

# Circular RNAs in thoracic diseases

Fan Yang, Ping Zhu, Jintao Guo, Xiang Liu, Sheng Wang, Guoxin Wang, Wen Liu, Shupeng Wang, Nan Ge

Endoscopy Center, Shengjing Hospital of China Medical University, Shenyang 110004, China

*Contributions:* (I) Conception and design: N Ge, J Guo; (II) Administrative support: X Liu, S Wang; (III) Provision of study materials or patients: S Wang, W Liu; (IV) Collection and assembly of data: F Yang, P Zhu; (V) Data analysis and interpretation: F Yang, G Wang; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

*Correspondence to:* Nan Ge. Endoscopy Center, Shengjing Hospital of China Medical University, Shenyang 110004, China. Email: gen@sj-hospital.org.

**Abstract:** Circular RNAs (circRNAs) are a class of noncoding RNAs with continuous, covalently closed circular structures. Investigators have shown previously that circRNAs are regulators of gene expression in mammals. These tissue-specific transcripts are produced primarily by exonic or intronic sequences of housekeeping genes. Several biosynthetic models have been proposed for circRNAs, and consensus is lacking. CircRNAs are widely expressed in the cytoplasm and highly conserved, what is more, unlike other noncoding RNAs, circRNAs are relatively stable. These properties suggest special roles of circRNAs, such as microRNA (miRNA) sponges, regulators of selective splicing, or even protein-coding sequences. The expression of circRNAs is associated with many pathologic conditions; therefore, circRNAs may have utility as biomarker for the diagnosis or prediction of diseases. Authors previously have demonstrated that circRNAs can regulate the expression of a variety of disease-related miRNAs. The circRNA-miRNA-target gene interaction network regulates several pathways that inhibit or promote the occurrence of certain diseases. Based on their potential clinical relevance, circRNAs are a crucial topic of disease prevention and treatment research. Herein, we review current research regarding circRNAs and explore their potential clinical applications for thoracic diseases diagnosis and treatment.

**Keywords:** Circular RNAs (circRNAs); thoracic diseases; diagnosis; treatment

Submitted Jun 13, 2017. Accepted for publication Oct 23, 2017.

doi: 10.21037/jtd.2017.10.143

View this article at: <http://dx.doi.org/10.21037/jtd.2017.10.143>

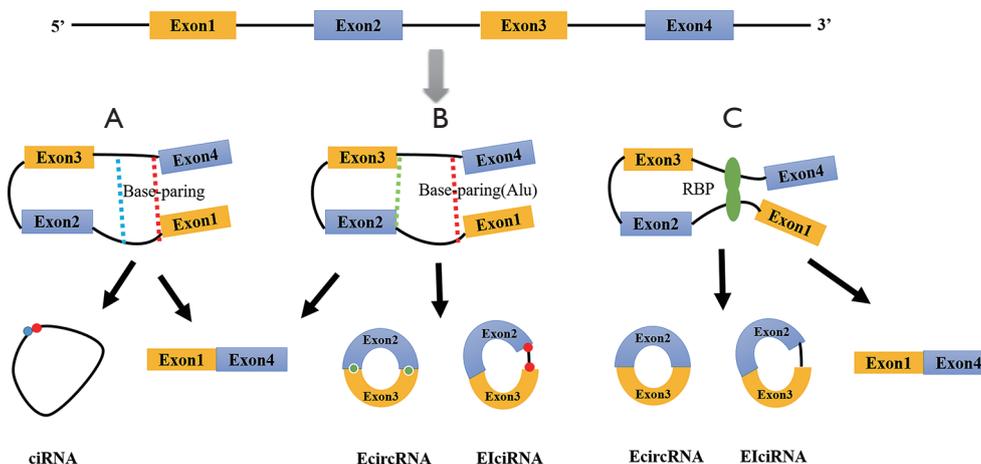
## Introduction

In the 1970s, circular RNAs (circRNAs) were identified as byproducts of RNA transcription with high thermal stability (1,2). With the emergence of next-generation sequencing—including RNA-sequencing technology—circRNAs have been further elucidated as a new class of noncoding RNAs with regulatory functions. Unlike linear RNAs, circRNAs are characterized by covalently closed loops with stable ring structure, species conservatism, and tissue specificity; these molecules are not readily cleaved by nucleases (3). Derived from exonic or intronic gene regions, circRNAs are abundant in eukaryotes and have been garnering attention because of their specificity of expression, complexity of regulation, and important role in pathogenesis (4-7). Like microRNAs (miRNAs) and long noncoding RNAs,

circRNAs have become a new research hotspot in the RNA field. This review focuses on new advances in the field of circRNAs and summarizes the relationship between circRNAs and thoracic diseases.

