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Landscape of Circular RNAs in the Clinical Application of Digestive System Neoplasm

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Abstract

It has been confirmed that noncoding RNAs (ncRNAs) play an important role in cellular development, differentiation, proliferation and apoptosis of various carcinomas. As a member of the ncRNAs family, circular RNAs (circRNAs) are getting new research hotspots because of their newly discovered and numerous potential functions such as acting as microRNA (miRNA) sponges and binding to RNA-binding proteins (RBPs) to modulate the gene transcription. Herein, we review the current understanding of the roles of circRNAs in the clinical application of digestive system neoplasm and provide a new insight into the potential implications in the diagnosis and targeted therapy of digestive system carcinomas.

Keywords: Circular RNA; Cancer; Targeted therapy; Diagnosis; Digestive system neoplasm

Introduction

Digestive system neoplasm is the most common group of malignancies, which are reported an estimated 304,930 new cases and an estimated 153,030 deaths in 2016 in the United States [1]. One of the major obstacles in improving patient survival for these cancers is the failure of early diagnosis. Thus, the identification of new molecular is crucial to develop more effective therapeutic strategies for digestive system neoplasm.

Noncoding RNAs (ncRNAs) have been shown involved in the regulation of cell structure, function, and physiological development in the previous studies [2]. Growing evidence has revealed ncRNAs are a new class of exosome-based cancer biomarkers for the detection of digestive system tumors and are potential therapeutic targets [3]. Moreover, some ncRNAs could be secreted into body fluids, suggesting that cancers may change their extracellular environments through RNA-based, hormone-like mechanisms [4]. As a new star in RNA research area, it is worth mentioning that circular RNAs (circRNAs), which are endogenous, abundant and stable in mammalian cells, have strong ties with the atherosclerotic vascular disease risk, neurological disorders, prion diseases and carcinomas so far [5-7].

In this review, we collected potentially eligible studies through searching electronic databases PubMed and Web of Science. We used circRNAs, circular RNAs, or cancer as the keywords for the search. The latest search was updated on October 4, 2017. In this article, we attempt to provide a comprehensive review on the most relevant information on several circRNAs in digestive system neoplasm, and their diagnostic, prognostic and therapeutic applications will also be discussed.

CircRNAs

Definition

CircRNAs, which were found in 1976 in the RNA virus, are recently identified as a naturally occurring family of ncRNAs after microRNA, (miRNAs) and long non-coding RNAs （lncRNAs) [8]. But more recently, the studies have found that it has the ability to code for proteins [9]. Unlike the better known linear RNAs which are terminated with 5′ caps and 3′ tails, circRNAs forms a covalently closed continuous loop structures with neither 5′-3′ polarities nor polyadenylated tails [10]. Its special closed loop structure makes it a very stable RNA molecule, and have the ability to be resistant to exonuclease-mediated degradation. At present, according to the sources in the genome and differences in constituent sequences, circRNAs can be divided into the following 3 main types: exon-shuffling-derived circRNA (ecRNA) only comprised of exons, circular intronic RNA (ciRNA) and exon–intron RNA (elciRNA), which have different production mechanism respectively [11,12].

Comparison of circRNAs and other ncRNAs

In the past few years, an accumulating body of evidence has deepened our understanding of ncRNAs, and a large amount of emerging ncRNAs have been identified, which play critical roles in the tumorigenesis of digestive system neoplasm. MiRNAs are a major class

of small ncRNAs, which are approximately 19-24 nt in length highly conserved, and expressed in a temporal and tissue-specific manner [13]. MiRNAs bind to their target gene transcripts to regulate gene expression and are found to be associated with digestive system neoplasms development, progression, and therapeutic response [14]. LncRNA named H19 was first reported with a structure of more than 200 nucleotides by Brannan and his colleagues in 1990. LncRNAs consist of exons and introns in structure and are not highly conserved [15]. Over the last ten years, the important role of lncRNAs played in the digestive system neoplasms are being confirmed by accumulating proof and suggested that lncRNAs might act as novel biomarkers for diagnosis and prognosis, as well as provide effective therapeutic targets for digestive system neoplasms treatment [16-18]. However, in recent years, the focus has shifted to circRNAs in the field of RNA research and probably play roles in regulating parental gene transcription, cell proliferation, and RNA-binding proteins, indicating their functional potential for development as diagnostic tools in digestive system neoplasm (Figure 1).

