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ORIGINAL ARTICLE

CircRNAs as Potential Biomarkers in Gastrointestinal Tract Tumors: Opportunities and Challenges

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SUMMARY

Most digestive system tumors have poor prognoses due to the lack of specific biomarkers. Circular RNAs (circRNAs) regulate the expression of genes and play essential roles in digestive system tumorigenesis. Here we review circRNA functions in gastrointestinal tract tumors. CircRNAs are promising biomarkers for clinical applications for gastrointestinal tract tumors.
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INTRODUCTION

The digestive system consists of the gastrointestinal tract, including the esophagus, stomach, and small and large intestine, plus the accessory organs of digestion such as the pancreas, liver, and gallbladder. The high morbidity and mortality rates of digestive system cancers remain a critical health problem worldwide [1]. Molecular analyses of tumor tissues at different stages of development have revealed genetic and expression alterations during tumor development that are correlated with its clinical aggressiveness.

Circular RNAs (circRNAs) are RNAs that are covalently closed loops and are stably expressed in various tissues. CircRNAs consist of exons from RNA transcripts in human cells [2]. A growing number of studies has hinted at the important functions of circRNAs in various biological processes [3]. CircRNAs have multiple functions, including acting as miRNA sponges [4] and modulating the expression of mRNA and proteins [5]. Furthermore, some circRNAs encode peptides [6]. CircRNA disorders could affect the development of various cancers [7].

CircRNAs are produced by end-to-end formation of RNA fragments during transcription. Although these

RNAs have been investigated for more than 40 years [8], they did not attract enough attention until they were observed to be highly expressed in various tissues [9-11]. CircRNAs often share the same transcript with their corresponding linear isomers, although they are formed via different splicing mechanisms [12,13]. In certain cancers, circRNAs are abnormally expressed in epithelial tumors such as laryngeal and digestive system cancers [14-16] and in stromal tumors such as gliomas [17]. Additionally, circRNAs play a strong regulatory function in cancers [18,19]. Compared with mRNAs, circRNAs are composed of a highly stable ring structure that may be utilized in qRT-PCR analyses.

Biogenesis of circRNAs

During the formation of circRNAs, specific sequences contribute to the generation of mature circRNAs by back splicing [20]. Although the efficiency of back splicing is much lower than in linear RNAs [3], circRNAs are highly abundant because of their stability and relatively long half-life [21].

One linear RNA molecule can be processed into different types of RNAs, including mRNAs, circRNAs, and lncRNAs through different splicing events. For example, HIPK3 pre-mRNAs can be spliced into HIPK3 mRNAs and its second exon can also form circRNA hsa_circ_0018082 [22]. There is also competition between inverted splicing of circRNAs, mRNAs, and lncRNAs during splicing [23], which may be a regulatory mechanism of circRNAs. Another regulatory protein is the Quaking (QKI) protein, which binds to specific downstream sites on the linear pre-mRNA sequence and promotes cycling and inverted splicing of circRNAs [24].

CircRNAs are less readily degraded than linear RNAs, mRNAs, and lncRNAs [12]. Thus, circRNAs are often predominant in extracellular spaces [18]. CircRNAs may also be utilized as biomarkers that are more stable than mRNAs or lncRNAs. CircRNAs play important regulatory roles in tumorigenesis [25,26].

Digestive system tumor strategies

Traditional diagnostic approaches for gastrointestinal tract tumors include X-ray fluoroscopy and gastric photo fluoroscopy [27]. Endoscopy is considered the gold standard for confirming gastrointestinal tumor differentiation and grading. Slight changes have also been observed in early-stage gastrointestinal tract tumors [28]. Noninvasive or minimally invasive methods for identifying gastrointestinal tract tumors are thus imperative. Blood- or serum-based biomarkers may thus improve the screening and diagnosis of gastrointestinal tract tumors [29]. Blood biomarkers generally have low sensitivity, ranging from 36.8% to 62.3% [30-32].

Blood biomarkers currently used in digestive system tumor testing include CEA, CA19-9, and CA72-4, although some patients show no detectable levels of CEA or CA19-9 [33-35]. There is currently a need to identify novel and sensitive digestive system tumor-associated biomarkers that may be utilized in the prognosis and treatment of patients with gastrointestinal tract tumors [36].

