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Review Article

The progress of circular RNAs in various tumors

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Abstract: Circular RNAs (circRNAs), a novel type of non-coding RNAs, presented as covalently closed continuous loops. Recent researches had found that circRNAs could function as microRNA sponges, regulators of gene transcription and encoding proteins. They were relatively stable and expressed widely in cytoplasm, which played important roles in carcinogenesis of cancers, such as esophageal cancer, gastric cancer, colorectal cancer, hepatocarcinoma, bladder cancer, glioma, breast cancer, osteosarcoma and so on. Furthermore, they were involved in many biological functions, like cell proliferation, drug resistance, cell cycle, invasion and metastasis. Therefore, the further studies were meaningful on the mechanism of cancers and circRNAs. In the review, we will summarize the current biogenesis of circRNAs and the roles of them in various cancers, which might be a novel biomarker and therapeutic avenue.

Keywords: circRNAs, cancers, biomarker, therapeutic targets

Introduction

CircRNAs were a members of ncRNAs and the length were from hundred to thousand nucleotides. In 1976, circRNAs were found in a viroid for the first time and considered that they were byproducts of splicing errors with low expression level [1, 2]. Recently, owing to the development of RNA sequencing, circRNAs were highly recognized and accepted in various diseases, like cardiovascular disease, type 2 diabetes mellitus, and some cancers [3-6], and were also found to have biological functions [7]. CircRNAs arose from exons or introns and existed proverbially in eukaryotes, which were participated in gene expressions at the transcriptional or post-transcriptional level [8, 9]. More importantly, circRNAs could act as miRNA sponges or ceRNAs or transcriptional regulators or even encoding peptides [10]. Accumulated evidences had been reported that circRNAs were variously expressed in many cancers, such as esophageal cancer [11], gastric cancer [12], colorectal cancer [13], hepatocarcinoma [14], glioma [5], bladder cancer [15], glioma [5], breast cancer [16], osteosarcoma [6] and et al. (**Table 1**). Because of the tissue-specific characteristics, circRNAs had attracted a growing interest and might be a new hotspot in cancers.

In this review, we provided an up-to-date overview of circRNAs, especially in various cancers which suggested they may be the potential biomarkers and therapeutic targets. And we believed that this review would increase the understanding of circRNAs in the functions and regulations of cancers.

CircRNA biogenesis

CircRNA, a novel type of ncRNA molecules, presented as covalently closed continuous loops and existed widely in eukaryotes. It is closed

Table 1. The expressions of circRNAs in various cancers

Cancers	circRNAs			
	Upregulated		Downregulated	
Esophageal cancer	circ_0067934	[32]	circITCH	[30]
Gastric cancer	circPVT1	[54]	circ_002059	[33]
	CiRS-7	[55]	circ_00001649	[34]
			circ_0000096	[36]
			circLARP4	[44]
			circ_104916	[45]
			circ_0006633	[46]
			circ_0000181	[47]
			circ_0003159	[48]
			circ_0000520	[49]
			circ_0014717	[50]
			circ_0003764	[51]
			circ_0061276	[51]
			circ_0000745	[52]
			circ_0001895	[53]
Colorectal cancer	CiRS-7	[56]	circ_001988	[62]
	circ_001569	[29]	circITCH	[63]
	circ_0000069	[58]	circ_0003906	[64]
	circBANP	[59]		
	circ_0020397	[60]		
	circ_000984	[61]		
Hepatocellular carcinoma	Cdr1as	[66]	circ_0001649	[70]
	circ_000839	[68]	circMTO1	[75]
	circ_0005075	[69]	circ_0005986	[76]
			circZKSCAN1	[77]
			circ_0004018	[78]
			circ_0003570	[78]
Bladder cancer	circTCF25	[15]	circHIPK3	[87]
	circMYLK	[85]	circ_0091017	[88]
	circPTK2	[86]	circ_0002024	[88]
Glima	cZNF292	[89]		
	circTTBK2	[5]		
Breast cancer	circ_0001785	[92]	circFoxo3	[102]
	circ_0001982	[93]		
	circABCB10	[95]		
	circDENND4C	[98]		
	circGFRA1	[100]		
Osteosarcoma	circUBAP2	[6]		
	circGLI2	[20]		
ccRCC			circHIAT1	[28]
LSCC	circ_100855	[106]	circ_104912	[107]

loops without 5'-3' polarity and polyA tail, thus they were very difficult to be degraded by RNase R and were relatively more durable, which may extremely be the research focus [8]. The cycling formations of circRNAs included exonic circRNA, intronic circRNA, exon-intron circRNA and intergenic circRNA [17-19]. Similar to other ncRNAs, the biogenesis of circRNAs was also influenced by *RBP* and *Quaking protein* [20] (**Figure 1**).