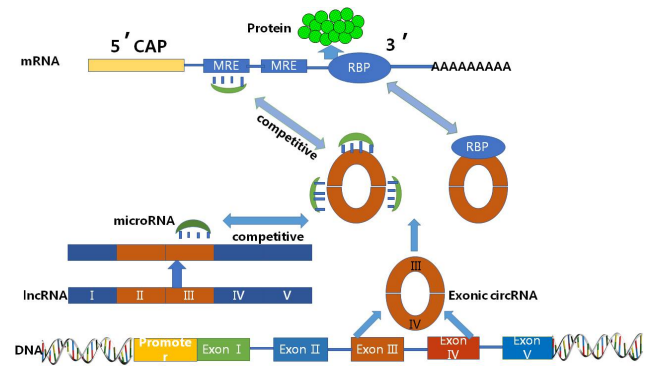

Figure 1: The interaction of circRNAs miRNA, lncRNA and mRNA. Exon-shuffling-derived circRNA (ecRNA), which is only comprised of exons spliced from DNA, are the most common types of circRNAs. CircRNA and lncRNA act as miRNA sponges by competing for miRNA binding to regulate the expression of miRNA and their target gene. Moreover, circRNAs may bind and sequester RNA-binding proteins (RBPs) to regulate gene expression.

Competing endogenous RNA (ceRNA), which includes mRNAs, pseudogenic RNAs, lncRNAs as well as circRNAs, are transcripts that cross-regulate each other by competing for shared miRNAs [19]. This hypothesis posits that RNAs could influence miRNA expression, inducing gene silencing, only if they share miRNA response elements (MREs) in their 3'untranslated regions (UTRs) [20]. In the ceRNA networks, the most important two elements are the miRNAs and MREs, the former as the core components and the latter as the structural foundation [21]. In recent years, complex crosstalk of ceRNAs has been found in various neoplasms, including digestive system neoplasm. Previous evidence has showed that the multifaceted roles of lncRNAs in tumorigenesis may be partially mediated by ceRNA crosstalk. The recent discovery of competitive RNA–RNA interactions coupled with the extensive complementarity of circRNAs to their linear mRNA counterparts has raised the possibility that these RNA circles may have an integral role in regulatory RNA networks. Newly discovered circRNAs can also function as miRNA sponges similarly to lncRNAs, playing important roles in miRNA regulation. The first microRNA sponge identified was human ciRS-7, which has been detected associated to cervical cancer, neuroblastoma, astrocytoma, renal cell and lung carcinoma [22]. The overexpression of ciRS-7 acts as an microRNA sponge, arresting miR-7 and therefore elevating the level of miR-7 targets, which regulates the epidermal control factor receptor (EGFR) expression that further regulates cell growth, proliferation, differentiation and signaling in human cancer cells [23].

Besides regulating miRNAs, circRNAs may bind and sequester RNA-binding proteins (RBPs) or even base-pair with RNAs, resulting in the formation of large RNA-protein complexes (RPCs) [24]. These RPCs can regulate the pool of RBPs or small RNAs capable of interacting with the canonical linear RNA counterpart [25].

The most worth mentioning is that few circRNAs can be translated, which is most significant difference from other ncRNAs. Recent research reported that engineered circRNAs that were inserted an IRES in upstream of the start codons of a protein could be translated *in vitro* or *in vivo* [26]. For example, HDV, which is a subviral satellite virus of the hepatitis B virus (HBV) [27]. The encapsulation of HDV with HBV virions results in the production of a single viral protein that is specific to pathogenicity, but the principle of translation is noncanonical and probably associated with specific viral agents [28,29]. However, to date, there is no evidence that suggests that naturally occurring endogenous circRNAs undergo translation [5,30].

CircRNAs and digestive system neoplasms

Growing evidence shows that circRNAs have critical functions in tumor and serve as the huge diagnostic and therapeutic potentials for cancer. Compared with other ncRNAs, circRNAs are more abundant, conserved and stable. Based on what has researched, circRNAs were thought to have a close relationship with the development of different cancers, including esophageal squamous cell carcinoma, colorectal cancer, gastric cancer, and so on. Table 1 lists some circRNAs which are linked closely to clinical application and provides potential biomarker and therapeutic target of digestive system neoplasm.

