Potential functions and implications of circular RNA in gastrointestinal cancer (Review)

XIAOXIA REN, YONGXING DU, LEI YOU* and YUPEI ZHAO*

Department of General Surgery, Peking Union Medical College Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing 100730, P.R. China

Received September 11, 2016; Accepted August 11, 2017

DOI: 10.3892/ol.2017.7118

Abstract. Circular RNAs (circRNAs) are a novel type of endogenous non-coding RNA that have gained attention from researchers for their involvement in multiple biological processes. circRNAs are ubiquitously expressed in eukaryotic cells and regulate gene expression at the transcriptional or post-transcriptional level by interacting with microRNAs (miRNAs) or other molecules. The present review provides an overview of circRNAs, as well as insights into their roles in the development and progression of gastrointestinal cancer. Furthermore, combined with reported data, the present review investigates the potential of circRNAs to become diagnostic or predictive biomarkers of gastrointestinal cancer and may provide novel insights into the treatment of associated cancer types.

Contents

1. Introduction
2. Features of circRNA
3. Biological functions across eukaryotes
4. Techniques for investigating circRNA
5. circRNA in gastrointestinal cancer
6. Conclusions and outlook

1. Introduction

Circular RNAs (circRNAs) are a type of endogenous non-coding RNA that have been a research hotspot in the field of RNA. To date, thousands of endogenous circRNAs have been identified and characterized. circRNAs exist ubiquitously in eukaryotes, predominantly in the cytoplasm, exhibiting a tissue- and developmental stage-specific pattern, serving as gene regulators in mammals (1-3). Furthermore, circRNAs may serve roles in neurological disorders, atherosclerotic vascular disease risk and diverse cancer types (4-6).

Gastrointestinal cancer is a class of cancer affecting the organs of the digestive system. The most frequently occurring types of gastrointestinal cancer are colorectal cancer (CRC), gastric cancer (GC), pancreatic cancer, hepatocellular carcinoma (HCC) and esophageal carcinoma. Although there are several options with regards to diagnostic and therapeutic methods, the 5-year survival rate of patients with gastrointestinal cancer remains poor due to a lack of effective tools for early diagnosis and therapy (7). Recently, mounting evidence has demonstrated that a number of circRNAs exhibit potential biological functions in gastrointestinal cancer, and consequently, may be prognostically and diagnostically relevant biomarkers (8-10).

The present review first briefly describes the features, biogenesis and biological functions of circRNAs across eukaryotes. Secondly, potential functions and implications of circRNA in gastrointestinal cancer are discussed, and their roles in gastrointestinal tumor occurrence and development are explored. Finally, the future of research progress and direction, in respect to circRNA in gastrointestinal cancer diagnosis and targeted therapy, are discussed.

2. Features of circRNA

Structure. circRNAs are characterized by covalently closed continuous loop structures with neither 5' to 3' polarity nor a polyadenylated tail, as well as the resistance to exonucleolytic degradation (2,3). As a result, circRNAs are highly stable *in vivo* compared with their linear counterparts.

Biogenesis. Studies have revealed that circRNAs may be generated from exons or introns (11-15). Two models of circRNA biogenesis have been proposed, namely lariat splicing and direct back-splicing (11,12). In lariat splicing, a looped intermediate containing exons is formed and the introns in the lariat are removed, generating exonic circRNA. In direct back-splicing, exons are spliced in non-canonical order, whereby the down-

Correspondence to: Dr Lei You or Professor Yupei Zhao, Department of General Surgery, Peking Union Medical College Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College, 1 Shuai Fu Yuan, Dong Cheng, Beijing 100730, P.R. China
E-mail: florayo@163.com
E-mail: zhao8028@263.net

*Contributed equally

Key words: circular RNA, microRNA sponge, biomarker, gastrointestinal cancer

stream 5' splice site is spliced to an upstream 3' splice site, generating a circular transcript. The principle distinction between the two models is in the first step of circRNA generation. In the two models, the canonical spliceosome has been implicated in the generation of circRNA (13,14). Additionally, Zhang *et al* (15) proposed a model of alternative circularization; the study demonstrated that the alternative formation of inverted repeated Alu pairs and the competition between them led to alternative circularization, resulting in multiple circRNA transcripts produced from a single gene.