The function of circRNAs in human cancer

CircRNAs are widely involved in various physiological and pathological processes, which include acting as an miRNA sponge [4], binding RBPs [5], and translating peptides [6,37]. CircRNAs acting as miRNA sponges are generally related to tumorigenesis. These harbor several miRNA binding sites that regulate miRNA and downstream gene expression through a ceRNA mechanism, thereby contributing to tumor progression. Several studies have focused on the function of circRNAs in human cancer [38]. CircRNAs are abundant in blood and in higher amounts than corresponding linear mRNAs, thereby suggesting that circRNAs may be utilized as novel biomarkers in standard clinical blood samples [39].

Serum exosomes are membrane vesicles that are secreted by maternal cells that contain various proteins, mRNAs, and miRNAs and have various functions including transmitting biological information and regulating the behavior of recipient cells [40,41]. More than 1,000 kinds of circRNAs occur in exosomes, and the enrichment degree of circRNAs (exo-circRNAs) is significantly greater than mother cells that secrete the vesicles; therefore, the circRNA/linRNA ratio in exosomes is also 6 - 10 times that of the mother cell [18]. This conclusion has been extensively validated in lung, colorectal, breast, stomach, liver, and cervical cancer cell lines [9]. Exo-circRNAs resist degradation by RNA exonuclease and maintain stability after 24 hours of incubation in serum at room temperature. They can eliminate the inhibitory function of miRNAs in recipient cells. Exo-circRNAs have been shown to stably exist in serum and retain their original ring-like structure and biological function. Furthermore, their abundance is closely related to the extent of the tumor load [18,42].

CircRNAs and colorectal cancer

A global reduction in circRNA abundance has been reported in CRC cell lines and tissues compared with that in healthy tissues, which in turn is correlated with uncontrolled cell proliferation [43,44]. CircRNAs were first associated with CRC using transcripts of DCC (deleted in CRC) [45]. The expression of circRNAs was reduced in tumor samples compared with that in normal colon mucosa samples. Similar findings were reported in 11 CRC cell lines, with even wider gaps in expression ratios [46]. A similar negative correlation between the circRNA index and proliferation has been observed in colon tissues and cell lines [46]. The back-splice machinery responsible for RNA circularization is dysfunctional in tumor cells, and this is due to an increase in its degradation by onco miRNAs [46,47]. An upregulated circRNA (circ_001569) has been reported to complex with the tumor suppressor miR-145 [48]. MiR-145 has been associated with patient survival after CRC diagno-

sis [49-51]. Expression of circ_001569 is significantly higher in the CRC tissues (n = 30) and is correlated with CRC aggressiveness, including distant metastasis and poor differentiation. It is overexpressed in SW480 and HCT116 and silenced in SW620 and LOVO. Overexpression of circ_001569 increases the proliferative and invasive ability, whereas silencing of circ_001569 decreases proliferation and invasion rates. Circ_001569 increased the expression of E2F5, BAG4, and FMNL2 in SW480 and HCT116 cells, and knockdown of the circRNA in SW620 and LOVO cells had the opposite effect. Circ_001569 directly inhibits the regulatory activity of miR-145 in CRC cells and subsequently upregulates its protein targets E2F5, BAG4, and FMNL2 [48, 52].

Hsa_circ_001988 is downregulated in CRC [14]. CircRNAs are enriched with CRC serum exosomes, thereby facilitating its differentiation from healthy controls [18]. CircRNAs have an extracellular function and significant translational potential as a circulating biomarker for cancer diagnosis. Cir-ITCH expression is downregulated in CRC, and cir-ITCH increases the level of ITCH and participates in the inhibition of the Wnt/β-catenin pathway. Cir-ITCH participates in the Wnt/β-catenin pathway in CRC [53].

