic biomarker for NSCLC.[74] Zhang et al revealed the expression profiles of circRNAs in NSCLC tissues and their adjacent lung tissue and found that a circPIP5K1A expression was higher, indicating it mays be as a new circular RNA biomarker in NSCLC.[75] Additionally, lung adenocarcinoma (LUAD) is a common pathological type of lung cancer, which belongs to non-small cell carcinoma. CDR1as is an extensively investigated circRNA, which has been reported to be involved in various cancers. A study indicated that the expression of CDR1as was significantly up-regulated in LUAD tissues in comparison to the matched controls. Moreover, the high-expression of CDR1as is related with the pemetrexed and cisplatin insensitivity of LUAD patients.[76] The same trend is that circ100146 is also highly expressed in NSCLC cell lines and the chemically induced malignant transformed bronchial cell line, 16HBE-T, as well as 40 paired tissue samples of NSCLC. Subsequently, circ100146 inhibited the proliferation and invasion of cells and promoted apoptosis by sponging miR-361-3p and miR-615-5p.[77] The functional mechanism of these identified circRNAs in LC may be not limited to miRNA sponges and others functions would be explored for LC diagnosis and therapy in future.

Bladder cancer

Bladder cancer (BC) is one of the ten most common tumors, which commonly diagnosed malignancy of the urinary system worldwide.[78] Growing evidence has suggested that circRNAs have been found own great correlation with BC. In BC cells, circHIPK3, derived from Exon2 of the *HIPK3* gene, was significantly down-regulate and targeted miR-558 to inhibit the growth and metastasis of BC *in vivo*.[79] And then, Xie et al reported that circHIPK3 islow-expressed in BC and its over-expression will promotes gemcitabine sensitivity in BC.[80] Results suggested that circHIPK3 could be as an independent prognostic biomarker for BC patients. Zhong et al performed a DE profile of circTCF25/miR-103a-3p/miR-107/CDK6 regulatory pathway in BC. They found that over-expression of circTCF25 could promote proliferation and migration of EJ and T24 BC cell lines.[81] The other study by Su et al showed that the expression of circTFRC could elevate the proliferation of BC cell line, which is related to the low tumor stage and survival rate.[82] Yu et al found that circPDSS1 was up-regulated in urothelial BC and promoted BC progress by sponging miR-16. Moreover, overexpression of miR-16 not only led to suppress proliferation, invasion and migration of urothelial BC cells, but also attenuated the effects the overexpression of circPDSS1.[83] Research found that CDR1as was low expressed in BC tissues compared with adjacent normal tissues. Further, over-expression of CDR1as can inhibit the proliferation and invasion of BC cells by sponging miR-135a.[84]

Esophageal carcinoma

Esophageal carcinoma (ESCC) is a highly malignant digestive tract tumor in the word, which is divided into esophageal adenocarcinoma and ESCC. Shi et al found that circ-PRKCI is obviously up-regulated in ESCC, which as a ceRNA to regulate AKT3 expression by sponging miR-3680-3p in ESCC.[85] For instance, a study has showed that circ_100876 is highly expressed in ESCC, which can promote cell proliferation, incursion, and distal metastasis, as well as the progress of EMT.[86] Circ-DLG1 was observed to be increased in ESCC tissues, cell lines, and plasma and can significantly promote cell proliferation.[87] Cir-ITCH was expressed at low levels in ESCC compared with peritumoral tissue, and may

inhibit ESCC by regulating the Wnt signaling pathway.[88] However, the specific regulatory function of cir-ITCH requires further study. Another research shows that the expression of circ_0067934 is significantly up-regulated in ESCC than normal tissues, suggesting its expression is concerned with ESCC differentiation and proliferation.[89]

Renal cell carcinoma

Renal cell carcinoma (RCC) has been increasing, accounting for 3% of cancer-related incidence rate, and there are over 400,000 as new cases and more than 170,000 deaths in 2018 worldwide.[61] circRAPGEF5 is derived from exons 2—6 of the *RAPGEF5* gene, and its down-regulation decreases the adsorption of miR-27a-3p, resulting in increasing the degradation of TXNIP and thus promoting RCC cells proliferation and migration[90] (Fig. 3). Previous studies have indicated that circ-ZNF609 can promote retinal glial cell proliferation.[91] Recently, Xiong and his colleagues investigated the effect of circ-ZNF609 on cell proliferation or invasion ability, and found that circ-ZNF609 is significantly increased in RCC lines by sponging miR-138-5p mediated FOXP4 expression to modulate tumor growth.[92] They demonstrated that the high expression of circ-ZNF609 promotes cell proliferation and invasion ability.