Notably, RNA-binding proteins (RBPs) may also regulate the biogenesis of circRNAs in certain conditions. Previously, studies have revealed that the RBPs, quaking and muscleblind (MBL), may serve as factors involved in circRNA biogenesis (13,16). The RNA-editing enzyme adenosine deaminase, RNA-specific is able to bind to double-stranded RNA to antagonize circRNA biogenesis (17).

Conservation. circRNA expression appears to be conserved across eukaryotic species. Thus far, circRNAs have been detected in yeasts, protists, plants and numerous animals, ranging from fly to human, which suggests that circRNAs are an ancient feature of gene expression that have been conserved over the course of eukaryotic evolution (2,3,18). To further support this view, circRNAs exhibit sequence conservation. A previous study revealed that 457 out of the 2,121 circRNAs in humans were identified in mice as circular orthologues (2). Another study demonstrated that between 15 and 20% of the circRNAs produced in a mouse brain utilize splice sites that are orthologous to those used in a pig brain (19). In addition, it has also been estimated that 23.6% of the circRNAs identified in murine neutrophils are also expressed in rat neutrophils (20).

3. Biological functions across eukaryotes

To date, numerous studies have identified the potential developmental functions of circRNAs in multiple biological processes, including microRNA (miRNA) sponges, alternative splicing, and transcriptional or post-transcriptional gene regulation. The dysregulation of circRNAs leads to abnormal cellular function and growth defects, and is involved in human development and disease.

miRNA sponges. Sponge RNAs contain complementary binding sites to miRNA, thereby serving as competitive inhibitors that suppress the ability of miRNA to bind to its mRNA targets. Numerous studies have provided evidence indicating that circRNAs are able to function as miRNA sponges (Fig. 1A); for example, cerebellar degeneration-related protein 1 (CDR1)-as, which is derived from the Cdr1 antisense locus, targets miR-7 as an miRNA sponge (1,2). The expression of CDR1-as, which contains >70 miR-7 binding sites, results in increased levels of miR-7 targets. Additionally, murine sex-determining region Y circRNA, a highly expressed circRNA in the testes, possesses 16 binding sites for miR-138, thereby acting as a miR-138 sponge (1,21). Similarly, circ-itchy E3 ubiquitin protein ligase (cir-*ITCH*) harbors numerous miRNA binding sites that are able to bind to the 3'-untranslated region of *ITCH*, and may act as a sponge of miR-7, miR-17 and miR-214 to increase the level of *ITCH* (6).

Alternative splicing. Previous studies (13,22,23) suggested that circRNAs contribute to alternative splicing (Fig. 1B); general splicing factor MBL may exhibit effects on alternative splicing that modulate the balance between circRNA biogenesis and canonical splicing (13). circMBL and its flanking introns contain conserved MBL binding sites, and are strongly and specifically bound by MBL. This suggests that circRNAs are able to function in gene regulation by competing with canonical pre-mRNA splicing. Conversely, alternative splicing may also increase circRNA diversity. Zhang *et al* (24) systematically annotated different types and landscapes of alternative back-splicing and alternative splicing events in circRNAs from various cell lines and provided a valuable resource for studying the potential functions of circRNAs. Collectively, the annotation of alternative splicing and circRNA provides a means to investigate the molecular mechanism of circRNA biogenesis and potential function in the future.