## Biosynthetic mechanism of circRNAs

With developments in RNA-sequencing and bioinformatics analyses, the total number of known circRNAs has reached more than 30,000 (8-10). The complexity of circRNA expression in certain species is correlated with its evolutionary degree (11). Despite the large number of circRNAs and their diverse distribution among species, the precise biosynthetic mechanism of circRNAs still is unclear. The results of recent investigations have demonstrated some general biosynthetic processes of circRNAs. A



**Figure 1** Biosynthesis models of circRNAs. (A) CiRNA formation by direct back-splicing; (B) ecircRNA and EIciRNA formation by direct back-splicing; (C) ecircRNA and EIciRNA formation by lariat-driven circularization.

rapid transcription event is coordinated by cis-regulatory elements, such as reverse complementary sequences or sequences recognized by RNA-binding proteins (RBPs), and intracellular accumulation results, similar to linear RNA biosynthesis (12). A single gene may encode multiple molecular forms of circRNAs, and once transcribed, circRNAs undergo alternative splicing (13) to yield circRNA-unique cassette exons that are absent of linear RNAs (14). The biosynthetic processes of certain tissue-specific or disease-specific circRNAs appears to be precisely regulated (15).

Two biosynthetic models have been proposed for circRNAs: direct back-splicing (6) and lariat-driven circularization (16,17) (Figure 1). In the model of direct back-splicing, circRNA biosynthesis involves noncanonical RNA splicing. Exons of pre-RNA connect the downstream 5' splice site to an upstream 3' splice site to generate a circRNA. Reverse-complementary sequences in introns are needed for this process (e.g., Alu elements with opposite directions) (18). The reverse-complementary sequence of introns in RNA splicing also may directly help the introns form circRNAs (19). This model can explain the biosynthesis of ciRNAs (i.e., circRNAs derived from introns), EIciRNAs (i.e., circRNAs derived from both exons and introns), and ecircRNAs (i.e., circRNAs derived from exons).

In the model of lariat-driven circularization, the introns “skip” multiple exons to form an O-shaped lariat during the splicing process of pre-RNA. This could isolate exon-containing RNA fragments and yield ecircRNAs

or EIciRNAs after exon splicing. Some RBPs (20-22) may be involved in this process, including the RNA splicing protein Quaking (QKI), a regulator of circRNA biosynthesis during human epithelial-mesenchymal transition (20). The role of QKI in the biosynthesis of circRNAs from pre-RNA indicates that the process is not stochastic but rather is a complex system regulated by specific cellular mechanisms (20).

Studies addressing circRNAs often involve large-scale histological screening to identify and evaluate specific circRNA molecules. Many circRNAs remain uncharacterized with regard to specific conditions of biosynthesis, the dynamic process, and the relationship between other linear and circRNAs of the same corresponding gene (23).

### Functions of circRNAs and their roles in thoracic diseases

Hallmarks of circRNAs are huge quantities, a high degree of sequence diversity, and tissue and disease specificity (24). As such, circRNAs have no common mode of action and regulate gene expression and protein synthesis in many different ways. The results of current research suggest that circRNAs function via four mechanisms: (I) circRNAs regulate parental gene expression in cis via polymerase II (Pol II) (5,19); (II) circRNAs can act as competitive endogenous RNAs (ceRNAs) to regulate gene expression by miRNA sponge effects (25-27); (III) circRNAs play biological functions through the formation of complexes with proteins