CircRNAs and hepatocellular carcinomas

Hsa_circ_0001649 is significantly downregulated in HCC tissues (n = 89) and may be a potential biomarker for HCC [15]. ZKSCAN1 is expressed in both linear RNA and circular RNA (circZKSCAN1) and forms in HCC tissues and cell lines. Both ZKSCAN1 mRNA and circZKSCAN1 are downregulated in the HCC samples compared with normal tissues (n = 102). The downregulation of ZKSCAN1 mRNA is associated with tumor size, and cirZKSCAN1 expression levels are associated with changes in tumor numbers, cirrhosis, vascular invasion, microscopic vascular invasion, and tumor grade. Silencing both ZKSCAN1 mRNA and circZKSCAN1 promotes cell proliferation, migration, and invasion. However, the overexpression of both forms of RNA represses HCC progression *in vivo* and *in vitro*. Cir-ZKSCAN1 may thus be a useful marker for the diagnosis of HCC [54].

Hsa_circ_0005075 is differentially expressed in HCC tissues as indicated by microarray analysis and validated by real-time qRT-PCR (n = 60, $p < 0.001$). The expression level of Hsa_circ_0005075 is associated with tumor size. Hsa_circ_0005075 may participate in cell adhesion during HCC development [55].

CircRNAs and gastric cancer

A total of 46 differentially expressed circRNAs were identified by a circRNA microarray of cancer and adjacent normal tissues, of which 8 were selected as potential indicators of early cancer recurrence. qRT-PCR showed that four circRNAs were differentially expressed between cancer and normal gastric tissues and may be potentially utilized as an indicator for early recurrence of stage III gastric cancer after radical surgery [56].

Hsa_circ_002059 is significantly downregulated in gastric cancer tissues compared with matched adjacent nontumor tissues. The lower expression levels were significantly correlated with distal metastasis and TNM stage [57]. Using Agilent microarray technology to profile circRNA expression of GC tissues and normal tissues, a total of 1,285 differentially expressed circRNAs were identified. The expression profiles of hsa_circRNA_400071, hsa_circRNA_000543, and hsa_circRNA_001959 coincided with the microarray analysis results. Further analysis of the interactions between circRNAs and miRNAs are warranted [58].

Prospects

CircRNAs are novel molecules that were initially considered to be products of transcriptional errors. Mature circRNAs are formed using two mechanisms that differ from selective splicing in linear RNAs; however, further details of its molecular mechanism remain unclear. There may be a third mechanism involving the formation of retained-intron circRNAs that contain both exons and introns, and this has also yet to be explored. Moreover, different types of proteins and miRNAs have been found to take part in the processing of pre-RNAs to produce circRNAs. The mechanism of circRNA formation has yet to be discovered.

Extensive studies indicate that circRNAs regulate other genes at the transcriptional and posttranscriptional levels. Some can even directly encode proteins and are thus involved in physiological and pathological processes, including influencing tumorigenesis. CircRNAs are thought to act as miRNA sponges that specifically bind to miRNAs and regulate gene expression by competing with competing endogenous RNA (ceRNA), including lncRNAs, mRNAs, and pseudogenes.

The participation of circRNAs in the ceRNA network renders it more complete and complex. CircRNAs compete with mRNAs from the same pre-RNAs during the splicing process, and circRNAs were recently found to encode proteins. This demonstrates their involvement in biological procedures, provides a more complete understanding of the RNA language, and enriches the central dogma. Our current understanding of circRNAs is limited, and the function of roughly 30,000 molecules have yet to be established.

CircRNAs have unique structures and are much more stable than linear RNAs, thereby allowing them to remain in the tissues and sera of patients. The differential expression of circRNAs in tissues and blood of cancer patients, which is lower than that of miRNAs and lncRNAs, suggests that they may be utilized as specific biomarkers for gastrointestinal cancers.

CircRNAs may also serve as potential targets for new drugs. These also function as miRNA sponges.

CONCLUSION

In China, the 5-year relative survival rate of patients with gastrointestinal tract tumors continues to increase. Thus, screening for novel molecular markers is essential for the diagnosis and prognosis of gastrointestinal tract tumors. CircRNAs are promising biomarkers for clinical applications for gastrointestinal tract tumors.

Declaration of Interest:
The authors declare that they have no conflict of interest regarding the publication of this paper.