Transcriptional or post-transcriptional gene regulation. Current evidence suggests that circRNAs may also serve a role in transcriptional or post-transcriptional gene regulation. For example, expression of the CDR1-as circRNA has been revealed to promote the expression of CDR1-sense mRNA (25). Exon-intron circRNAs were recently demonstrated to enhance the expression of their parental genes in *cis* through interaction with U1 small nuclear ribonucleoprotein and RNA polymerase II, which are components of splicing and transcriptional machinery, respectively (Fig. 1C) (26). The interplay between circRNAs and the transcriptional machinery assists with the characterization of gene expression, although the precise molecular mechanism by which this is achieved is unknown and requires further investigation.

4. Techniques for investigating circRNA

Since the initial discovery of circRNAs, various biochemical, molecular biology, high-throughput sequencing and bioinformatic technologies have been developed to investigate the properties, biogenesis and functions of circRNA. Among the various tools to validate circRNAs, ribonuclease R, an exoribonuclease that progressively degrades RNA from its 3' to 5' end, does not degrade circRNAs, and as such, is often used to assess abundance of, as well as enrich, circRNAs in combination with reverse transcription-quantitative polymerase chain reaction, in sequencing libraries (27). In addition to exoribonuclease treatment, ribosomal RNA- and polyadenylation-depletion are also used to enrich and quantify circRNA expression via modified RNA sequencing approaches. For *in silico* analyses, the online databases Circ2Traits (28), CircBase (29), CircNet (30), deepBase v2.0 (31) and CircInteractome (32) allow researchers to study circRNA expression profiles and circRNA-associated molecular interactions that associate with diseases. Furthermore, several circRNA-specific prediction or detection tools, including UROBORUS (33), find_circ (2) and DCC-CircTest (34), have also been developed.

5. circRNA in gastrointestinal cancer

CRC. CRC was the third most commonly diagnosed cancer worldwide in 2014 (35). A study by Bachmayr-Heyda *et al* (36)

Table I. Identified circRNAs associated with gastrointestinal cancer.

circRNA	Type of cancer	Expression	Potential roles	(Refs.)
cir-*ITCH*	Colorectal, esophageal	↓	miRNA sponge, oncogene, biomarker	(9)
hsa_circ_001988	Colorectal	↓	Biomarker, invasion	(37)
hsa_circ_0006229	Colorectal	↓	Proliferation, biomarker	(36)
hsa_circ_0007374	Colorectal	↑	Proliferation, biomarker	(36)
hsa_circ_002059	Gastric	↓	Biomarker	(10)
CDR1-as	Hepatocellular	↑	miRNA sponge, proliferation, invasion, oncogene	(43)
hsa_circ_0005075	Hepatocellular	↑	Biomarker	(8)
hsa_circ_0001649	Hepatocellular	↓	Metastasis, biomarker	(44)

↑, upregulated; ↓, downregulated; circRNA, circular RNA; cir-*ITCH*, circ-itchy E3 ubiquitin protein ligase; miRNA, microRNA; hsa, *Homo sapiens*; CDR1, cerebellar degeneration-related protein 1.