**Table 1** The roles of circRNAs in thoracic diseases and their possible mechanisms

CircRNAs	Diseases	Features and potential function	Ref.
hsa_circ_0067934	ESCC	Correlate with tumor stage and inhibit cell proliferation	(34)
Cir-ITCH	ESCC; lung cancer	Sponge miR-7, miR-17, and miR-214 to increase ITCH expression, then degrade Dvl2 phosphorylation to further inhibit the Wnt signaling pathway	(35,36)
CircRNA_001059, CircRNA_000167	Esophageal cancer	RT resistance	(37)
CDR1as	Lung cancer	Sponge miR-7 to inhibit apoptosis of cancer cells	(38)
	MI	Sponge miR-7a to regulate PARP and SP1	(39)
Circ-ZEB1	Lung cancer	Sponge miR-200 to regulate ZEB1 expression	(40)
Circ_100876	NSCLC	Correlate with tumor stage and survival time	(41)
CircSLC8A1-1	Heart disease	Most abundant heart-specific circRNAs	(42)
RBM20-dependent TTN circRNAs	DCM	Correlate with pathogenesis of DCM	(43)
HRCR	HCM	Sponge miR-233 to regulate ARC	(44)
CircRNA_081881	AMI	Sponge miR-548 to regulate PPAR $\gamma$	(45)
MICRA	MI	Predict LV function	(46)
hsa_circ_0124644	CAD	Diagnostic biomarker	(47)
CircRNA_000203	MF	Sponge miR-26b-5p to regulate Colla2 and CTGF	(48)

ESCC, esophageal squamous cell carcinoma; RT, radiation therapy; MI, myocardial infarction; LV, left ventricular; NSCLC, non-small cell lung cancer; DCM, dilated cardiomyopathy; HCM, hypertrophic cardiomyopathy; AMI, acute myocardial infarction; CAD, coronary artery disease; MF, myocardial fibrosis; TTN, titin; ARC, apoptosis repressor with CARD domain.

(21,28); and (IV) circRNAs can translate protein via base-modification N<sup>6</sup>-methyladenosine (m<sup>6</sup>A) (29).

Evidence regarding the structure and functions of circRNAs has indicated that these molecules play a significant role in the pathogenesis of atherosclerosis (30), neurological disorders (31), diabetes (32), cancer (8), and other diseases (33). Herein, we summarize the role of circRNAs in thoracic diseases and their possible mechanisms (Table 1).

### CircRNAs in esophageal cancer

Esophageal cancer is among the most prevalent of the thoracic and digestive cancers. Esophageal squamous cell carcinoma (ESCC) is the most deadly of these cancers, and the prognosis of ESCC remains poor (34). CircRNA hsa\_circ\_0067934 was found to be upregulated in ESCC and promote cell proliferation (35). In a retrospective analysis of 51 patients with ESCC, the expression of circRNA hsa\_circ\_0067934 was significantly higher in the tumor than in adjacent tissues. Moreover, expression of hsa\_circ\_0067934

was positively correlated with tumor stage. Results of *in vitro* analyses suggested that hsa\_circ\_0067934 interference significantly inhibited cell proliferation and led to cell cycle arrest (35). In another study of ESCC in which 684 tumors were compared with paired adjacent nontumor tissues, the expression level of the circRNA cir-ITCH generally was low in ESCC. This molecule competitively sponged miR-7, miR-17, and miR-214, leading to an increase in ITCH expression, the latter of which could degrade Dvl2 phosphorylation and inhibited Wnt signaling pathways to block the growth of ESCC (37).

Radiation therapy (RT) is essential in the treatment of esophageal cancer; however, RT resistance can diminish the therapeutic effects of RT and can lead to local tumor recurrence or treatment failure. Su *et al.* observed differential expression of circRNAs between the RT-resistant esophageal cancer cell line, KYSE-150R, and its parental cell line, KYSE-150 (37). In the study, these authors identified 57 upregulated and 17 downregulated circRNAs. CircRNA\_001059 and circRNA\_000167 were considered most likely to be associated with RT

resistance of KYSE-150 (49). However, these authors did not determine the mechanism by which these circRNAs influence RT resistance.