CircRNAs could act as miRNA sponges regulating the gene expression through binding to miRNAs [21]. For example, circHIPK3 was observed to sponge to miR-124 and inhibited the activity of miR-124 [10]. CircRNA_000203 could sponge to miR-26b-5p specifically [22]. Indeed, almost any circRNA have many binding sites on miRNAs and thereby the regulation of circRNAs was a complex network. Additionally, circRNAs were found that it also could regulate the parental genes then influenced the biological function. For instance, circFoxo3 could increase the level of *Foxo3* protein [23]. What's more, circRNAs functioned as a regulator of splicing and transcription [24]. Interestingly, Li explored that exsomes, nano-sized vesicles secreted by serious cells, were rich in circRNAs than the producer cells [25]. Increasing studies confirmed that exsomes could be absorbed by surrounding cells or distant cells thus increased the risk of metastasis. Tang et al. showed that drug-resistant cells exosomes could pass miRNAs to sensitive cells then increased their inhibitory concentration 50% [26], which gave us an novo strategy on circRNAs of cancers in future studies and whether exosomes could pass circRNAs? Furthermore, circRNAs played an important role in numerous biological progresses, such as cell cycle [27], apoptosis [23], invasion and metastasis [28], proliferation [29] and so on (**Figure 2**).

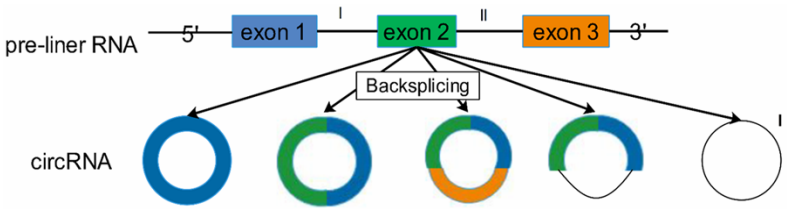

Figure 1. The different formations of circRNA: one exon; two or more exons; exons and introns; one intron; two or more introns.

In present, there were several available databases referring to circRNAs, like circbase (http://www.circbase.org/), cir2traits databse (http://gyanxet-beta.com/circdb/), circnet (http://circnet.mbc.nctu.edu.tw/), deepbase 2.0 (http://deepbase.sysu.edu.cn/) and circpedia (http://www.picb.ac.cn/rnomics/circpedia/), cancer-specific circRNAs database (http://gb.whu.edu.cn/CSCD/).

Based on the characteristics, circRNAs might be important to be biomarkers and therapeutic targetss for human cancers.

Esophageal squamous cell carcinoma (ESCC)

CircITCH was downregulated in ESCC tissues and had positive correlation with liner *ITCH* [30]. *ITCH*, a novel *Dvl*-interacting protein, promoted the degradation and ubiquitinated the phosphorylated form of *Dvl* then inhibiting *Wnt/β-catenin* signaling pathway [31]. Circ_0067934 was overexpressed in ESCC tissues and was significantly associated with TNM stage and poor differentiation. Additionally, silencing circ_0067934 decreased the proliferation and migration. However, circ_0067943 had no correlation with its host gene, the reason of which was possible participated in post-transcriptional regulation [32]. Furthermore, the molecular mechanisms are deserved for further studies.

As we known, radiotherapy is a main treatment of esophageal cancer, however, radiotherapy resistance became an important reason for tumor recurrence. The expression profiles chose 74 significant difference circRNAs from radiotherapy resistant cells and sensitive cells [11], which suggested that circRNAs were participated in radiotherapy.