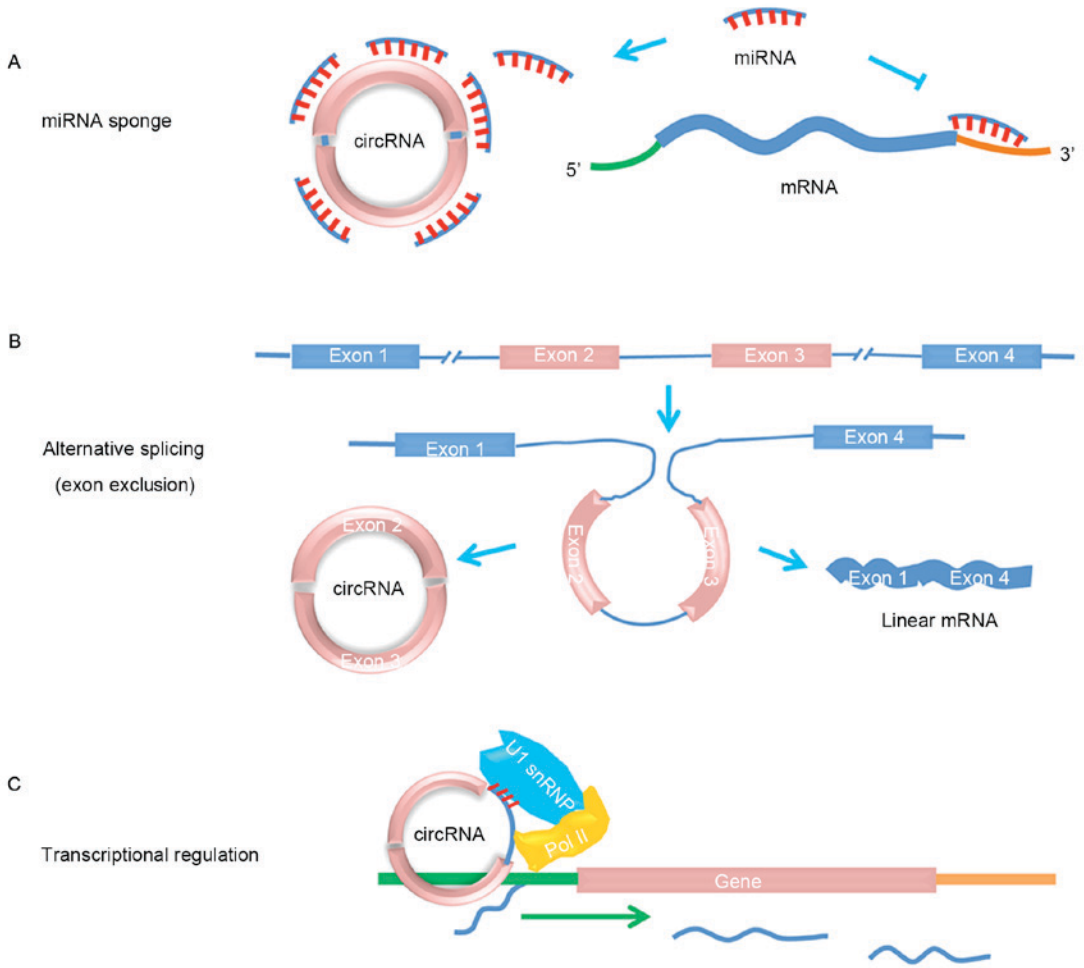

Figure 1. Typical functions of circRNA-mediated gene expression regulation. (A) circRNAs may function as miRNA sponges to inhibit their activity. (B) Exon skipping leads to the generation of a circRNA containing the skipped exons 2 and 3 and truncated mRNA consisting of exons 1 and 4. (C) The exon-intron ciRNA-U1 complex recruits Pol II to the promoter of the host gene which stimulates transcription initiation. circRNA, circular RNA; miRNA, microRNA; Pol II, RNA polymerase II; U1 snRNP, U1 small nuclear ribonucleoprotein.

revealed that the ratio of circular to linear RNA isoforms was consistently decreased in tumors compared with normal colon samples, and demonstrated that this ratio correlated negatively with the proliferation index; to the best of our knowledge, this was the first negative correlation between global circRNA abundance and proliferation in CRC to be identified. Specifically, the study also demonstrated that the expression of *Homo sapiens* (hsa)_circ_0006229 and hsa_circ_0007374 was dysregulated in CRC compared with normal colon mucosa tissues. In addition, Huang *et al* (9) identified that

cir-*ITCH* was significantly downregulated in CRC tissues, and demonstrated that cir-*ITCH* functions as an miRNA sponge serving an inhibitory role in CRC by regulating the Wnt/β-Catenin pathway. Wang *et al* (37) reported that the expression of hsa_circ_001988 was also decreased in tumor tissues compared with normal mucosa, and that it was significantly associated with perineural invasion and differentiation. The aforementioned results suggest that specific circRNAs may be potential novel biomarkers and targets for the treatment of patients with CRC. Additionally, another previous study demonstrated that certain circRNAs are enriched in exosomes and that by assessing levels of exosomal circRNAs, patients with CRC were able to be distinguished from healthy controls (38). Therefore, exosome-based circRNAs may also be potential cancer biomarkers.