Osteosarcoma

Osteosarcoma (OS) is a common malignant bone tumor and mainly affects young adults. Accumulating studies indicated that circRNAs play a critical role in the pathogenesis of OS. As reported by Li et al circGLI2 is up-regulated in OS tissue and cells, and promotes OS cell proliferation, migration, and invasion by targeting miR-125b-5p.[93] It was discovered by a research team that in chemoresistant OS patients, hsa_circ 0004674 was the most up-regulated circRNA, and was negatively correlated with prognosis.[94] Another research group found that circ-HIPK3 was down-regulated in OS and correlated with poor prognosis, up-regulation of circ-HIPK3 suppressed cell proliferation, migration and invasion of OS cells.[95]

Prostate cancer

Prostate cancer (PC) is a common malignant tumor of the male genitourinary system, and its incidence ranks is the highest among man malignancies in worldwide, especially in Western countries. It were reported that there were 1,276,106 new cases of prostate cancer in 2018 from the United States data, and the disease resulted in 358,989 deaths.[96] Feng et al investigated that circ0005276 increased migration and proliferation in prostate cancer.[97] Additionally, Kong et al revealed circ-SMARCA5 exhibited high expression levels in PC samples than in matched noncancerous prostate tissues, implying that circ-SMARCA5 could be an oncogenic circRNA.[98]

Cervical cancer

Cervical cancer (CC) is also one of the common gynecologic cancers effecting female health in worldwide, accounting for a large proportion of death cancer-related throughout the world. Zheng et al investigated the expression profiles of circRNAs by transfecting E7 siRNA in CC Caski cells with high-throughput microarray technology.[99] A total of 526 dys-regulated circRNAs were identified. Further bioinformatics analysis indicated that DE circRNAs might implicate in the mTOR signaling pathway, suggesting these DE circRNAs have the relationship between dys-regulation and CC progression. A recently functional investigation by Ji et al[100] revealed that knockdown of circSLC26A4 repressed the proliferation, invasion, and tumor growth in cervical cancer tissue and cells by sponging miR-1287-5p implying circSLC26A4 may be as an oncogene in CC tumorigenesis.

Oral squamous cell carcinoma

Oral cancer has become a severe public issue worldwide and threat to people's health.[101] Currently, some studies on circRNAs in Oral squamous cell carcinoma (OSCC) have been reported. A study showed that hsa_circ_0008309 was down-regulated in OSCC tissues compared with adjacent normal control tissues by application of RNA sequencing and qRT-PCR analysis.[102] Besides, circRNA can be as a cancer suppressor. For example, cir-cDOCK1 could inhibit cell apoptosis via inhibition of miR-196a-5p by targeting BIRC3 in OSCC.[103]

Ovarian cancer

Ovarian cancer (OC) is one of the most common malignant tumors and threatening female reproductive system causing over 25,000 deaths annually.[104] Actually, accumulating researches indicated that dys-regulated expression of circRNAs played a significant role in the occurrence and progression of OC. Xu et al[105] identified 5917 circRNAs and performed their DE analysis between ovarian normal and ovarian cancer tissues. They found that circ0004390 could promote ovarian cancer cells proliferation by sponging miR-198. The similar trend has been reported that hsa_circ_0013958 was up-regulated in OC tissues and knockdown of hsa_circ_0013958 inhibited proliferation, migration, and invasion of OC cells.[106] Sheng et al reported that circRNAUBAP2 was highly expressed in OC tissues and promoted the progression of OC by sponging miRNA-144.[107] These results might provide a valuable reference for clinical diagnosis and treatment of OC.