Correlation of circRNAs to esophageal carcinoma

Esophageal squamous cell carcinoma (ESCC) is one of the most prevalent and deadly types of cancer worldwide especially in Eastern Asia, because of its poor effective early diagnosis method, the prognosis of ESCC still remains poor. Recent evidence suggests that circRNAs play an important role in ESCC.

It has been found that circRNA ITCH has an inhibitory effect on ESCC by suppressing the Wnt/beta-catenin pathway. AS miR-7, miR-17 and miR-214 'sponge', circ-ITCH increases the expression of ITCH, reduces ESCC cells viability, and inhibits its proliferation. Overexpression of ITCH can promote the ubiquitination and degradation of Dvl-2 (Dishevelled 2) protein, thereby inhibit the Wnt/beta-catenin pathway and thereby inhibit the development and progression of ESCC [31].

A novel circRNA termed hsa_circ_0067934 was confirmed significantly overexpressed in ESCC tissues compared with paired adjacent normal tissues and high expression level of hsa_circ_0067934 was associated with poor differentiation, I-II T stage, and I-II TNM stage. Silence of hsa_circ_0067934 *in vitro* inhibits migration and proliferation of ESCC cells and blocks cell cycle progression, suggesting that hsa_circ_0067934 represents a novel potential biomarker for the treatment of ESCC [32].

Su et al. investigated the role of circRNA in radiation resistance of esophageal cancer by bioinformatics analysis, and found significant upregulation of 57 circRNAs and downregulation of 17 circRNAs in human radioresistant esophageal cancer cell line KYSE-150R among the detected candidate 3752 circRNA genes. GO analysis revealed that more than 400 target genes including most microRNAs enrichment on Wnt signaling pathway. CircRNA_001059 and circRNA_000167 were the two largest nodes in circRNA/microRNA co-expression network. These dysregulated circRNAs have a hand in the development of radiation resistance [33].

Correlation of circRNAs to gastric cancer

Gastric cancer (GC) is one of the most common cancers worldwide. Diagnosis and treatment have improved over the last decades, but the 5-year survival rate remains low in patients with advanced GC. The expression levels and potential roles of circRNAs in GC are becoming the research hotspot and may clarify the molecular mechanisms of gastric cancer.

Some circRNAs are confirmed to be significantly differently expressed in gastric cancer tissues compared to non-tumorous tissues and play a tumor suppressor role. The hsa_circ_0003159 levels were first detected in 108 paired gastric cancer tissues and adjacent non-tumorous tissues from surgical patients with gastric cancer. Compared with paired adjacent non-tumorous tissues, hsa_circ_0003159 expression was significantly down-regulated in gastric cancer tissues and significantly negatively associated with gender, distal metastasis, and tumor-node-metastasis stage [34]. Similarly, hsa_circ_0014717 was significantly down regulated as well in gastric cancer tissues and related to tumor stage, distal metastasis, tissue carcinoembryonic antigen and carbohydrate antigen 19-9 expression [35]. However, some circRNAs are upregulated in GC tissues and play a vital role in promoting the development of gastric cancer. Chen J discovered that the expression of circPVT1 was upregulated in GC tissues and may promote cell proliferation by acting as a sponge for members of the miR-125 family. Besides, CircPVT1 could serve as an independent prognostic marker for overall survival and disease-free survival in patients with GC, which makes it a novel proliferative factor and prognostic marker in GC [36].

In addition to tissues, the expression of circRNAs in plasma samples from patients with gastric cancer is also researched. Chen S et al. found hsa_circ_0000190 was down-expressed in gastric cancer plasma and were significantly correlated with tumor diameter, lymphatic metastasis, distal metastasis, TNM stage, and CA19-9 levels. These results suggest that hsa_circ_0000190 may be a novel noninvasive biomarker for the diagnosis of gastric cancer with a better sensitivity and specificity than commonly used biomarkers [37]. Taken together, circRNA paints a beautiful blueprint for the research of gastric cancer and further studies are required to explore their potential as biomarkers for GC as well as their pathologic role.