GC. GC was the second most common cause of cancer-associated mortality worldwide in 2012 (39). According to bioinformatic analysis using two circRNA databases (CircBase and circ2Traits), a series of circRNAs may be associated with GC (28). In particular, hsa_circ_002059, a commonly detected circRNA, was identified to be significantly downregulated in GC tissues compared with paired adjacent non-tumor tissues (10). This suggests that certain circRNAs, including hsa_circ_002059, may be potential novel and stable biomarkers for the diagnosis of gastric carcinoma.

Pancreatic cancer. Pancreatic ductal adenocarcinoma (PDAC) was the fourth-leading cause of cancer-associated mortality worldwide in 2014, despite accounting for only 2.2% of all types of cancer (40). Qu *et al* (41) used Arraystar Human Circular RNA Microarray, which is able to test for circRNA gene expression, to explore the expression profile of circRNAs in 4 PDAC samples alongside paired adjacent normal tissues. The study revealed that the circRNA expression signatures of PDAC were dysregulated; these results indicate that circRNAs may be involved in the initiation and progression of PDAC, and may serve a role as novel diagnostic and treatment strategies for the disease. However, thus far, specific circRNAs with the potential to serve as biomarkers have not been identified in pancreatic cancer. Therefore, the identification of novel differentially expressed circRNAs may be a crucial step towards an improved understanding of PDAC in future research and clinical application.

HCC. HCC ranked as the fifth most-common tumor, and the third-leading cause for cancer-associated mortality, worldwide in 2010 (42). As in other gastrointestinal cancers, there was a significant difference in the global circRNA expression profile between HCC and adjacent normal liver tissue; particularly, Yu *et al* (43) demonstrated that CDR1-as expression was upregulated in HCC tissues compared with adjacent non-tumor tissues. Furthermore, knockdown of CDR1-as suppressed HCC cell proliferation and invasion, and suppressed the expression of miR-7, which suggests that CDR1-as may act as an oncogene partly through targeting miR-7. In addition, the aforementioned studies revealed that hsa_circ_0005075 (8) and hsa_circ_0001649 (44) exhibit a significant difference in expression between HCC and normal tissues, and identified them as potential HCC biomarkers.

Esophageal cancer. Esophageal cancer is the eighth most common type of cancer and the sixth most common cause of cancer-associated mortality worldwide in 2013 (45). The expression of circRNAs is altered during the development of esophageal squamous cell carcinoma (ESCC). One study revealed that cir-*ITCH* expression was usually decreased in ESCC compared with that in the peritumoral tissue (46). Li *et al* (6) suggested that cir-*ITCH* may exhibit an inhibitory effect on ESCC by regulating the Wnt pathway. Studies such as these further support the role of cir-*ITCH* as a candidate for novel strategies for RNA-based esophageal cancer diagnosis and therapy. Notably, a unique set of circRNAs and their expression profiles were observed in radioresistant esophageal cancer cells (47). The aberrant expression of circRNAs may serve a role in the generation of radiation-resistant esophageal cancer cells.

6. Conclusions and outlook

The studies explored in the present review demonstrate that circRNAs are able to regulate various biological processes. In particular, circRNAs may serve roles in gastrointestinal tumor occurrence and development (Table I). These findings support the hypothesis that circRNAs may be potential novel biomarkers for the diagnosis of gastrointestinal cancer, and may be a tractable target in the treatment of such cancer types.

Although the number of circRNAs with known functions is expanding, the functions of thousands of circRNAs remain unknown. Further studies are required to screen novel differentially expressed circRNAs and confirm their roles in the development of gastrointestinal cancer. More importantly, studying the specific molecular mechanisms of the regulation of gastrointestinal cancer occurrence and development by circRNA may be a promising research field. If the regulation, mechanism and function of circRNA are conserved across diseases, results may be positively validated in, and applied to, other types of cancer and diseases.