References:

1. Kolakofsky D. Isolation and characterization of Sendai virus DI-RNAs. Cell 1976;8(4):547-55 (PMID: 182384).
2. Pasman Z, Been MD, Garcia-Blanco MA. Exon circularization in mammalian nuclear extracts. RNA 1996;2(6):603-10 (PMID: 8718689).
3. Cocquerelle C, Mascrez B, Hetuin D, Bailleul B. Mis-splicing yields circular RNA molecules. FASEB J 1993;7(1):155-60 (PMID: 7678559).
4. Hansen TB, Jensen TI, Clausen BH, et al. Natural RNA circles function as efficient microRNA sponges. Nature 2013;495(7441):384-8 (PMID: 23446346).
5. Li Z, Huang C, Bao C, et al. Exon-intron circular RNAs regulate transcription in the nucleus. Nat Struct Mol Biol 2015;22(3):256-64 (PMID: 25664725).
6. Granados-Riveron JT, Aquino-Jarquin G. The complexity of the translation ability of circRNAs. Biochim Biophys Acta 2016;1859(10):1245-51 (PMID: 27449861).
7. Szabo L, Salzman J. Detecting circular RNAs: bioinformatic and experimental challenges. Nat Rev Genet 2016;17(11):679-92 (PMID: 27739534).
8. Wilusz JE, Sharp PA. Molecular biology. A circuitous route to noncoding RNA. Science 2013;340(6131):440-1 (PMID: 23620042).
9. Salzman J, Gawad C, Wang PL, Lacayo N, Brown PO. Circular RNAs are the predominant transcript isoform from hundreds of human genes in diverse cell types. PloS One 2012;7(2):e30733 (PMID: 22319583).
10. Chen L, Huang C, Wang X, Shan G. Circular RNAs in Eukaryotic Cells. Curr Genomics 2015;16(5):312-8 (PMID: 27047251).
11. Chen I, Chen CY, Chuang TJ. Biogenesis, identification, and function of exonic circular RNAs. Wiley Interdiscip Rev RNA 2015;6(5):563-79 (PMID: 26230526).
12. Jeck WR, Sorrentino JA, Wang K, et al. Circular RNAs are abundant, conserved, and associated with ALU repeats. RNA 2013;19(2):141-57 (PMID: 23249747).
13. Jeck WR, Sharpless NE. Detecting and characterizing circular RNAs. Nat Biotechnol 2014;32(5):453-61 (PMID: 24811520).
14. Wang X, Zhang Y, Huang L, et al. Decreased expression of hsa_circ_001988 in colorectal cancer and its clinical significances. Int J Clin Exp Pathol 2015;8(12):16020-5 (PMID: 26884878).
15. Qin M, Liu G, Huo X, et al. Hsa_circ_0001649: A circular RNA and potential novel biomarker for hepatocellular carcinoma. Cancer Biomark 2016;16(1):161-9 (PMID: 26600397).
16. Xuan L, Qu L, Zhou H, et al. Circular RNA: a novel biomarker for progressive laryngeal cancer. Am J Transl Res 2016;8(2):932-99 (PMID: 27158380).
17. Zeng J, Du T, Song Y, et al. Knockdown of long noncoding RNA CCAT2 inhibits cellular proliferation, invasion, and EMT in glioma cells. Oncol Res 2016 Epub 2016 Nov 17 (PMID: 27938499).
18. Li Y, Zheng Q, Bao C, et al. Circular RNA is enriched and stable in exosomes: a promising biomarker for cancer diagnosis. Cell Res 2015;25(8):981-4 (PMID: 26138677).
19. Guarnerio J, Bezzi M, Jeong JC, et al. Oncogenic Role of Fusion-circRNAs Derived from Cancer-Associated Chromosomal Translocations. Cell 2016;165(2):289-302 (PMID: 27040497).
20. Vicens Q, Westhof E. Biogenesis of Circular RNAs. Cell 2014;159(1):13-4 (PMID: 25259915).
21. Qu S, Yang X, Li X, et al. Circular RNA: A new star of noncoding RNAs. Cancer Lett 2015;365(2):141-8 (PMID: 26052092).
22. Zheng Q, Bao C, Guo W, et al. Circular RNA profiling reveals an abundant circHIPK3 that regulates cell growth by sponging multiple miRNAs. Nat Commun 2016;7:11215 (PMID: 27050392).
23. Chen LL, Yang L. Regulation of circRNA biogenesis. RNA Biol. 2015.12(4):381-8 (PMID: 25746834).
24. Conn SJ, Pillman KA, Toubia J, et al. The RNA binding protein quaking regulates formation of circRNAs. Cell 2015;160(6):1125-34 (PMID: 25768908).
25. Yang W, Du WW, Li X, Yee AJ, Yang BB. Foxo3 activity promoted by non-coding effects of circular RNA and Foxo3 pseudogene in the inhibition of tumor growth and angiogenesis. Oncogene 2016;35(30):3919-31 (PMID: 26657152).
26. Salzman J: Circular RNA Expression: Its Potential Regulation and Function. Trends Genet 2016;32(5):309-16 (PMID: 27050930).
27. Hamashima C, Shibuya D, Yamazaki H, et al. The Japanese guidelines for gastric cancer screening. Jpn J Clin Oncol 2008;38(4):259-67 (PMID: 18344316).
28. Leja M, You W, Camargo MC, Saito H. Implementation of gastric cancer screening - the global experience. Best Pract Res Clin Gastroenterol 2014;28(6):1093-106 (PMID: 25439074).
29. Stemmermann GN, Samloff IM, Nomura AM, Heilbrun LK. Serum pepsinogens I and II and stomach cancer. Clin Chim Acta 1987;163(2):191-8 (PMID: 3568423).
30. Mizuno S, Kobayashi M, Tomita S, et al. Validation of the pepsinogen test method for gastric cancer screening using a follow-up study. Gastric Cancer 2009;12(3):158-63 (PMID: 19890696).
31. Yanaoka K, Oka M, Mukoubayashi C, et al. Cancer high-risk subjects identified by serum pepsinogen tests: outcomes after 10-year follow-up in asymptomatic middle-aged males. Cancer Epidemiol Biomarkers Prev 2008;17(4):838-45 (PMID: 18398025).