### ***CircRNAs in lung cancer***

Lung cancer is one of the most common cancers and is the leading cause of cancer-related deaths worldwide (38). CircRNA CDR1as was found to be frequently coexpressed with the miRNA miR-7 in lung cancer. Elevated miR-7 was associated with poor prognosis of lung cancer. Moreover, CDR1as could sponge a large number of miR-7, incrementally inducing miR-7 inhibition and apoptosis in lung cancer cell lines. In combination with CDR1as, miR-671 could activate endonucleolytic cleavage, induce breakage in CDR1as, and release sponged miR-7 (36). Furthermore, cir-ITCH can suppress lung cancer proliferation via the same mechanism as in ESCC (40). The ZEB1 gene-derived circRNA can act as a ceRNA and sponge miR-200, a well-known lung cancer-related miRNA that has been shown to function as a regulator of ZEB1 gene expression in lung cancer. Thus, ZEB1 gene-derived circRNA affects lung cancer by competing with miR-200 (50).

Non-small cell lung cancer (NSCLC) accounts for approximately 85% of all primary cases of lung cancer, and the prognosis is poor (41). A major breakthrough in NSCLC research was the identification of circRNA\_100876, a novel prognostic biomarker for NSCLC. The expression of circRNA\_100876 was significantly elevated in NSCLC tissue compared with paired adjacent nontumor tissues, and levels of this circRNA were closely correlated with lymph node metastasis and tumor staging in NSCLC. Results of Kaplan-Meier survival analysis indicated that the overall survival time of NSCLC patients with low levels of circRNA\_100876 expression was significantly longer than those with high levels of circRNA\_100876 (51).

### ***CircRNAs in heart disease***

CircRNAs are closely related to cardiac development, physiology, and pathology. Werfel *et al.* analyzed the expression and localization of circRNAs in tissues from humans, mice, and rats at different developmental stages and in physiologic and pathologic conditions. The authors suggested that circRNAs were closely related to heart function, but the mechanism involved required further

exploration. In particular, several highly conserved circRNA molecules arising from the *titin* (*TTN*) gene were of great research value (42) in the field of biomarkers or their mechanisms. Another group evaluated the expression profiles of circRNAs in heart specimens of humans and mice by means of RNA-sequencing. These investigators showed that the expression levels of 15,318 circRNAs in human myocardial tissue and 3,017 circRNAs in mouse tissue were generally correlated with the expression levels of their cognate linear RNAs. Moreover, myocardium-specific genes—such as *TTN*, *RYR2*, and *DMD*—had the highest content of circRNAs. The most abundant circRNA was circSLC8A1-1 (52). These findings open a new avenue of research regarding circRNAs in heart disease.

### ***CircRNAs in dilated cardiomyopathy (DCM)***

DCM is a chief cause of heart failure (43). In a recent study, authors suggested that the RNA-binding motif protein 20 (RBM20), an important pathogenic gene of DCM, regulated the biosynthesis of circRNAs from the *TTN* gene. Results of this study may lend insight into the pathogenesis of DCM. The authors performed circRNA profiling with hypertrophic cardiomyopathy (HCM) and unaffected heart tissues. Eighty circRNAs were found to be expressed from the *TTN* gene. Some of these were specifically regulated in DCM rather than HCM and corresponded to a region inside *TTN* gene called the I-band, an important site related to sarcomere strength. Investigators previously had shown that RBM20 was involved in RNA splicing associated with the I-band region. A mutation in RBM20 could lead to abnormal splicing in the I-band region, which could in turn affect functioning of the *TTN* protein. RBM20 null mice had no detectable expression of these *TTN* circRNAs. The investigators concluded that these RBM20-dependent *TTN* circRNAs are highly correlated with pathogenesis of DCM (53).

### ***CircRNAs in HCM***

HCM is another major cause of heart failure (44). Wang *et al.* determined that a novel circRNA termed HRCR could act as an endogenous miR-223 sponge to inhibit and sequester miR-223 activity, resulting in elevated expression of the apoptosis repressor with CARD domain (ARC) (45). MiR-223 and ARC then were found to influence HCM and heart failure in mice. The regulatory pathway comprising HRCR, miR-223, and ARC may have utility as therapeutic targets for the treatment of HCM and heart failure (45).