Correlation of circRNAs to hepatocellular carcinoma

The high frequency of disease metastasis and recurrence makes hepatocellular carcinoma (HCC) becomes one of the most predominant subjects of liver malignancies, which arouses global concern in the recent years [38]. It has been found that circRNAs are diversely expressed in HCC, and can regulate pathogenesis and metastasis of HCC. Previous study revealed the expression of hsa_circ_0001649 in HCC tissues was significantly down-regulated and was associated with tumor size in HCC and tumor embolization. This result indicates hsa_circ_0001649 might serve as a novel potential biomarker for HCC and may play a part in tumorigenesis and metastasis of HCC [39].

In regard to research on mechanisms, Han D identified miR-9 as the circMTO1-associated miRNA *in vivo* precipitation in HCC cells. Silencing of circMTO1 in HCC could down-regulate p21, the target of oncogenic miR-9, resulting in the promotion of HCC cell proliferation and invasion. Moreover, tumor-promoting effect of circMTO1 silencing was blocked by miR9 inhibitor [40]. Therefore, the improved understanding of circRNAs in HCC pathogenesis and metastasis proposed a novel basis for the early diagnosis in HCC patients and provides a useful resource to explore the pathogenesis of HCC.

Correlation of circRNAs to pancreatic ductal adenocarcinoma

Pancreatic ductal adenocarcinoma (PDAC) is a common form of cancer, but there is no reliable biological target for routine clinical practice of the disease. Through the comparative analysis of the expression of circRNAs in human pancreatic cancer and its adjacent normal tissues, the researchers found that abnormal expression of circRNAs in PDAC. The microarray expression profiles exhibited that 209 up-regulated circRNAs and 142 down-regulated circRNAs were significantly differentially expressed in six paired PDAC samples. That indicates that circRNAs may be involved in the occurrence and development process of PDAC. And it can be a potential biological target for the diagnosis and treatment of PDAC. And the circRNAs expression profile of PDAC using the microarray analysis is first reported in 2016 [41,42].

Correlation of circRNAs to colorectal cancer

Colorectal cancer (CRC) is the world's third most frequently diagnosed cancer, but also the world's fourth largest cause of cancer deaths [43]. At present, CRC lacks low cost and noninvasive testing and becomes a serious health problem. In this regard, the potential biomarkers for early detection of CRC have recently been of interest. Recent studies have shown that circRNA may play an important role in colorectal cancer, and it is hopeful to be a new molecular marker of CRC. A new circRNA named hsa_circ_001988 was selected from the sequence database, and then verified. The result showed that hsa_circ_001988 was decreased in tumor tissues and the expression of hsa_circ_001988 was significantly correlated with differentiation and peripheral nerve infiltration. It means that hsa_circ_001988 can be treated as a new potential biomarker for the diagnosis of colorectal cancer and a potential new target for the treatment of colorectal cancer [44].

Another study showed that hsa_circ_001569 was an active regulator of cell proliferation and colorectal cancer invasion. In addition, hsa_circ_001569 plays its role as a sponge of miR-145 and upregulated miR-145 functional target E2F5, BAG4 and FMNL2. The correlation analysis showed the negative correlation of circ_001569 with miR-145, and the relationship is similar between miR-145 and E2F5, BAG4 and FMNL2 expression in the CRC tissue. Thus circ_001569 regulates in the CRC cell proliferation and invasion [45].

Cancer type	CircRNA name	Expression level	samples	Clinical significance				First author	Year	Country	Reference
				TNM stage	metastasis	Tumor size	differentiaon				
esophageal carcinoma	circ_0067934	↑	tissues	Yes	No	No	Yes	Xia W	2016	China	[32]
gastric carcinoma	circ_0003159	↓	tissues	Yes	Yes	No	No	Tian M	2017	China	[34]
	circ_0014717	↓	tissues	Yes	Yes	No	No	Shao Y	2017	China	[35]
	circ_0001895	↓	tissues	No	No	No	Yes	Shao Y	2017	China	[46]
	circ_0000190	↓	tissues and plasma	Yes	Yes	Yes	No	Chen S	2017	China	[37]
	circ_002059	↓	tissues and plasma	Yes	Yes	No	No	Li P	2015	China	[47]
hepatoma carcinoma	circ_ZKSCAN1	↓	tissues	Yes	No	No	No	Yao Z	2017	China	[48]
	circ_ciRS-7	↓	tissues	No	No	No	No	Xu L	2017	China	[49]
	circ_0005075	↑	tissues	No	No	Yes	No	Shang X	2016	China	[50]
	circ_0001649	↓	tissues	No	No	Yes	No	Qin M	2016	China	[39]
Colorectal Cancer	circRNA_103809	↓	tissues	Yes	Yes	No	No	Zhang P	2017	China	[51]
	circRNA_104700	↓	tissues	No	Yes	No	No	Zhang P	2017	China	[51]
	circ_0000069	↑	tissues	Yes	Yes	No	No	Guo JN	2016	China	[52]
	circ_001988	↓	tissues	No	No	No	Yes	Wang X	2015	China	[44]