32. Kang JM, Kim N, Yoo JY, et al. The role of serum pepsinogen and gastrin test for the detection of gastric cancer in Korea. Helicobacter 2008;13(2):146-56 (PMID: 18321304).

33. Tian SB, Yu JC, Kang WM, et al. Combined detection of CEA, CA 19-9, CA 242 and CA 50 in the diagnosis and prognosis of resectable gastric cancer. Asian Pac J Cancer Prev 2014,15(15): 6295-300 (PMID: 25124614).

34. Zhou YC, Zhao HJ, Shen LZ. Preoperative serum CEA and CA19-9 in gastric cancer--a single tertiary hospital study of 1,075 cases. Asian Pac J Cancer Prev 2015;16(7):2685-91 (PMID: 258 54347).

35. Mattar R, Alves de Andrade CR, DiFavero GM, Gama-Rodrigues JJ, Laudanna AA. Preoperative serum levels of CA 72-4, CEA, CA 19-9, and alpha-fetoprotein in patients with gastric cancer. Rev Hosp Clin Fac Med Sao Paulo 2002;57(3):89-92 (PMID: 12118264).

36. Zhao J, Liu Y, Huang G, Cui P, Zhang W, Zhang Y. Long non-coding RNAs in gastric cancer: versatile mechanisms and potential for clinical translation. Am J Cancer Res 2015;5(3):907-27 (PMID: 26045977).

37. Wang Y, Wang Z. Efficient backsplicing produces translatable circular mRNAs. RNA 2015;21(2):172-9 (PMID: 25449546).

38. Dong Y, He D, Peng Z, et al. Circular RNAs in cancer: an emerging key player. J Hematol Oncol 2017;10(1):2 (PMID: 280494 99).

39. Memczak S, Papavasileiou P, Peters O, Rajewsky N. Identification and Characterization of Circular RNAs As a New Class of Putative Biomarkers in Human Blood. PloS One 2015;10(10): e0141214 (PMID: 26485708).

40. Zhang L, Zhang S, Yao J, et al. Microenvironment-induced PTEN loss by exosomal microRNA primes brain metastasis outgrowth. Nature 2015;527(7576):100-4 (PMID: 26479035).