Acknowledgements

The present review was supported by the Research Special Fund for Public Welfare Industry of Health (grant no. 201402001) and the Research Fund for the Doctoral Program of Higher Education (grant nos. 20131106110008 and 20121106120048).

References

1. Hansen TB, Jensen TI, Clausen BH, Bramsen JB, Finsen B, Damgaard CK and Kjems J: Natural RNA circles function as efficient microRNA sponges. Nature 495: 384-388, 2013.
2. Memczak S, Jens M, Elefsinioti A, Torti F, Krueger J, Rybak A, Maier L, Mackowiak SD, Gregersen LH, Munschauer M, *et al*: Circular RNAs are a large class of animal RNAs with regulatory potency. Nature 495: 333-338, 2013.
3. Salzman J, Chen RE, Olsen MN, Wang PL and Brown PO: Cell-type specific features of circular RNA expression. PloS Genet 9: e1003777, 2013.
4. Burd CE, Jeck WR, Liu Y, Sanoff HK, Wang Z and Sharpless NE: Expression of linear and novel circular forms of an INK4/ARF-associated non-coding RNA correlates with atherosclerosis risk. PLoS Genet 6: e1001233, 2010.
5. Hansen TB, Kjems J and Damgaard CK: Circular RNA and miR-7 in cancer. Cancer Res 73: 5609-5612, 2013.

