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REVIEW

Novel insights into circular RNAs in clinical application of carcinomas

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Abstract: Circular RNAs (circRNAs), formed by nonsequential back-splicing of pre-messenger RNA (pre-mRNA) transcripts, have been widely concerned in recent years. With advances in high-throughput RNA sequencing (RNA-seq) technology, previous work has revealed that a large number of circRNAs, which are endogenous, abundant and stable in mammalian cells, may be involved in atherosclerotic vascular disease risk, neurological disorders, prion diseases and carcinomas. Remarkably, interaction between circRNAs and microRNA has already been observed to perform a significant role in a variety of cancers, including gastric cancer and colorectal cancer. Recent work has suggested that circRNAs may play critical roles in the initiation and development of cancers and could become potential new biomarkers for cancers. Herein, we review the current understanding of the roles of circRNAs in cancers and the potential implications of circRNAs in cancer-targeted therapy.

Keywords: circular, targeted therapy, diagnosis, microRNA, noncoding RNA

Introduction

Circular RNAs (circRNAs), a special class of endogenous noncoding RNAs, were identified in the early 1990s as transcripts and continued to be reported expressed in viruses, plants, archaea and animals.[1–3] Unlike linear RNAs, which are terminated with 5′ caps and 3′ tails, circRNAs present in a circular form whose 3′ head and 5′ tail ends covalently bond together.[4] Recent reports revealed that circRNAs could function as competing endogenous RNAs or microRNA sponges, regulating alternative splicing or transcription and modulating the expression of parental genes.[5–7]

With advances in high-throughput RNA sequencing (RNA-seq) technology, recent work has revealed that a large number of circRNAs, which are endogenous, abundant and stable in mammalian cells, may be involved in atherosclerotic vascular disease risk, neurological disorders, prion diseases and carcinomas.[8–12] Remarkably, interaction between circRNAs and microRNA has already been observed to perform a significant role in a variety of cancers, including gastric cancer and colorectal cancer, which illuminates pathways to provide diagnostic or predictive biomarkers for cancers.[13] For example, Sand et al confirmed a total of 322 circRNAs (143 up- and 179 downregulated) expressed in cutaneous squamous cell carcinoma, and a total of 1603 microRNA response elements (MREs) were found to be part of the differentially expressed circRNAs, which suggested that circRNAs play an important role in tumor formation by interfering with relevant microRNAs. Additionally, this study group analyzed microarray circRNA expression profiles and identified 23 upregulated and 48 downregulated circRNAs with 354 MREs in the basal cell carcinoma (BCC) as well.[14] Taken together, these findings indicated that circRNAs have great potential to

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become new clinical diagnostic and prognostic markers and provide new insights into the treatment of carcinoma.

In this review, we briefly delineate the current understanding of the roles of circRNAs and emphasize its potential implications in cancer-targeted therapy.

Categories of circRNAs

circRNAs, which form a covalently closed continuous loop, are involved in transcriptional and posttranscriptional gene expression regulation.[15] circRNAs can be generated from any region of the genome, resulting in a great diversity of lengths. Like the classification system of long noncoding RNAs (lncRNAs), Qu et al classified circRNAs into five types based on their genomic proximity to the neighboring gene: 1) sense or exonic, if it originates from one or more exons of the linear transcript on the same strand; 2) intronic, if it arises from an intron of the linear transcript; 3) bidirectional or intragenic, if it is transcribed from the same gene location of the linear transcript but in close genomic proximity; 4) antisense, if it overlaps one or more exons of the linear transcript on the opposite strand; and 5) intergenic, if it is located between the genomic interval of two genes.[16] Beyond this type of classification, another sort of way is established based on the mechanism.[4] First, circular viral RNA genomes could be ligated to form 3′,5′- or 2′,5′-phosphodiester bonds with the involvement of host cellular enzymes. Second, circRNA midbodies can be produced during permuted transfer RNA (tRNA) biogenesis in algae and archaea or ribosomal RNA (rRNA) processing. Third, a large amount of housekeeping noncoding RNAs, such as the ribozyme RNase P, were all recognized in circular forms in archaea. Finally, abundant circRNAs may derive from spliced introns and exons.