41. Pant S, Hilton H, Burczynski ME. The multifaceted exosome: biogenesis, role in normal and aberrant cellular function, and frontiers for pharmacological and biomarker opportunities. Biochem Pharmacol 2012;83(11):1484-94 (PMID: 22230477).

42. Liu J, Liu T, Wang X, He A. Circles reshaping the RNA world: from waste to treasure. Mol Cancer 2017;16(1):58 (PMID: 28279 183).

43. Yang Y, Du Y, Liu X, Cho WC. Involvement of Non-coding RNAs in the Signaling Pathways of Colorectal Cancer. Adv Exp Med Biol 2016;937:19-51 (PMID: 27573893).

44. Arvelo F, Sojo F, Cotte C. Biology of colorectal cancer. Ecancermedicalscience 2015;9:520 (PMID: 25932044).

45. Nigro JM, Cho KR, Fearon ER, et al. Scrambled exons. Cell 1991;64(3):607-13 (PMID: 1991322).

46. Bachmayr-Heyda A, Reiner AT, Auer K, et al. Correlation of circular RNA abundance with proliferation--exemplified with colorectal and ovarian cancer, idiopathic lung fibrosis, and normal human tissues. Sci Rep 2015;5:8057 (PMID: 25624062).

47. Ragusa M, Barbagallo C, Statello L, et al. Non-coding landscapes of colorectal cancer. World J Gastroenterol 2015;21(41):11709-39 (PMID: 26556998).

48. Xie H, Ren X, Xin S, et al. Emerging roles of circRNA_001569 targeting miR-145 in the proliferation and invasion of colorectal cancer. Oncotarget 2016;7(18):26680-91 (PMID: 27058418).

49. Li JM, Zhao RH, Li ST, et al. Down-regulation of fecal miR-143 and miR-145 as potential markers for colorectal cancer. Saudi Med J 2012;33(1):24-9 (PMID: 22273643).

50. Slattery ML, Wolff E, Hoffman MD, Pellatt DF, Milash B, Wolff RK. MicroRNAs and colon and rectal cancer: differential expression by tumor location and subtype. Genes Chromosomes Cancer 2011;50(3):196-206 (PMID: 21213373).

51. Michael MZ, SM OC, van Holst Pellekaan NG, Young GP, James RJ. Reduced accumulation of specific microRNAs in colorectal neoplasia. Mol Cancer Res 2003;1(12):882-91 (PMID: 145 73789).

52. Taborda MI, Ramirez S, Bernal G. Circular RNAs in colorectal cancer: Possible roles in regulation of cancer cells. World J Gastrointest Oncol 2017;9(2):62-9 (PMID: 28255427).

53. Huang G, Zhu H, Shi Y, Wu W, Cai H, Chen X. cir-ITCH plays an inhibitory role in colorectal cancer by regulating the Wnt/beta-catenin pathway. PloS One 2015;10(6):e0131225 (PMID: 261106 11).

54. Yao Z, Luo J, Hu K, et al. ZKSCAN1 gene and its related circular RNA (circZKSCAN1) both inhibit hepatocellular carcinoma cell growth, migration, and invasion but through different signaling pathways. Mol Oncol 2017;11(4):422-37 (PMID: 28211215).

55. Shang X, Li G, Liu H, et al. Comprehensive Circular RNA Profiling Reveals That hsa_circ_0005075, a New Circular RNA Biomarker, Is Involved in Hepatocellular Crcinoma Development. Medicine (Baltimore) 2016;95(22):e3811 (PMID: 27258521).

56. Zhang Y, Li J, Yu J, et al. Circular RNAs signature predicts the early recurrence of stage III gastric cancer after radical surgery. Oncotarget 2017 Apr 4;8(14):22936-43 (PMID: 28206972).

57. Li P, Chen S, Chen H, et al. Using circular RNA as a novel type of biomarker in the screening of gastric cancer. Clin Chim Acta 2015;444:132-6 (PMID: 25689795).

58. Sui W, Shi Z, Xue W, et al. Circular RNA and gene expression profiles in gastric cancer based on microarray chip technology. Oncol Rep 2017;37(3):1804-14 (PMID: 28184940).