Table 1: Summary of well-studied digestive system neoplasms-related circular RNAs.

Future Challenges and Perspectives

CircRNAs, a recently discovered RNA family, were thought to be the products of transcription errors earlier. Until 2012, along with the development of high-throughput sequencing technologies and bioinformatics, Salzman made a comprehensive and systematic report on circRNAs about that their general features of the gene expression program in human cells, and then people began to re-understand and study it, making it popular [30]. In this review, we focus on the research progress made in the area of circRNAs in digestive system neoplasms recently, as well as the newly proposed hypothesis of ceRNAs networks, presenting an overview of circRNAs research. According to the circulation of circRNAs participate in and its role in it, circRNA has the dual function of anticancer and promoting cancer. Given that the interactions between circRNAs and digestive system neoplasms are very complex, circRNAs research will likely take a large step forward with the identification of more molecules, which will also contribute to the knowledge of digestive system neoplasm tumor biology. Multiple studies have already demonstrated the potential clinical applications of several circRNAs in digestive system neoplasms diagnosis and prognosis; however, there are considerable limitations, such as the small sample sizes and the invasive monitoring methods. In a word, the research on circRNA is still in its infancy at present, and it is far away from the deep-seated biological function and specific mechanism. Thus, more research on functional consequences of circRNA, especially the circRNA biogenesis may be needed.

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References

1. Siegel RL, Miller KD, Jemal A (2016) Cancer statistics, 2016. CA Cancer J Clin 66: 7-30.
2. Zhang M, Du X (2016) Noncoding RNAs in gastric cancer: Research progress and prospects. World J Gastroenterol 22: 6610-6618.
3. Taft RJ, Pang KC, Mercer TR, Dinger M, Mattick JS (2010) Non-coding RNAs: regulators of disease. J Pathol 220: 126-139.
4. Kahlert C, Kalluri R (2013) Exosomes in tumor microenvironment influence cancer progression and metastasis. J Mol Med (Berl) 91: 431-437.