Biological functions of circRNAs

circRNAs function as competing endogenous RNAs or microRNA sponges

circRNAs have been confirmed to function as microRNA sponges or potent competing endogenous RNA molecules, thereby influencing the posttranscriptional actions of microRNAs as suppressors of the translation in recent literature, in which the association between circRNAs and miR-7 was reported most frequently.[17,18] The first microRNA sponge identified was human ciRS-7, which has been detected to be associated with cervical cancer, neuroblastoma, astrocytoma and renal cell and lung carcinoma.[19] The overexpression of ciRS-7 acts as a microRNA sponge, arresting miR-7 and therefore elevating the level of miR-7 targets, which regulates the epidermal growth factor receptor (EGFR) expression that further regulates cell growth, proliferation, differentiation and signaling in human cancer cells.[20] Similarly, another cir-ITCH, derived from the *ITCH* gene, presents a sequence enriched with three microRNA-binding sites (miR-7, miR-17 and miR-214) in esophageal squamous cell carcinoma (ESCC).[21] Additionally, hsa_circ_001569 was selected as a potential regulator of colorectal cancer progression and had an interaction with miR-145.[19] Therefore, the circ-miRNA axis, regardless of promotion or suppression, played an important role in cancer-related pathways and worth further study (Figure 1).

circRNAs regulate alternative splicing or transcription

Previous studies have suggested that circRNAs are competing with alternative splicing or transcription. For example, Ashwal-Fluss et al demonstrated that circMbl is generated by the second exon of the splicing factor muscleblind (MBL), which competes with canonical pre- messenger RNA (pre-mRNA) splicing. circMbl and its flanking introns contain conserved muscle blind-binding sites, which are strongly and specifically bound by MBL. Modulation of MBL levels strongly affects circMbl biosynthesis, and this effect is dependent on the MBL-binding sites.[5] Therefore, this suggests that circRNAs can function in gene regulation by competing with linear splicing.

circRNAs regulate the expression of parental gene

Recent advances have revealed that circRNAs could regulate the expression of parental genes. Still taking cir-ITCH

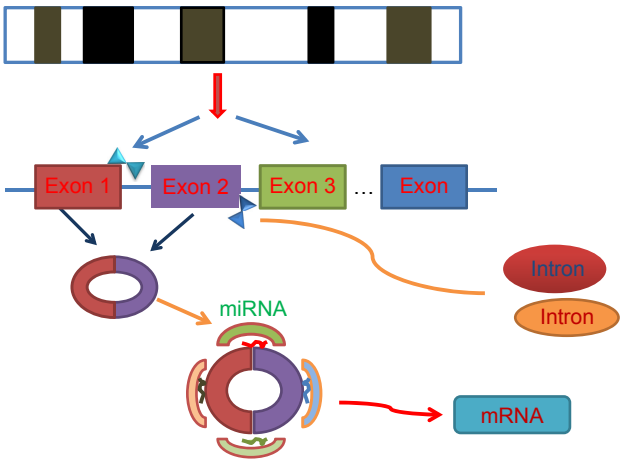

Figure 1 Mechanism of circRNAs functioning as competing endogenous RNAs or miRNA sponges.
Abbreviations: circRNAs, circular RNAs; miRNA, microRNA; mRNA, messenger RNA.

as an example, Li et al found that both cir-ITCH and the 3′-untranslated region (UTR) of ITCH share some microRNA-binding sites. Further study indicated that the interactions of cir-ITCH with miR-7, miR-17 and miR-214 might increase the level of ITCH. As a result, it could be speculated that exon-only circRNA may fulfill regulatory functions in the cytoplasm, whereas intronic circRNAs seem to be efficient for transcriptional regulation in the nucleus.[21]

Correlation between circRNAs and carcinomas

circRNAs have been reported to be involved in many human diseases, especially in carcinomas. Recent works have suggested that circRNAs may play important roles in the initiation and development of cancers and could potentially become new biomarkers for cancers. Up to date, the most frequently studied were that circRNAs mainly serve as microRNA sponges to regulate gene expression. MicroRNAs regulate a variety of essential biological functions such as cellular differentiation, apoptosis and proliferation and thus play a critical role in cancer progression. Based on these clues, circRNAs were found to be closely related to the development of a variety of cancers, all of which are listed in Table 1. In this review, we have listed the expression of circRNAs in various types of cancers and provide potential implications in cancer-targeted therapy (Table 1).

Previous studies revealed that circRNAs showed large capabilities in gene regulation by playing microRNA sponge effects. Some circRNAs present as a downward trend to regulate the pathways. For instance, hsa_circ_002059, a typical circRNA, was first found to be significantly down-regulated in gastric cancer tissues compared with paired adjacent nontumor tissues, and further research found that lower expression levels of hsa_circ_002059 in plasma were significantly correlated with distal metastasis, tumor–node–metastasis (TNM) stage, gender and age, which might be a potential novel and stable biomarker for the diagnosis of gastric carcinoma.[22] In a study of lung cancer, the expression of cir-ITCH was significantly decreased in lung cancer tissues. Ectopic expression of cir-ITCH markedly elevated its parental cancer-suppressive gene, ITCH, expression and inhibited proliferation of lung cancer cells.[23] Altogether, these findings suggested that circRNAs may play an inhibitory role in some cancer progression by enhancing its parental gene expression.