Colorectal cancer

Colorectal cancer (CRC) is also most commonly diagnosed cancer, which led to 9.2% of all cancer-related deaths each year. Study found that CiRS-122, exosome-delivered circRNA, can promotes glycolysis to induce chemoresistance by miR-122 sponging and PKM2 up-regulation in CRC.[108] Recently, Li et al[109] verified that circVAPA was significantly up-regulated and promoted CRC progression by sponging miR-101, indicating circVAPA may be as a promising biomarker to predict chemoradiation resistance in CRC. Xie et al[110] found that has-circ-001569 could promote the proliferation and invasion of CRC cells via sponging miR-145 to enhance the expression of E2F5, BAG4, and FMNL2.

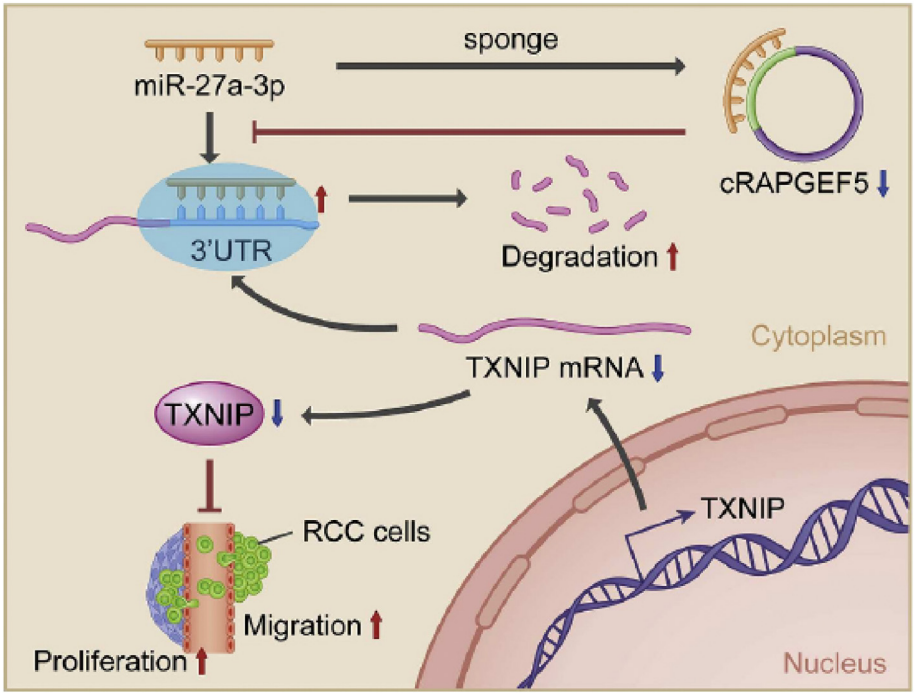

Figure 3 Schematic diagram of the circRAPGEF5-mediated pathway in RCC cells.

Another report demonstrated that circHIPK3 could promote CRC cells growth and metastasis by directly sponging miR-7.[111] They further found that circHIPK3 is frequently up-regulated partly caused by the overexpression of transcription factor c-Myb, then circHIPK3 sequester and inhibit miR-7 activity via sponging miR-7, thereby result in enhancing the expression proto-oncogenes including *FAK*, *IGF1R*, *EGFR*, and *YY1*, which promoting CRC development and progression (Fig. 4).

CircRNAs and other human diseases

Age-related cataract

Age-related cataract (ARC) is the most cause of vision loss among the aged population.[112] Liu et al[113] revealed that circHIPK3 expression was down-regulated in all three subtypes of ARC compared with the control. Moreover, circHIPK3 silencing in ARC cases stimulated the human lens epithelial cells apoptosis mediated by oxidative stress by the circHIPK3/miR-193a/CRYAA axis, suggesting the role of circHIPK3 as a functional regulator and providing a novel insight into the pathogenesis of ARC.

Psoriasis

Psoriasis is one of the most common chronic inflammatory skin conditions, with 1—3% of the adult population affected worldwide.[114] Moldovan et al firstly performed circRNA profiling of paired lesional and non-lesional skin from patients with psoriasis by RNA sequencing. This research provided fundamental information regarding DE circRNAs. However, whether circRNA is a cause or a consequence of the disease, the specific roles of circRNA is need to be further revealed.[115]

System lupus erythematosus

System lupus erythematosus (SLE) is a prototypic autoimmune disease. The study of Li et al firstly screened circRNAs profiles in SLE patients' peripheral blood plasma. Some circRNA candidates were selected for validation and potential circRNA/miRNA interaction networks were also constructed.[116] Result implied that circRNAs may associate with SLE. In another study, Luan et al investigated circRNA profiles in renal samples from SLE patients and health controls.[117] They spotted circHLA-C as a probable regulator for miR-150 because of circHLA-C and miR-150 displaying a negative correlation, indicating the potential roles of circHLA-C in SLE. Future studies should focus on their regulatory mechanism between circRNAs and SLE.