Gastric cancer (GC)

Circ_002059 and circ_00001649 were low expressions in GC and significantly associated with distal metastasis and TNM stage [33, 34]. Zhang et al. found that circRNAs could predict the early recurrence of gastric cancer in stage III [35], however, the extensional mechanisms are little known. At the latest time, an interesting phenomenon was performed on circ_0000096. It was downregulated in GC tissues compared with the non-cancer tissues and correlated with invasion, gender and TNM stage, however, downregulated it could inhibit cells proliferation through decreasing the expressions of *Ki67*, *VEGF*, *MMP-2* and *MMP-9* in vitro and vivo [36]. *MMP-2/-9* were involved in so many key pathways of cancers, such as *p38-MAPK* and *PI3K* signaling pathways [37, 38], however, whether circ_0000096 regulated them are largely unknown. Furthermore, the authors explained the results that circ_0000096 acted as ceRNA relationship and had an extraordinary complex network. MiR-224 expression was decreased whereas miR-200a was increased after down-expressed circ_0000096 [36, 39]. Many studies demonstrated that miR-224 promoted tumor progression and miR-200a had the adverse effect [40-43]. MiR-224 promoted GC cells proliferation and invasion by targeting at *LATS1*, while circLARP4 could reverse the effect by sponging miR-224. In addition, circLARP4 was down-expressed in GC tissues and was correlated with independent prognosis [44]. Additionally, circ_104916 had a lower level in GC tissues and significantly related with invasion and metastasis. It reduced cell proliferation, invasion and migration via *EMT* process, including *N-cadherin* and *Vimentin* [45]. The expression of circ_0006633 was lower in cancer tissues and cells, which was related with distal metastasis and *CEA* level [46]. Various studies showed that circ_0000181, circ_0003159, circ_0000520, circ_0014717, circ_0003764 and circ_0061276, circ_0000745 were also downregulated in tissues and plasm of GC and was associated with the sizes, metastasis and *CEA* level [47-52]. Moreover, circ_0001895 was lower in GC tissues and was related with cell differentiation, however was not related with sizes, metastasis and TNM stages [53]. In general, the exuberant molecular mechanisms have not been explored and the further researched need to be found.

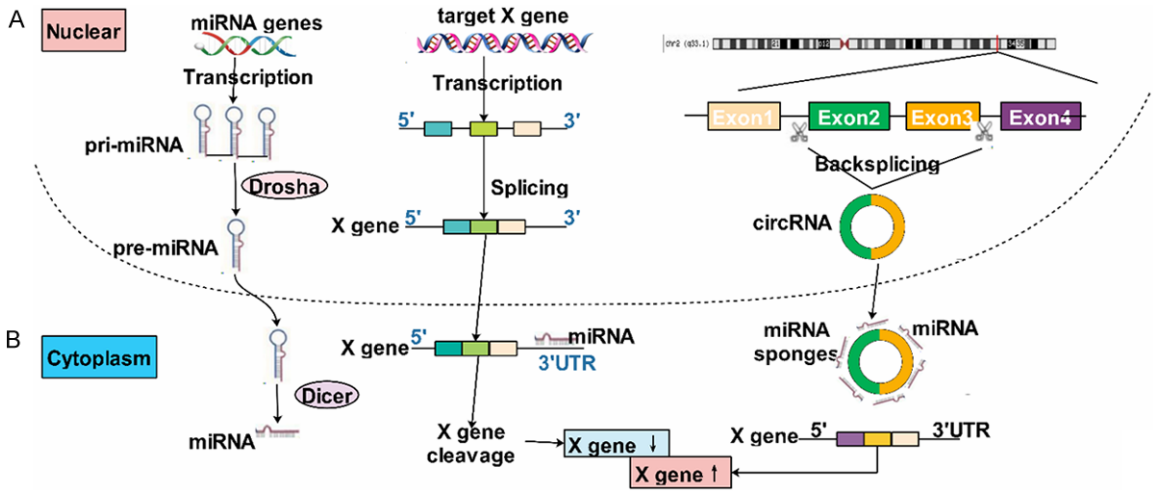

Figure 2. The function of circRNA acts as miRNA sponges: (A) miRNAs could downregulated the expression of mRNA through targeting at its 3'UTR; (B) circRNAs could act as a sponge of miRNAs and inhibit its expression resulting in upregulating of mRNAs.