However, not all circRNAs play a downward regulation in cancer progress. Yu et al demonstrated that Cdr1as expression was upregulated in hepatocellular carcinoma (HCC) tissues compared with the adjacent nontumor tissues. Moreover, overexpression of miR-7 could suppress the direct target gene CCNE1 and PIK3CD expression. Knockdown of Cdr1as suppressed the expression of miR-7 and also inhibited the CCNE1 and PIK3CD expression. Furthermore, knockdown of Cdr1as suppressed the HCC cell proliferation and invasion through targeting miR-7, suggesting that Cdr1as acted as an oncogene partly through targeting miR-7 in HCC.[24] Shang et al also did a study of circRNAs in HCC and reported that three circRNAs played roles (hsa_circ_0000520, hsa_circ_0005075 and hsa_circ_0066444) in HCC and only hsa_circ_0005075 exhibited significant difference in expression between HCC and normal tissues. The hsa_circ_0005075 expression correlated with HCC tumor size and showed good diagnostic potential.[25] Subsequently, Zhong et al used microarray assay to screen circRNA expression profiles of bladder carcinoma and predicted that circTCF25 could downregulate miR-103a-3p and miR-107, increase CDK6 expression and promote proliferation and migration in vitro and in vivo, suggesting that circTCF25 might be a new promising marker for bladder cancer.[26]

Intriguingly and strikingly, Xuan et al investigated the expression of circRNAs in four paired laryngeal squamous cell cancer (LSCC) tissues and adjacent nontumor tissues by microarray analysis. The results showed significant upregulation (n=302) or downregulation (n=396) of 698 circRNAs in LSCC tissues. They further detected hsa_circ_100855 as the most upregulated circRNA and hsa_circ_104912 as the most downregulated circRNA using quantitative real-time-PCR methods. Additionally, patients with T3–4 stages, neck nodal metastasis or advanced clinical stage had higher hsa_circ_100855 expression, and patients with T3–4 stages, neck nodal metastasis, poor differentiation or advanced clinical stage had a lower hsa_circ_104912 expression. Overall, their data suggest that circRNAs play an important role in the tumorigenesis of LSCC and may serve as novel and stable biomarkers for the diagnosis and progression of LSCC.[27] Sand et al identified 23 upregulated and 48 down-regulated circRNAs with 354 MREs capable of sequestering microRNA target sequences of the BCC miRNome through microarray circRNA expression profiles and described a variety of circRNAs that are potentially involved in the molecular pathogenesis of BCC.[28]

Conclusion and perspective

In the past, circRNAs were considered impossible to play a key role in the biological process because they were thought to be a byproduct of aberrant splicing events or intermediates that had escaped from intron lariat debranching. Thanks to the advancements in high-throughput sequencing