### CircRNAs in myocardial infarction (MI)

Acute myocardial infarction (AMI) poses sizeable morbidity and mortality risks (39). In a study of circRNA expression in human AMI, Deng *et al.* found that 160 circRNAs were differentially expressed in plasma samples between AMI patients and healthy volunteers. Of these, circRNA\_081881 was substantially downregulated in AMI and contained seven competitive binding sites for miR-548. Results of additional bioinformatics analysis showed that miR-548 could regulate the *PPAR $\gamma$*  gene, a heart-protective factor, in AMI. The pathway constituting circRNA\_081881–miR-548–*PPAR $\gamma$*  was found to influence foam-cell formation (46). In addition to its role in lung cancer, CDR1as promotes MI by sponging miR-7a on expression of its target genes, including *PARP* and *SPI* (47).

After MI, identification of left ventricular (LV) remodeling and dysfunction would be beneficial for personalized medicine. A novel biomarker predicting LV function and outcomes of MI was found: the circRNA MICRA was specific to patients with MI, and detection of MICRA in peripheral blood was predictive of LV function (48).

### CircRNAs in coronary artery disease (CAD)

Zhao *et al.* determined that 22 peripheral blood circRNAs had substantially different levels of expression between patients with CAD and controls. Further study revealed that hsa\_circ\_0124644 obtained the best AUC (i.e., area under the curve). In a large independent cohort study comprising 137 patients in the CAD group and 115 patients in the control group, it was shown that hsa\_circ\_0124644 could be used as a diagnostic biomarker for CAD (54).

### CircRNAs in myocardial fibrosis (MF)

MF is closely related to hypertension, chronic heart failure, HCM, DCM, diabetes, and other diseases and serves as a potential risk factor for sudden cardiac death (55). Tang *et al.* found that circRNA\_000203 was upregulated in the myocardium in a mouse model of diabetes. This suggested a signaling pathway in the regulation of MF: miR-26b-5p binds to the 3'-UTR (i.e., untranslated region) of *Col1a2* and *CTGF* and prevents their expression. CircRNA\_000203 acted as a ceRNA, and its combination with miR-26b-5p could promote the expression of genes related to MF (56).

### Conclusions and perspectives

Current research regarding circRNAs is in the early stages, but many investigators have demonstrated that

circRNAs likely are formed by direct back-splicing or lariat-driven circularizing pre-RNA and function in regulating transcription or modifying protein. Mechanisms of circRNA biogenesis, regulation, and associated biological functions are not understood fully.

Much progress has been made to elucidate the relationship between circRNAs and thoracic disease. The characteristic O-shaped closure structure of circRNAs has no free terminus. As such, circRNAs are different from linear RNAs and proteins that are easy to degrade by exonucleases, RNases, or proteases. Therefore, it is expected that clinical applications of circRNAs will be found in tissues, blood (57), saliva (58), and other bodily fluids (59). CircRNAs show promise as a new biomarker that can replace previous indicators (60), or they are possible to build novel models for prognosis together with various other biomarkers and thus improve the diagnosis accuracy and specificity of certain diseases.

Characteristics of circRNAs—including the unique role of ceRNA and protein translation via m<sup>6</sup>A—suggest that these molecules will provide new targets to interfere with disease pathogenesis and enhance treatment effects, or even as potential targets for developing new drugs (61). As mentioned before, circRNAs could mediate, or sponge miRNAs to further influence the expression of target genes, the circRNA–miRNA–target gene interaction network can also provide us some new treatment target for diseases, such as cancer, atherosclerosis (30), cardiomyopathy, and diabetes mellitus (62). On the other hand, the various peptides encoded by circRNAs can also act as potential treatment target. Moreover, fusion-circRNAs (63), first found in leukemia, and circRNAs in exosomes (64) are a lot worthy of study about their therapeutic potency.

Investigators have not implicated circRNAs in asthma, intractable cough, or several other thoracic diseases. What's more, the role of circRNAs in exosomes (64) and fusion-circRNAs in thoracic diseases remains unknown. Although multiple features of circRNAs have been determined, there remain many circRNAs that appear extraneous in thoracic disease.