6. Li F, Zhang L, Li W, Deng J, Zheng J, An M, Lu J and Zhou Y: Circular RNA ITCH has inhibitory effect on ESCC by suppressing the Wnt/β-catenin pathway. Oncotarget 6: 6001-6013, 2015.
7. Torre LA, Bray F, Siegel RL, Ferlay J, Lortet-Tieulent J and Jemal A: Global cancer statistics, 2012. CA Cancer J Clin 65: 87-108, 2015.
8. Shang X, Li G, Liu H, Li T, Liu J, Zhao Q and Wang C: Comprehensive circular RNA profiling reveals that hsa_circ_0005075, a new circular RNA biomarker, is involved in hepatocellular crcinoma development. Medicine (Baltimore) 95: e3811, 2016.
9. Huang G, Zhu H, Shi Y, Wu W, Cai H and Chen X: cir-ITCH plays an inhibitory role in colorectal cancer by regulating the Wnt/beta-catenin pathway. PLoS One 10: e0131225, 2015.
10. Li P, Chen S, Chen H, Mo X, Li T, Shao Y, Xiao B and Guo J: Using circular RNA as a novel type of biomarker in the screening of gastric cancer. Clin Chim Acta 444: 132-136, 2015.
11. Jeck WR, Sorrentino JA, Wang K, Slevin MK, Burd CE, Liu J, Marzluff WF and Sharpless NE: Circular RNAs are abundant, conserved, and associated with ALU repeats. RNA 19: 141-157, 2013.
12. Jeck WR and Sharpless NE: Detecting and characterizing circular RNAs. Nat Biotechnol 32: 453-461, 2014.
13. Ashwal-Fluss R, Meyer M, Pamudurti NR, Ivanov A, Bartok O, Hanan M, Evantal N, Memczak S, Rajewsky N and Kadener S: circRNA biogenesis competes with Pre-mRNA splicing. Mol Cell 56: 55-66, 2014.
14. Starke S, Jost I, Rossbach O, Schneider T, Schreiner S, Hung LH and Bindereif A: Exon circularization requires canonical splice signals. Cell Rep 10: 103-111, 2015.
15. Zhang XO, Wang HB, Zhang Y, Lu X, Chen LL and Yang L: Complementary sequence-mediated exon circularization. Cell 159: 134-147, 2014.
16. Conn SJ, Pillman KA, Toubia J, Conn VM, Salmanidis M, Phillips CA, Roslan S, Schreiber AW, Gregory PA and Goodall GJ: The RNA binding protein quaking regulates formation of circRNAs. Cell 160: 1125-1134, 2015.
17. Ivanov A, Memczak S, Wyler E, Torti F, Porath HT, Orejuela MR, Piechotta M, Levanon EY, Landthaler M, Dieterich C, *et al*: Analysis of intron sequences reveals hallmarks of circular RNA biogenesis in animals. Cell Rep 10: 170-177, 2015.
18. Wang PL, Bao Y, Yee MC, Barrett SP, Hogan GJ, Olsen MN, Dinneny JR, Brown PO and Salzman J: Circular RNA is expressed across the eukaryotic tree of life. PloS One 9: e90859, 2014.
19. Venø MT, Hansen TB, Venø ST, Clausen BH, Grebing M, Finsen B, Holm IE and Kjems J: Spatio-temporal regulation of circular RNA expression during porcine embryonic brain development. Genome Biol 16: 245, 2015.
20. You X, Vlatkovic I, Babic A, Will T, Epstein I, Tushev G, Akbalik G, Wang M, Glock C, Quedenau C, *et al*: Neural circular RNAs are derived from synaptic genes and regulated by development and plasticity. Nat Neurosci 18: 603-610, 2015.
21. Capel B, Swain A, Nicolis S, Hacker A, Walter M, Koopman P, Goodfellow P and Lovell-Badge R: Circular transcripts of the testis-determining gene Sry in adult mouse testis. Cell 73: 1019-1030, 1993.
22. Memczak S, Jens M, Elefsinioti A, Torti F, Krueger J, Rybak A, Maier L, Mackowiak SD, Gregersen LH, Munschauer M, *et al*: Circular RNAs are a large class of animal RNAs with regulatory potency. Nature 495: 333-338, 2013.
23. Salzman J, Chen RE, Olsen MN, Wang PL and Brown PO: Cell-type specific features of circular RNA expression. PLoS Genet 9: e1003777, 2013.
24. Zhang XO, Dong R, Zhang Y, Zhang JL, Luo Z, Zhang J, Chen LL and Yang L: Diverse alternative back-splicing and alternative splicing landscape of circular RNAs. Genome Res 26: 1277-1287, 2016.
25. Hansen TB, Wiklund ED, Bramsen JB, Villadsen SB, Statham AL, Clark SJ and Kjems J: miRNA-dependent gene silencing involving Ago2-mediated cleavage of a circular antisense RNA. EMBO J 30: 4414-4422, 2011.
26. Li Z, Huang C, Bao C, Chen L, Lin M, Wang X, Zhong G, Yu B, Hu W, Dai L, *et al*: Exon-intron circular RNAs regulate transcription in the nucleus. Nat Struct Mol Biol 22: 256-264, 2015.