Table 1 Literature of circRNAs and carcinomas

Type of cancer	First author	Received date	Journal	Sequence name or more content	Expression
Cutaneous squamous cell carcinoma[14]	Sand M	2016/6/15	*J Dermatol Sci*	Picking out 322 circRNAs	cir-143↑, cir-179↓
BCC[28]	Sand M	2016/4/21	*Epigenomics*	Screening out 71 circRNAs	23 circRNAs↑, 48 circRNAs↓
Epithelial ovarian carcinoma[29]	Ahmed I	2016/4/28	*Oncotarget*	Altered expression pattern	Unclear
Ovarian carcinoma[30]	Bachmayr-Heyda A	2016/5/14	*Oncotarget*	Unclear	Unclear
Cervical cancer[31]	Abdelmohsen K	2017/1/13	*RNA Biol*	CircPABPN1 (hsa_circ_0031288)	Unclear
Laryngeal cancer[27]	Xuan L	2016/5/10	*Am J Transl Res*	hsa_circ_104912, hsa_circ_100855	hsa_circ_104912↓, hsa_circ_100855↑
Hepatoma carcinoma[32]	Qin M	2015/11/26	*Cancer Biomark*	hsa_circ_0001649	hsa_circ_0001649↓
Hepatoma carcinoma[24]	Yu L	2016/7/9	*PLoS One*	circRNA Cdr1	circRNA Cdr1↑
Hepatoma carcinoma[25]	Shang X	2016/6/4	*Medicine (Baltimore)*	hsa_circ_0000520, hsa_circ_0005075, hsa_circ_0066444	Unclear
Hepatoma carcinoma[33]	Xu L	2016/9/12	*J Cancer Res Clin Oncol*	ciRS-7 (Cdr1as)	ciRS-7 (Cdr1as)↓
Pancreatic ductal carcinoma[34]	Qu S	2015/10/21	*Genom Data*	Microarray expression profile	Unclear
Neuroglioma[35]	Song X	2016/2/14	*Nucleic Acids Res*	Screening out 476 circRNAs	Unclear
Neuroglioma[36]	Barbagallo D	2015/12/20	*Oncotarget*	Unclear	Unclear
Neuroglioma[37]	Yang P	2016/9/11	*Oncotarget*	cZNF292 circRNA	cZNF292 circRNA↓
Colorectal cancer[38]	Wang X	2016/2/18	*Int J Clin Exp Pathol*	hsa_circ_001988	hsa_circ_001988↓
Colorectal cancer, ovarian carcinoma[39]	Bachmayr-Heyda A	2015/1/28	*Sci Rep*	The percent of circ/line	The percent of circ/line↓
Colorectal cancer[12]	Xie H	2016/4/9	*Oncotarget*	hsa_circ_001569	hsa_circ_001569↑
Colorectal cancer[40]	Huang G	2015/6/26	*PLoS One*	cir-ITCH	cir-ITCH↓
Colorectal cancer[41]	Zhu M	2017/1/20	*Biomed Pharmacother*	circ-BANP	circ-BANP↑
KRAS mutant colon cancer[42]	Dou Y	2016/11/29	*Sci Rep*	circRNA	circRNA↓
Gastric carcinoma[22]	Li P	2015/2/18	*Clin Chim Acta*	hsa_circ_002059	hsa_circ_002059↓
Gastric carcinoma[43]	Li P	2017/1/13	*Br J Cancer*	hsa_circ_0000096	hsa_circ_0000096↓
Gastric carcinoma[44]	Chen S	2017/1/29	*Clin Chim Acta*	hsa_circ_0000190	hsa_circ_0000190↓
Esophageal carcinoma[12]	Xia W	2016/10/19	*Sci Rep*	hsa_circ_0067934	hsa_circ_0067934↑
Radio-resistant esophageal cancer[45]	Su H	2016/7/29	*J Transl Med*	hsa_circ_001059, hsa_circ_100385, hsa_circ_104983, hsa_circ_000167, hsa_circ_101877, hsa_circ_102913, hsa_circ_000695	hsa_circ_001059↑, hsa_circ_100385↑, hsa_circ_104983↑, hsa_circ_000167↓, hsa_circ_101877↓, hsa_circ_102913↓, hsa_circ_000695↓
Esophageal carcinoma[21]	Li F	2015/3/10	*Oncotarget*	cir-ITCH	cir-ITCH↓
Hematopoiesis malignancies[46]	Bonizzato A	2016/10/16	*Blood Cancer J*	Screening out the expression of circRNAs	Unclear
Bladder carcinoma[26]	Zhong Z	2016/8/4	*Sci Rep*	circTCF25	circTCF25↑
Bladder carcinoma[47]	Huang M	2016/7/1	*Oncotarget*	circRNA M, YLK	Unclear
Clear cell renal cell carcinoma[48]	Wang K	2017/1/17	*Cancer Lett*	circHIAT1	circHIAT1↓
Breast cancer[49]	Yang W	2015/12/15	*Oncogene*	Foxo3 circRNA	Foxo3 circRNA↑
Breast cancer[50]	Nair AA	2016/11/10	*Oncotarget*	Unclear	Unclear
Lung cancer[23]	Wan L	2016/9/20	*Biomed Res Int*	circRNA-ITCH	circRNA-ITCH↓
Seven cancers[51]	Zheng Q	2016/4/7	*Nat Commun*	circHIPK3	circHIPK3↓
Cancer[52]	Du WW	2016/2/11	*Nucleic Acids Res*	circ-Foxo3	circ-Foxo3↓
Cancer[53]	Hansen TB	2011/10/4	*EMBO J*	CDR1	Unclear
Carcinoma[54]	Du WW	2016/11/26	*Cell Death Differ*	circ-Foxo3	circ-Foxo3↓

Notes: ↓ means downregulated. ↑ means upregulated.
Abbreviations: circRNAs, circular RNA; BCC, basal cell carcinoma.

technologies and bioinformatics, circRNAs were found to be broadly expressed and perform regulation in atherosclerotic vascular disease, neurological disorders, prion diseases and carcinomas. In summary, functional roles of circRNAs in the regulation of protein-coding gene expression through acting as microRNA sponges, regulating alternative splicing or transcription and modulating the expression of parental genes confer a great variety of functional potential to circRNAs. The fact that circRNAs are found abundant in clinical blood or tissue samples makes circRNA a promising diagnostic biomarker for cancer screening and prognostic evaluation.

Although the number of circRNAs with known functions is expanding, there are still thousands of circRNAs whose functions remain unknown. A deeper understanding of circRNA biogenesis may be needed to shed light on the road of functional consequences of circRNA.

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Disclosure

The authors report no conflicts of interest in this work.

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