The study of circRNAs broadens our understanding of the eukaryotic genome and provides new directions for comprehensive understanding of common diseases. Further research regarding circRNAs may uncover biogenesis-induced factors, functions of different types of these molecules, whether circRNAs can interact directly with the genome (akin to long noncoding RNAs), and the kinetic mechanisms of circRNA degradation. Assessments

of regulatory networks of noncoding RNAs may explain or overturn the theories of previous studies. We anticipate that the role of circRNAs will attract even more attention as research progresses.

### Acknowledgements

*Funding:* This study was supported by the National Natural Science Foundation of China (Grant No. 81470908).

### Footnote

*Conflicts of Interest:* The authors have no conflicts of interest to declare.

### References

- Sanger HL, Klotz G, Riesner D, et al. Viroids are single-stranded covalently closed circular RNA molecules existing as highly base-paired rod-like structures. *Proc Natl Acad Sci U S A* 1976;73:3852-6.
- Hsu MT, Coca-Prados M. Electron microscopic evidence for the circular form of RNA in the cytoplasm of eukaryotic cells. *Nature* 1979;280:339-40.
- Qu S, Yang X, Li X, et al. Circular RNA: A new star of noncoding RNAs. *Cancer Lett* 2015;365:141-8.
- Lu Z, Filonov GS, Noto JJ, et al. Metazoan tRNA introns generate stable circular RNAs in vivo. *RNA* 2015;21:1554-65.
- Li Z, Huang C, Bao C, et al. Exon-intron circular RNAs regulate transcription in the nucleus. *Nat Struct Mol Biol* 2015;22:256-64.
- Wang Y, Wang Z. Efficient backsplicing produces translatable circular mRNAs. *RNA* 2015;21:172-9.
- AbouHaidar MG, Venkataraman S, Golshani A, et al. Novel coding, translation, and gene expression of a replicating covalently closed circular RNA of 220 nt. *Proc Natl Acad Sci U S A* 2014;111:14542-7.
- Wang Y, Mo Y, Gong Z, et al. Circular RNAs in human cancer. *Mol Cancer* 2017;16:25.
- Salzman J, Gawad C, Wang PL, et al. Circular RNAs are the predominant transcript isoform from hundreds of human genes in diverse cell types. *PLoS One* 2012;7:e30733.
- Grouse L. Galileo in Bethesda: The future of gene editing. *J Transl Int Med* 2016;4:143-6.
- Dong R, Ma XK, Chen LL, et al. Increased complexity of circRNA expression during species evolution. *RNA Biol* 2017;14:1064-74.
- Zhang Y, Xue W, Li X, et al. The Biogenesis of Nascent Circular RNAs. *Cell Rep* 2016;15:611-24.
- Gao Y, Wang J, Zheng Y, et al. Comprehensive identification of internal structure and alternative splicing events in circular RNAs. *Nat Commun* 2016;7:12060.
- Zhang XO, Dong R, Zhang Y, et al. Diverse alternative back-splicing and alternative splicing landscape of circular RNAs. *Genome Res* 2016;26:1277-87.
- Xin Z, Ma Q, Ren S, et al. The understanding of circular RNAs as special triggers in carcinogenesis. *Brief Funct Genomics* 2017;16:80-6.
- Jeck WR, Sorrentino JA, Wang K, et al. Circular RNAs are abundant, conserved, and associated with ALU repeats. *RNA* 2013;19:141-57.
- Wilusz J. Circular RNA and Splicing: Skip Happens. *J Mol Biol* 2015;427:2411-3.
- Lev-Maor G, Ram O, Kim E, et al. Intronic Alus influence alternative splicing. *PLoS Genet* 2008;4:e1000204.
- Zhang Y, Zhang XO, Chen T, et al. Circular intronic long noncoding RNAs. *Mol Cell* 2013;51:792-806.
- Conn SJ, Pillman KA, Toubia J, et al. The RNA binding protein quaking regulates formation of circRNAs. *Cell* 2015;160:1125-34.
- Ashwal-Fluss R, Meyer M, Pamudurti NR, et al. circRNA biogenesis competes with pre-mRNA splicing. *Mol Cell* 2014;56:55-66.
- Ivanov A, Memczak S, Wyler E, et al. Analysis of intron sequences reveals hallmarks of circular RNA biogenesis in animals. *Cell Rep* 2015;10:170-7.
- Salzman J, Chen RE, Olsen MN, et al. Cell-type specific features of circular RNA expression. *PLoS Genet* 2013;9:e1003777.
- Vidal AF, Sandoval GT, Magalhaes L, et al. Circular RNAs as a new field in gene regulation and their implications in translational research. *Epigenomics* 2016;8:551-62.
- Memczak S, Jens M, Elefsinioti A, et al. Circular RNAs are a large class of animal RNAs with regulatory potency. *Nature* 2013;495:333-8.
- Hansen TB, Jensen TI, Clausen BH, et al. Natural RNA circles function as efficient microRNA sponges. *Nature* 2013;495:384-8.
- Taulli R, Loretelli C, Pandolfi PP. From pseudo-ceRNAs to circ-ceRNAs: a tale of cross-talk and competition. *Nat Struct Mol Biol* 2013;20:541-3.
- Chao CW, Chan DC, Kuo A, et al. The mouse formin (Fmn) gene: abundant circular RNA transcripts and gene-targeted deletion analysis. *Mol Med* 1998;4:614-28.