Pulmonary tuberculosis

Pulmonary tuberculosis (PT), caused by *Mycobacterium tuberculosis*, is still remaining severe threat to public health. Recent study has revealed that circRNAs are intensively associated with PT.[118] A report by Zhang et al showed 170 dys-regulated circRNAs in PT compared with healthy control. The findings indicated an important role of circRNA mediating gene regulation in the pathogenesis of PT.[119] Yi et al performed the plasma circRNA expression profiles of active PT patients and found that hsa_circRNA_103571 was significantly decreased in active PT patients.[120] At present, study on the regulatory mechanism of circRNAs in PT is at drawn. These circRNAs potential function in PT will be explained in future.

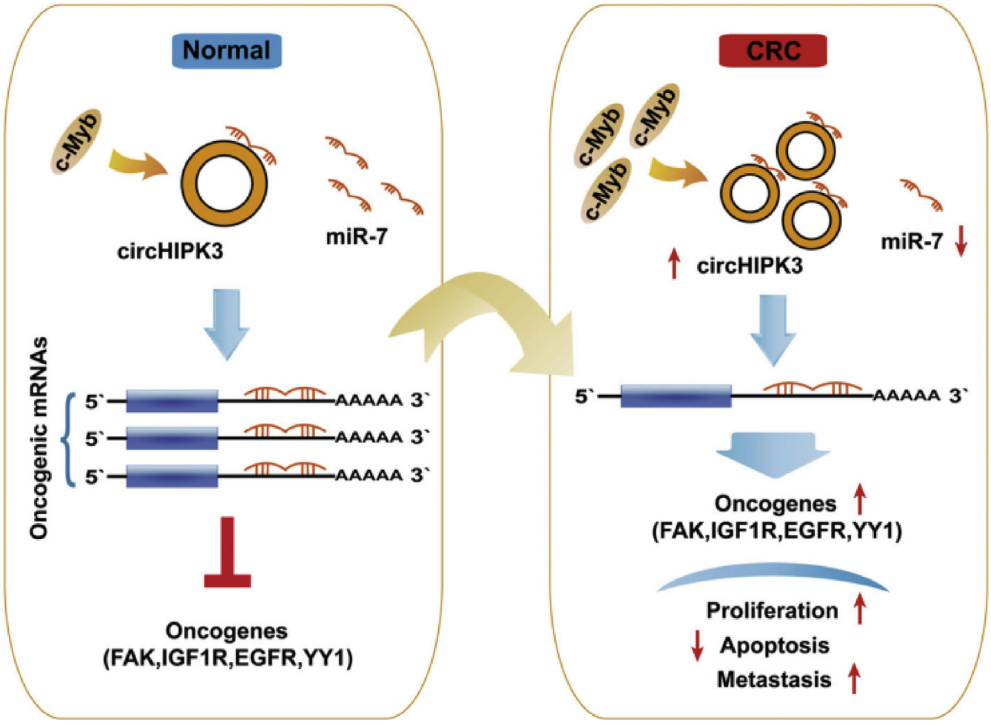

Figure 4 The schematic diagram of the c-Myb/circHIPK3/miR-7 axis in CRC.