A higher level of circPVT1 was observed in GC tissues and might promote cell proliferation through sponging miR-125b, which could target with *E2F2* [54]. CiRS-7, a cirRNA sponge for miR-7, was upregulated in GC tissues and was involved in TNM stages and poor survival. CiRS-7 reduced cell apoptosis through inhibiting miR-7, which increased *PTEN/PI3K/AKT* signaling [55]. At present, circRNAs presented high specificity in GC, which might be the biomarkers.

Colorectal cancer (CRC)

CiRS-7, a novel circular RNA, was confirmed that was overexpressed in CRC tissues. Upregulation of ciRS-7 inhibited the effects of miR-7 and subsequently activated *EGFR* and *RAF1* [56]. *RAF1* could interacted with kinase *ROK* and had an effect on tumorigenesis, which was conferred in *ERK* pathway [57]. Xie et al. disclosed that the expression of circ_001569 was especially higher in CRC than the normal tissues and was associated with aggressive characteristics. At length, circ_001569 upregulated the expressions of *E2F5*, *BAG4* and *FMNL2* through inhibiting miR-145, which interfered with cell cycle and promoted cell proliferation and invasion [29]. According to Guo et al., in vitro, downregulated circ_0000069 inhibited cell proliferation, migration and invasion and induced G0/G1 phase arrest [58]. Zhu et al. showed that circBANP was overexpressed in CRC cancerous tissues and increased the proliferation of CRC cells [59]. Zhang found that circ_0020397 was upregulated in CRC tissues, meanwhile, it increased viability and decreased apoptosis of CRC cells via *miR-138-TERT/PD-L1* pathway [60]. Overexpressed circ_000984 was confirmed in CRC tissues, mechanistically, circ_000984 acted as a ceRNA by competitively binding miR-106b and effectively upregulating the expression of *CDK6*, thereby inducing proliferation, invasion and migration [61].

Wang et al. found that circ_001988 was downregulated in CRC and was related to perineural invasion and differentiation, which might be a potential biomarker [62]. The level of circITCH was low in CRC compared to the paired tissues. Overexpressed circITCH could decrease cell proliferation and regulated *Wnt/β-carenin* pathway through inhibiting *c-myc* and *cyclinD1* [63]. Zhuo disclosed that circ_0003906 was downexpressed in cancer tissues and cells, which was also correlated with poorer differentiation and metastasis [64].

Additionally, Xiong et al. validated that 71 circRNAs had significantly difference between 5-FU resistance cells and sensitive cells by microarray analysis [13]. Dou et al. showed the abundance of circRNAs in mutant *KRAS* of CRC, and, interestingly, circRNAs were plenty in exosomes than parental cells [65]. However, the exuberant molecular mechanisms are largely unknown (**Figure 3**).

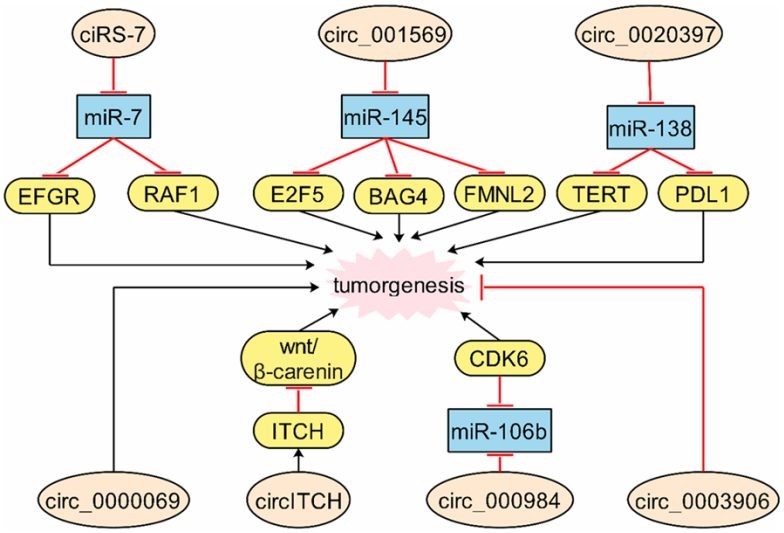

Figure 3. The molecular mechanisms of circRNAs are in colorectal cancer. CiRS-7, circ_001569, circ_0020397, and circ_000984 promote tumorgenesis, while circITCH and circ_0003906 inhibit tumorgenesis.