29. Yang Y, Fan X, Mao M, et al. Extensive translation of circular RNAs driven by N<sup>6</sup>-methyladenosine. *Cell Res* 2017;27:626-41.
30. Holdt LM, Stahringer A, Sass K, et al. Circular non-coding RNA ANRIL modulates ribosomal RNA maturation and atherosclerosis in humans. *Nat Commun* 2016;7:12429.
31. Floris G, Zhang L, Follesa P, et al. Regulatory Role of Circular RNAs and Neurological Disorders. *Mol Neurobiol* 2017;54:5156-65.
32. Xu H, Guo S, Li W, et al. The circular RNA Cdr1as, via miR-7 and its targets, regulates insulin transcription and secretion in islet cells. *Sci Rep* 2015;5:12453.
33. Sullenger BA, Nair S. From the RNA world to the clinic. *Science* 2016;352:1417-20.
34. Ozgul G, Cetinkaya E, Ozgul MA, et al. Efficacy and safety of electromagnetic navigation bronchoscopy with or without radial endobronchial ultrasound for peripheral lung lesions. *Endosc Ultrasound* 2016;5:189-95.
35. Xia W, Qiu M, Chen R, et al. Circular RNA has\_circ\_0067934 is upregulated in esophageal squamous cell carcinoma and promoted proliferation. *Sci Rep* 2016;6:35576.
36. Hansen TB, Kjems J, Damgaard CK. Circular RNA and miR-7 in cancer. *Cancer Res* 2013;73:5609-12.
37. Li F, Zhang L, Li W, et al. Circular RNA ITCH has inhibitory effect on ESCC by suppressing the Wnt/beta-catenin pathway. *Oncotarget* 2015;6:6001-13.
38. Dietrich CF, Jenssen C, Herth FJ. Endobronchial ultrasound elastography. *Endosc Ultrasound* 2016;5:233-8.
39. Gong XH, Yu JM, Mao Y, et al. Anticoagulant therapy for non-ST-segment elevation acute coronary syndrome in China: A multi-center observational study. *J Transl Int Med* 2016;4:25-8.
40. Wan L, Zhang L, Fan K, et al. Circular RNA-ITCH Suppresses Lung Cancer Proliferation via Inhibiting the Wnt/beta-Catenin Pathway. *Biomed Res Int* 2016;2016:1579490.
41. Arya N, Sahai AV, Paquin SC. Credentialing for endoscopic ultrasound: A proposal for Canadian guidelines. *Endosc Ultrasound* 2016;5:4-7.
42. Werfel S, Nothjunge S, Schwarzmayr T, et al. Characterization of circular RNAs in human, mouse and rat hearts. *J Mol Cell Cardiol* 2016;98:103-7.
43. Dietrich CF, Fusaroli P, Jenssen C. European Federation of Societies for Ultrasound in Medicine and Biology guidelines 2015 on interventional endoscopic ultrasound. *Endosc Ultrasound* 2016;5:143-8.
44. Dhillon SS, Harris K. Endobronchial ultrasound for the detection of chronic pulmonary artery thrombus. *Endosc Ultrasound* 2016;5:272-3.
45. Wang K, Long B, Liu F, et al. A circular RNA protects the heart from pathological hypertrophy and heart failure by targeting miR-223. *Eur Heart J* 2016;37:2602-11.
46. Deng YY, Zhang W, She J, et al. GW27-e1167 Circular RNA Related to PPAR $\gamma$  Function as ceRNA of microRNA in Human Acute Myocardial Infarction. *J Am Coll Cardiol* 2016;68:C51-2.
47. Geng HH, Li R, Su YM, et al. The Circular RNA Cdr1as Promotes Myocardial Infarction by Mediating the Regulation of miR-7a on Its Target Genes Expression. *PLoS One* 2016;11:e0151753.
48. Vausort M, Salgado-Somoza A, Zhang L, et al. Myocardial Infarction-Associated Circular RNA Predicting Left Ventricular Dysfunction. *J Am Coll Cardiol* 2016;68:1247-8.
49. Su H, Lin F, Deng X, et al. Profiling and bioinformatics analyses reveal differential circular RNA expression in radioresistant esophageal cancer cells. *J Transl Med* 2016;14:225.
50. Xie W, Yuan S, Sun Z, et al. Long noncoding and circular RNAs in lung cancer: advances and perspectives. *Epigenomics* 2016;8:1275-87.
51. Yao JT, Zhao SH, Liu QP, et al. Over-expression of CircRNA\_100876 in non-small cell lung cancer and its prognostic value. *Pathol Res Pract* 2017;213:453-6.
52. Tan WL, Lim BT, Anene-Nzulu CG, et al. A landscape of circular RNA expression in the human heart. *Cardiovasc Res* 2017;113:298-309.
53. Khan MA, Reckman YJ, Aufiero S, et al. RBM20 Regulates Circular RNA Production From the Titin Gene. *Circ Res* 2016;119:996-1003.
54. Zhao Z, Li X, Gao C, et al. Peripheral blood circular RNA hsa\_circ\_0124644 can be used as a diagnostic biomarker of coronary artery disease. *Sci Rep* 2017;7:39918.
55. Chazal RA. China may hold answers to addressing cardiovascular disease epidemic. *J Transl Int Med* 2016;4:11-3.
56. Tang CM, Zhang M, Huang L, et al. CircRNA\_000203 enhances the expression of fibrosis-associated genes by derepressing targets of miR-26b-5p, Col1a2 and CTGF, in cardiac fibroblasts. *Sci Rep* 2017;7:40342.
57. Zhang YG, Yang HL, Long Y, et al. Circular RNA in blood corpuscles combined with plasma protein factor for early prediction of pre-eclampsia. *BJOG* 2016;123:2113-8.
58. Bahn JH, Zhang Q, Li F, et al. The landscape of