5. Jeck WR, Sorrentino JA, Wang K, Slevin MK, Burd CE, et al. (2013) Circular RNAs are abundant, conserved, and associated with ALU repeats. RNA 19: 141-157.
6. Guo JU, Agarwal V, Guo H, Bartel DP (2014) Expanded identification and characterization of mammalian circular RNAs. Genome Biol 15: 409.
7. Burd CE, Jeck WR, Liu Y, Sanoff HK, Wang Z, et al. (2010) Expression of linear and novel circular forms of an INK4/ARF-associated non-coding RNA correlates with atherosclerosis risk. PLoS Genet 6: e1001233.
8. Sanger HL, Klotz G, Riesner D, Gross HJ, Kleinschmidt AK (1976) Viroids are single-stranded covalently closed circular RNA molecules existing as highly base-paired rod-like structures. Proc Natl Acad Sci U S A 73: 3852-3856.
9. Pamudurti NR, Bartok O, Jens M, Ashwal-Fluss R, Stottmeister C, et al. (2017) Translation of CircRNAs. Mol Cell 66: 9-21.
10. Chen LL, Yang L (2015) Regulation of circRNA biogenesis. RNA Biol 12: 381-388.
11. Zhang Y, Zhang XO, Chen T, Xiang JF, Yin QF, et al. (2013) Circular intronic long noncoding RNAs. Mol Cell 51: 792-806.
12. Kelly S, Greenman C, Cook PR, Papantonis A (2015) Exon Skipping Is Correlated with Exon Circularization. J Mol Biol 427: 2414-2417.
13. Kim VN, Nam JW (2006) Genomics of microRNA. Trends Genet 22: 165-173.
14. Song JH, Meltzer SJ (2012) MicroRNAs in pathogenesis, diagnosis, and treatment of gastroesophageal cancers. Gastroenterology 143: 35-47.
15. Derrien T, Johnson R, Bussotti G, Tanzer A, Djebali S, et al. (2012) The GENCODE v7 catalog of human long noncoding RNAs: analysis of their gene structure, evolution, and expression. Genome Res 22: 1775-1789.
16. Xu MD, Qi P, Weng WW, Shen XH, Ni SJ, et al. (2014) Long non-coding RNA LSINCT5 predicts negative prognosis and exhibits oncogenic activity in gastric cancer. Medicine (Baltimore) 93: e303.
17. Yang F, Bi J, Xue X, Zheng L, Zhi K, et al. (2012) Up-regulated long non-coding RNA H19 contributes to proliferation of gastric cancer cells. FEBS J 279: 3159-3165.
18. Yang C, Tang R, Ma X, Wang Y, Luo D, et al. (2015) Tag SNPs in long non-coding RNA H19 contribute to susceptibility to gastric cancer in the Chinese Han population. Oncotarget 6: 15311-20.
19. Salmena L, Poliseno L, Tay Y, Kats L, Pandolfi PP (2011) A ceRNA hypothesis: the Rosetta Stone of a hidden RNA language. Cell 146: 353-358.
20. Guo LL, Song CH, Wang P, Dai LP, Zhang JY, et al. (2015) Competing endogenous RNA networks and gastric cancer. World J Gastroenterol 21: 11680-11687.
21. Qi X, Zhang DH, Wu N, Xiao JH, Wang X, et al. (2015) ceRNA in cancer: possible functions and clinical implications. J Med Genet 52: 710-718.
22. Peng L, Yuan XQ, Li GC (2015) The emerging landscape of circular RNA ciRS-7 in cancer (Review). Oncol Rep 33: 2669-2674.
23. Cohen S, Carpenter G, King L (1980) Epidermal growth factor-receptor-protein kinase interactions. Co-purification of receptor and epidermal growth factor-enhanced phosphorylation activity. J Biol Chem 255: 4834-4842.
24. Wilusz JE, Sharp PA (2013) Molecular biology. A circuitous route to noncoding RNA. Science 340: 440-441.
25. Summerton J (1999) Morpholino antisense oligomers: the case for an RNase H-independent structural type. Biochim Biophys Acta 1489: 141-158.
26. Thomas LF, Sætrom P (2014) Circular RNAs are depleted of polymorphisms at microRNA binding sites. Bioinformatics 30: 2243-2246.
27. Kos A, Dijkema R, Arnberg AC, van der Meide PH, Schellekens H (1986) The hepatitis delta (delta) virus possesses a circular RNA. Nature 323: 558-560.
28. Abbas Z, Afzal R (2013) Life cycle and pathogenesis of hepatitis D virus: A review. World J Hepatol 5: 666-675.
29. Alves C, Branco C, Cunha C (2013) Hepatitis delta virus: a peculiar virus. Adv Virol 2013: 560105.
30. Salzman J, Gawad C, Wang PL, Lacayo N, Brown PO (2012) Circular RNAs are the predominant transcript isoform from hundreds of human genes in diverse cell types. PLoS One 7: e30733.
31. Li F, Zhang L, Li W, Deng J, Zheng J, et al. (2015) Circular RNA ITCH has inhibitory effect on ESCC by suppressing the Wnt/β-catenin pathway. Oncotarget 6: 6001-6013.