27. Suzuki H, Zuo Y, Wang J, Zhang MQ, Malhotra A and Mayeda A: Characterization of RNase R-digested cellular RNA source that consists of lariat and circular RNAs from pre-mRNA splicing. Nucleic Acids Res 34: e63, 2006.
28. Ghosal S, Das S, Sen R, Basak P and Chakrabarti J: Circ2Traits: A comprehensive database for circular RNA potentially associated with disease and traits. Front Genet 4: 283, 2013.
29. Glazar P, Papavasileiou P and Rajewsky N: circBase: A database for circular RNAs. RNA 20: 1666-1670, 2014.
30. Liu YC, Li JR, Sun CH, Andrews E, Chao RF, Lin FM, Weng SL, Hsu SD, Huang CC, Cheng C, *et al*: CircNet: A database of circular RNAs derived from transcriptome sequencing data. Nucleic Acids Res 44: D209-D215, 2016.
31. Zheng LL, Li JH, Wu J, Sun WJ, Liu S, Wang ZL, Zhou H, Yang JH and Qu LH: deepBase v2.0: Identification, expression, evolution and function of small RNAs, LncRNAs and circular RNAs from deep-sequencing data. Nucleic Acids Res 44: D196-D202, 2016.
32. Dudekula DB, Panda AC, Grammatikakis I, De S, Abdelmohsen K and Gorospe M: CircInteractome: A web tool for exploring circular RNAs and their interacting proteins and microRNAs. RNA Biol 13: 34-42, 2016.
33. Song X, Zhang N, Han P, Moon BS, Lai RK, Wang K and Lu W: Circular RNA profile in gliomas revealed by identification tool UROBORUS. Nucleic Acids Res 44: e87, 2016.
34. Cheng J, Metge F and Dieterich C: Specific identification and quantification of circular RNAs from sequencing data. Bioinformatics 32: 1094-1096, 2016.
35. Stewart BW and Wild CP (eds): World Cancer Report 2014. World Health Organization, International Agency for Research on Cancer, Lyon, 2014.
36. Bachmayr-Heyda A, Reiner AT, Auer K, Sukhbaatar N, Aust S, Bachleitner-Hofmann T, Mesteri I, Grunt TW, Zeillinger R and Pils D: Correlation of circular RNA abundance with proliferation-exemplified with colorectal and ovarian cancer, idiopathic lung fibrosis, and normal human tissues. Sci Rep 5: 8057, 2015.
37. Wang X, Zhang Y, Huang L, Zhang J, Pan F, Li B, Yan Y, Jia B, Liu H, Li S, *et al*: Decreased expression of hsa_circ_001988 in colorectal cancer and its clinical significances. Int J Clin Exp Pathol 8: 16020-16025, 2015.
38. Li Y, Zheng Q, Bao C, Li S, Guo W, Zhao J, Chen D, Gu J, He X and Huang S: Circular RNA is enriched and stable in exosomes: A promising biomarker for cancer diagnosis. Cell Res 25: 981-984, 2015.
39. Torre LA, Bray F, Siegel RL, Ferlay J, Lortet-Tieulent J and Jemal A: Global cancer statistics, 2012. CA Cancer J Clin 65: 87-108, 2015.
40. Jones OP, Melling JD and Ghaneh P: Adjuvant therapy in pancreatic cancer. World J Gastroenterol 20: 14733-14746, 2014.
41. Qu S, Song W, Yang X, Wang J, Zhang R, Zhang Z, Zhang H and Li H: Microarray expression profile of circular RNAs in human pancreatic ductal adenocarcinoma. Genom Data 5: 385-387, 2015.
42. Yu L, Gong X, Sun L, Yao H, Lu B and Zhu L: miR-454 functions as an oncogene by inhibiting CHD5 in hepatocellular carcinoma. Oncotarget 6: 39225-39234, 2015.
43. Yu L, Gong X, Sun L, Zhou Q, Lu B and Zhu L: The circular RNA Cdr1as act as an oncogene in hepatocellular carcinoma through targeting miR-7 expression. PLoS One 11: e0158347, 2016.
44. Qin M, Liu G, Huo X, Tao X, Sun X, Ge Z, Yang J, Fan J, Liu L and Qin W: Hsa_circ_0001649: A circular RNA and potential novel biomarker for hepatocellular carcinoma. Cancer Biomark 16: 161-169, 2016.
45. Sakai NS, Samia-Aly E, Barbera M and Fitzgerald RC: A review of the current understanding and clinical utility of miRNAs in esophageal cancer. Semin Cancer Biol 23: 512-521, 2013.
46. Wei W, Li M, Wang J, Nie F and Li L: The E3 ubiquitin ligase ITCH negatively regulates canonical Wnt signaling by targeting dishevelled protein. Mol Cell Biol 32: 3903-3912, 2012.
47. Su H, Lin F, Deng X, Shen L, Fang Y, Fei Z, Zhao L, Zhang X, Pan H, Xie D, *et al*: Profiling and bioinformatics analyses reveal differential circular RNA expression in radioresistant esophageal cancer cells. J Transl Med 14: 225, 2016.