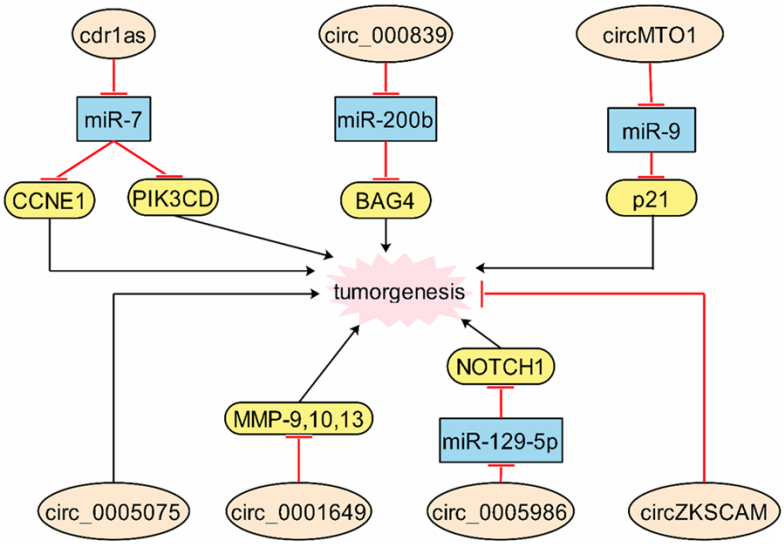

Figure 4. The molecular mechanisms of circRNAs are in hepatocellular carcinoma. Crd1as, circ_000839, circ_MTO1, circ_0005986 and circ_0005075 promote tumorgenesis, while circZKSCAM and circ_0001649 inhibit tumorgenesis.

Hepatocellular carcinoma (HCC)

Cdr1as was upregulated in HCC tissues and low-expression of Cdr1as decreased the proliferation and invasion of HCC cells. In detail, the mechanism was that downregulated expression of Cdr1as increased expression of miR-7 with suppressing *CCNE1* and *PIK3CD* expressions [66]. Interestingly, another study showed that Cdr1as had no significance between HCC tumors and adjacent normal tissues, however, it was significantly associated with *AFP* level and MVI, which were indirect with HCC [67]. In our knowledge, we consider that these two studies were from different departments and all patients had individual differences, which need us expand the numbers to confirm the results. The high expression of circ_000839 was confirmed in HCC tissues, and in detail, miR-200b negatively regulated *RhoA*, which targeted at circ_000839 [68]. Circ_0005075 was found that it was upregulated in HCC tissues and associated with the tumor size, which was involved in cell proliferation and metastasis by GO and KEGG pathway analysis [69]. However, the extensional mechanisms remain unclear and the detailed functions of circ_0005075 are value for further investigation.

Circ_0001649 was downregulated in HCC tissues and correlated with tumor size and embolus. Furthermore, decreasing circ_0001649 could increase the expressions *MMP9*, *MMP10* and *MMP13* [70]. Large amounts of researches disclosed that *MMPs* were important malignant factors of invasion and metastasis in various cancers [71-74], therefore, we fully believe that circRNAs were extremely participate in regulating cancer invasion and metastasis. CircMTO1 had a low expression level in HCC tissues and was related with longer survival. Silenced circMTO1 accelerated cell proliferation and invasion through acting as sponge of miR-9 to promote *p21* [75]. Circ_0005986 downregulated in HCC tissues and knockdown

circ_0005986 promoted cell proliferation and cycle by *miR-129-5p/NOTCH1* pathway [76]. Low expressed circZKSCAN1 was showed in HCC tissues and cells, and overexpressed circZKSCAN1 could inhibited proliferation and invasion [77]. Clinical assay data disclosed that circ_0004018 and circ_0003570 showed tight sensitivity and specificity with clinical characteristics of HCC patients, which might be the biomarkers of them [78] (**Figure 4**).