Duchenne muscular dystrophy

Duchenne muscular dystrophy (DMD) is a severe muscular disorder involving a progressive deterioration of muscle function and is caused by frame-shifting deletions or nonsense mutations in the *DMD* gene resulting in the absence or reduced production of the dys-trophin protein.[121] Study has shown that two circRNAs (circQKI and circBNC2) were up-regulated during *in vitro* differentiation of normal myoblasts as described above and were down-regulated in the DMD conditions, well correlating with the notion that dystrophic cells have altered progression into the differentiation process.[122] In addition, circ-ZNF609 was found to be down-regulated during myogenesis in control myoblasts, which was highly expressed in differentiated DMD myoblasts.[34]

Nervous system diseases

CircRNAs involved in nervous system diseases have been largely reported. Hong's research group has reported that circDLGAP4 participated in the progression of Parkinson's disease.[123] Zhao et al found that sporadic Alzheimer's disease is associated with an aberrant miRNA/circRNA system in the hippocampal CA1 region.[124] Another study showed that Alzheimer's disease mediated by CDR1as-miR-7 axis. Moreover, they found that CDR1as is significantly reduced in Alzheimer patients indicating that CDR1as may have a function in Alzheimer disease.[125] Several studies demonstrated that circRNAs associated with the process of stroke. For example, Dong et al identified different expression of circRNAs in patients with acute ischemic stroke and healthy

Table 2 Summary of circRNAs involving in other human diseases.

Disease types	Representative circRNA	Putative functions and mechanisms	Reference
Thyroid cancer	cRAPGEF5	miR-198/FGFR1 pathway	128
Laryngeal cancer	circ-CCND1	miRNA sponge (miR-646)	129
Pancreatic cancer	circRNA_0007334	miRNA sponge (miR-144-3p and miR-577)	130
Kidney cancer	circ-HIAT1	miR-29a-3p/29c-3p/195-5p pathway	131
Glioma	cZNF292	Inhibits cell proliferation	132
Melanoma	circRNA_0084043	miRNA sponge (miR-153-3p)	133
Cholangiocarcinoma	circ_0001649	Induces cell tumor apoptosis	134
Hematological malignancy	f-circM9 and f-circPR	Induces cell tumor apoptosis	135
Leukemia	circAF4	miRNA sponge (miR-128)	136
Cardiovascular disease	cZNF609	miRNA sponge (miR-615-5p)	137
Osteoarthritis	circRNA-CER	miRNA sponge (miR-136)	29
Heart failure	cZNF292	Induces tube formation and endothelial cells sprouting	138

control by RNA sequencing.[126] Wu et al[127] also found that circTLK1 can aggravate neuronal injury via miR-335-3p/TIPARP resulting in neurological deficits and AIS. The great an effort is needed to develop new approaches to treat nervous system diseases complications in future. In addition to above diseases, more and more circRNAs associated with various disease are gradually being discovered. A brief summary of some other human disease-related circRNAs were summarized in Table 2. It was believed that more dys-regulated circRNAs will be identified in various types of cancer with development of cancer specific algorithms for RNA-seq data and their detailed functions are waiting to be elaborated in near future.

Conclusions and perspectives

With the advancement of RNA sequencing technology and the rapid development of bioinformatics, a large number of circRNAs were discovered. Moreover, emerging as a new regulatory RNA molecules, circRNAs have been widely focused on RNA research world, especially in biomedical fields. It was proved that circRNAs play multiple roles in gene expression regulation involving in life processes and initiation and development of diverse diseases. Furthermore, circRNAs function as oncogenic factors or tumor suppressors that participate in cancer occurrence and progression through multiple mechanisms. CircRNAs often had expressed in a tissue and developmental stage specific manner with abundance in certain specific pathological tissue. It has partially proven that circRNAs could be used as biomarkers or regulators for the diagnosis and prognosis of tumors. Currently, some methods have been developed to identify circRNAs, for example, RNA sequencing, circRNAs microarray, northern blotting, circRNA sequencing, PCR-based analyses, RNA fluorescence in situ hybridization.[139,140] With the prompt advance of molecular biology techniques, these methods may be more accurate for detecting or quantifying circRNA although each technique might has specific advantages and disadvantages in this area. Up to now, the most important and most widely studied function of circRNAs is in their role as miRNA sponges. However, miRNAs sponge mechanism does not represent all the functions of circRNAs. Understanding the full aspect of functions for these molecules is only the tip of the iceberg and other functions of circRNAs require further study. Taken together, more challenging functional studies of circRNAs needed to be uncovered in both physiological and pathological conditions. It is widely believed that the regulatory function of a large number of circRNAs will be revealed gradually in human diseases.

Authors contribution

Yong Huang: conceptualization, design of the study, writing original draft.

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Conflict of Interests

The authors declare that they have no conflict of interest.

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