- microRNA, Piwi-interacting RNA, and circular RNA in human saliva. *Clin Chem* 2015;61:221-30.
59. Qu S, Zhong Y, Shang R, et al. The emerging landscape of circular RNA in life processes. *RNA Biol* 2017;14:992-9.
60. Abu N, Jamal R. Circular RNAs as Promising Biomarkers: A Mini-Review. *Front Physiol* 2016;7:355.
61. Chen Y, Li C, Tan C, et al. Circular RNAs: a new frontier in the study of human diseases. *J Med Genet* 2016;53:359-65
62. Zhao Z, Li X, Jian D, et al. Hsa\_circ\_0054633 in peripheral blood can be used as a diagnostic biomarker of pre-diabetes and type 2 diabetes mellitus. *Acta Diabetol* 2017;54:237-45.
63. Guarnerio J, Bezzi M, Jeong JC, et al. Oncogenic Role of Fusion-circRNAs Derived from Cancer-Associated Chromosomal Translocations. *Cell* 2016;165:289-302.
64. 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;25:981-4.

**Cite this article as:** Yang F, Zhu P, Guo J, Liu X, Wang S, Wang G, Liu W, Wang S, Ge N. Circular RNAs in thoracic diseases. *J Thorac Dis* 2017;9(12):5382-5389. doi: 10.21037/jtd.2017.10.143