Bladder carcinoma

CircTCF25 was higher in bladder carcinoma tissues than adjacent normal tissues, which could suppress *miR-103a/miR-107-CDK6* pathway then increased cell proliferation and migration [15]. MiR-103a was unclosed that it targeted at *FEZF1/CDC25A*, *ADAM10* and *Wnt* signaling pathway, which were all involved in tumorigenesis [79-81]. Similarly, miR-107 could mediate the expression of *HMGCS2*, *tropomyosin 1*, and *let-7* [82-84]. These genes were all covered in proliferation, invasion and metastasis of cancers, while circTCF25 could potentially regulate these genes through targeting at miR-103a/miR-107. Zhong found that circMYLK was upregulated in bladder cancer tissues and positively related to *VEGFA*. Moreover, they confirmed that circMYLK could accelerate cell proliferation, tube formation, angiogenesis, and migration by binding to miR-29a directly and then relieving the suppression of VEGFA. In addition, overexpressed circMYLK induced *EMT* and *Ras/ERK* pathway through miR-29a [85]. The extensional mechanism explored that circMYLK acted as ceRNA for miR-29a. CircPTK2 was overexpressed in tumor tissues and predicted for poorer differentiated tumors and lymph node metastasis, which promoted cell proliferation and migration [86].

CircHIPK3 was downregulated in cancers and negatively related to invasion, grade and lymph node metastasis, which could inhibit cell invasion, metastasis as well as angiogenesis, in vitro and vivo, by sponging miR-558 to target *HPSE*, *VEGFA* and *MMP-9* [87]. Young et al. found circ_0091017 and circ_0002024 were significantly reduced in bladder cancer tissues, however, the prccise reason remained unknown [88].

Glioma

cZNF292 silencing decreased cell proliferation and tube formation through *Wnt/β-catenin* pathway.

What's more, cZNF292 silencing decreased transcription factor activity of *E2F1*, *NF-κB*, *Sp1*, *HIF-1*, *AP-1*, *STAT3*, and *STAT5* [89]. Additionally, *circ-TTBK2/miR-217/HNF1β/Derlin-1* axis was found to be important in glioma. At length, circTTBK2 was negatively related with miR-217, which targeted at *HNF1β* 3'UTR and inhibited its expression. Furthermore, *Derline-1*, involved in tumor malignant progression, could be activated by *HNF1β* [5]. *HNF1β*, a liver-specific transcription factor, contributed to malignance of various tumors, like ovarian carcinoma, HCC and CRC [90]. *Derlin-1* was participant in regulation of *ERK/MMP* and *PI3K/AKT/Bcl-2* signaling pathways [91]. According to all of these, we proposed that circTTBK2 may exert an effect in cancers through the pathways, which warrant further investigation.

Breast cancer

In breast cancer patients, the expression level of circ_0001785 was higher and related to histological grade, TNM and metastasis, while has no significant association with age or hormone receptors [92]. Circ_0001982 was upregulated both in breast cancer tissues and cells and promoted cell proliferation and invasion, and reduced cell apoptosis through targeting miR-143 [93]. MiR-143 was found that could be participate in various biological processes like invasion and metastasis through regulating multiple genes, such as *TAK1*, *MAPK1* and so on [94]. Whether circ_0001982 could influence tumorigenesis by some important genes through miR-143 or not, which might be a new strategy for miRNAs. Liang et al. showed that circABCB10 was upregulated in breast cancer tissues and could increase cell proliferation and induce apoptosis by targeting miR-1271 [95]. MiR-1271 was participated in tumor proliferation and apoptosis [96, 97]. CircDENND4C had been found that was upregulated in breast cancer tissues and affected cell proliferation, which was positively correlated to *HIF1α* [98]. *HIF1α*, a transcriptional factor, could help can-

cer cells avoid hypoxic damage through regulating *MMPs*, *VEGF* and so on [99]. In triple negative breast cancer, circGFRA1 was upregulated and associated with poor survival. Additionally, decreased expression of circGFRA1 could inhibit cell proliferation and promote apoptosis as serving as a sponge for miR-34a, which acted as ceRNAs with *GFRA1* [100]. Especially, Gao et al. showed that circ_0006528 was related with adriamycin resistance through *miR-7-5p-Raf1* axis in breast cancer [101].