32. Xia W, Qiu M, Chen R, Wang S, Leng X, et al. (2016) Circular RNA has_circ_0067934 is upregulated in esophageal squamous cell carcinoma and promoted proliferation. Sci Rep 6: 35576.
33. Su H, Lin F, Deng X, Shen L, Fang Y, et al. (2016) Profiling and bioinformatics analyses reveal differential circular RNA expression in radioresistant esophageal cancer cells. J Transl Med 14: 225.
34. Tian M, Chen R, Li T, Xiao B (2017) Reduced expression of circRNA hsa_circ_0003159 in gastric cancer and its clinical significance. J Clin Lab Anal e22281.
35. Shao Y, Li J, Lu R, Li T, Yang Y, et al. (2017) Global circular RNA expression profile of human gastric cancer and its clinical significance. Cancer Med 6: 1173-1180.
36. Chen J, Li Y, Zheng Q, Bao C, He J, et al. (2017) Circular RNA profile identifies circPVT1 as a proliferative factor and prognostic marker in gastric cancer. Cancer Lett 388: 208-219.
37. Chen S, Li T, Zhao Q, Xiao B, Guo J (2017) Using circular RNA hsa_circ_0000190 as a new biomarker in the diagnosis of gastric cancer. Clin Chim Acta 466: 167-171.
38. Lin KT, Shann YJ, Chau GY, Hsu CN, Huang CY (2016) Identification of latent biomarkers in hepatocellular carcinoma by ultra-deep whole-transcriptome sequencing. Oncogene 35: 5078.
39. Qin M, Liu G, Huo X, Tao X, Sun X, et al. (2016) Hsa_circ_0001649: A circular RNA and potential novel biomarker for hepatocellular carcinoma. Cancer Biomark 16: 161-169.
40. Han D, Li J, Wang H, Su X, Hou J, et al. (2017) Circular RNA circMTO1 acts as the sponge of microRNA-9 to suppress hepatocellular carcinoma progression. Hepatology 66: 1151-1164.
41. Qu S, Song W, Yang X, Wang J, Zhang R, et al. (2015) Microarray expression profile of circular RNAs in human pancreatic ductal adenocarcinoma. Genom Data 5: 385-387.
42. Li H, Hao X, Wang H, Liu Z, He Y, et al. (2016) Circular RNA Expression Profile of Pancreatic Ductal Adenocarcinoma Revealed by Microarray. Cell Physiol Biochem 40: 1334-1344.
43. Torre LA, Bray F, Siegel RL, Ferlay J, Lortet-Tieulent J, et al. (2012) Global cancer statistics, 2012. CA Cancer J Clin 65: 87-108.
44. Wang X, Zhang Y, Huang L, Zhang J, Pan F, et al. (2015) Decreased expression of hsa_circ_001988 in colorectal cancer and its clinical significances. Int J Clin Exp Pathol 8: 16020-16025.
45. Xie H, Ren X, Xin S, Lan X, Lu G, et al. (2016) Emerging roles of circRNA_001569 targeting miR-145 in the proliferation and invasion of colorectal cancer. Oncotarget 7: 26680-26691.
46. Shao Y, Chen L, Lu R, Zhang X, Xiao B, et al. (2017) Decreased expression of hsa_circ_0001895 in human gastric cancer and its clinical significances. Tumour Biol 39: 1010428317699125.
47. Li P, Chen S, Chen H, Mo X, Li T, et al. (2015) Using circular RNA as a novel type of biomarker in the screening of gastric cancer. Clin Chim Acta 444: 132-136.
48. Yao Z, Luo J, Hu K, Lin J, Huang H, et al. (2017) ZKSCAN1 gene and its related circular RNA (circZKSCAN1) both inhibit hepatocellular carcinoma cell growth, migration, and invasion but through different signaling pathways. Mol Oncol 11: 422-437.
49. Xu L, Zhang M, Zheng X, Yi P, Lan C, et al. (2017) The circular RNA ciRS-7 (Cdr1as) acts as a risk factor of hepatic microvascular invasion in hepatocellular carcinoma. J Cancer Res Clin Oncol 143: 17-27.
50. Shang X, Li G, Liu H, Li T, Liu J, et al. (2016) Comprehensive Circular RNA Profiling Reveals That hsa_circ_0005075, a New Circular RNA Biomarker, Is Involved in Hepatocellular Crcinoma Development. Medicine (Baltimore) 95: e3811.

51. Zhang P, Zuo Z, Shang W, Wu A, Bi R, et al. (2017) Identification of differentially expressed circular RNAs in human colorectal cancer. Tumour Biol 39: 1010428317694546.

52. Guo JN, Li J, Zhu CL, Feng WT, Shao JX, et al. (2016) Comprehensive profile of differentially expressed circular RNAs reveals that hsa_circ_0000069 is upregulated and promotes cell proliferation, migration, and invasion in colorectal cancer. Onco Targets Ther 9: 7451-7458.