Yang group disclosed that circFoxo3 suppressed cell progression of breast cancer through upregulating *Foxo3* expression, in detail, one of the mechanisms of which were by binding to some miRNAs [102]. Increasing the expression of *Akt* induced the loss of *PTEN* then downregulated *Foxo3* expression [103]. Another study found that silencing expression of circFoxo3 decreased the rate of cells in G1 phase and increased the rate of cell proliferation through regulating *p21* and *CDK2*, which were cell cycle proteins [27]. Yan et al. showed that circVRK1 could reduce the expansion and self-renewal capacity of breast cancer stem cells [104]. In addition, TCGA data showed that, the number of circRNAs were higher in normal adjacent tissues than tumors in ER+ breast cancer and might be associated with cell proliferation [105]. According to the analysis, we considered that circRNAs might be useful in diagnosis and treatment of breast cancer.

Osteosarcoma

Zhang et al. found that circUBAP2, associated with cancer progression and prognosis, was significantly increased in osteosarcoma tissues than matched controls, which increased cancer growth and inhibited apoptosis. Mechanistically, circUBAP2 could inhibit miR-143 expression, then increasing *Bcl-2*, an anti-apoptotic protein [6]. CircGLI2 was significantly overexpressed in osteosarcoma tissues than non-tumor tissue, and silenced the expression effectively suppressed cell proliferation, invasion and metastasis through targeting miR-125b-5p [20].

In others

Besides the cancers listed previously, there were some researches paying attentions to circRNAs of other cancers, which contained very few studies of one cancer. For example, in ccRCC, the expression of circHIAT1 was lower than normal tissues and AR could suppress ccRCC metastasis via regulating *circHIAT1-miR-195/29a/29c-CDC42* axis [28]. The level of circ_100855 was higher in LSCC tissues than normal tissues and was associated with T3-T4 stage and metastasis. Conversely, circ_104912 was lower in LSCC with T3-T4 stages, metastasis and poor differentiation [106]. In cervical carcinoma, circPABPN1 could bind to *HuR* and prevent *HuR* binding to *PABPN1* then suppressed the expression of *PABPN1* [107]. *HuR*, a RBP, regulated protein expression through numerous RNAs [108]. In ovarian cancer, circRNAs might be new candicates [109].

In conclusion and prospects

CircRNAs are novel identified type of endogenous ncRNAs and are stable, abundant, widely expressed, and tissue special. At this time, the studied of circRNAs and their functions in cancers were still limited. However, given to comprehensive consideration, circRNAs had unique advantages, like abundance, stable, widespread, and will be new-fashioned usage diagnosis and treatment of cancers.

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Disclosure of conflict of interest

None.

Abbreviations

circRNAs, circular RNAs; ncRNAs, non-coding RNAs; miRNA, microRNAs; ceRNA, compete endogenous RNAs; RBP, RNA spliceosome and RNA binding protein; FOXO3, forkhead box O3; ESCC, esophageal squamous cell carcinoma; GC, gastric cancer; VEGF, vascular endothelial growth factor; MMPs, matrix metallopeptidases; MAPK, mitogen-activated protein kinase;

PI3K, phosphatidylinositol-4,5-bisphosphate 3-kinase; LATS1, large tumor suppressor kinase 1; CEA, carcinoembryonic antigen; E2F2, E2F transcription factor 2; PTEN, phosphatase and tensin homolog; CRC, colorectal cancer; EGFR, epidermal growth factor receptor; RAF1, serine/threonine kinase; E2F5, E2F transcription factor 5; BAG4, BCL2 associated athanogene 4; FMNL2, formin like 2; 5-FU, 5-fluorouracil; HCC, hepatocellular carcinoma; CCNE1, cyclinE1; PIK3CD, phosphoinositide 3-kinase catalytic subunit delta; MVI, microvascular infiltration; AFP, alpha-fetoprotein; CDK6, cyclin-dependent kinase 6; ADAM10, adamalysine 10; HPSE, heparanase; EMT, epithelial-mesenchymal transition; STAT3, signal transducer and activator of transcription 3; STAT5, signal transducer and activator of transcription 5; HNF1β, hepatocyte nuclear factor 1β; TAK1, TGF-beta-activated kinase 1; MAPK1, mitogen-activated protein kinase 1; HIF1α, hypoxia-inducible transcription factor 1α; ccRCC, clear cell renal cell carcinoma; LSCC, laryngeal squamous cell cancer.

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