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TOPIC HIGHLIGHT

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Competing endogenous RNA networks and gastric cancer

Lei-Lei Guo, Chun-Hua Song, Peng Wang, Li-Ping Dai, Jian-Ying Zhang, Kai-Juan Wang

Lei-Lei Guo, Section of Infection Control of the Zhengzhou Central Hospital Affiliated to Zhengzhou University, Zhengzhou 450007, Henan Province, China

Chun-Hua Song, Peng Wang, Li-Ping Dai, Jian-Ying Zhang, Kai-Juan Wang, Department of Epidemiology and Statistics, College of Public Health, Zhengzhou University, Zhengzhou 450001, Henan Province, China

Chun-Hua Song, Peng Wang, Li-Ping Dai, Jian-Ying Zhang, Kai-Juan Wang, Henan Key Laboratory of Tumor Epidemiology, Zhengzhou 450001, Henan Province, China

Correspondence to: Kai-Juan Wang, PhD, Department of Epidemiology and Statistics, College of Public Health, Zhengzhou University, No. 100 Science Avenue, Zhengzhou 450001, Henan Province, China. kjwang@163.com
Telephone: +86-371-67781454

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Abstract

Recent studies have showed that RNAs regulate each other with microRNA (miRNA) response elements (MREs) and this mechanism is known as "competing endogenous RNA (ceRNA)" hypothesis. Long non-coding RNAs (lncRNAs) are supposed to play important roles in cancer. Compelling evidence suggests that lncRNAs can interact with miRNAs and regulate the expression of miRNAs as ceRNAs. Several lncRNAs such as H19, HOTAIR and MEG3 have been found to be associated with miRNAs in gastric cancer (GC), generating regulatory crosstalk across the transcriptome. These MRE sharing elements implicated in the ceRNA networks (ceRNETs) are able to regulate mRNA expression. The ceRNA regulatory networks including mRNAs, miRNAs, lncRNAs and circular RNAs may play critical roles in tumorigenesis, and the perturbations of ceRNETs may contribute to the pathogenesis of GC.

Key words: Competing endogenous RNA; Competitive endogenous RNAs networks; Gastric cancer; MicroRNA response elements; Perturbation

Core tip: Competitive endogenous RNAs (ceRNAs) share microRNA (miRNA) response elements and compete common miRNAs, thereby regulating each other's expression. The ceRNA regulatory networks including mRNAs, miRNAs, long non-coding RNAs and circular RNAs play critical roles in tumorigenesis, and the perturbations of ceRNA networks may contribute to the pathogenesis of gastric cancer.

Guo LL, Song CH, Wang P, Dai LP, Zhang JY, Wang KJ.

INTRODUCTION

Gastric cancer (GC) is the second leading cause of cancer-related death worldwide and is a major cause of cancer-related mortality in China[1]. Since the carcinogenesis in GC is a complex process with etiological factors, genetic and epigenetic alterations involved[2], the molecular basis of GC, especially efforts to identify clusters of predictive markers, has been widely studied. Previous studies have demonstrated that several genetic abnormalities such as aberrant genes, copy number variants (CNV), microRNAs (miRNAs) and long noncoding RNAs (lncRNAs) were involved in the initiation and progression of GC[3], but the pathogenic mechanisms contributing to biological feature of GC remain to be elucidated.

Non-coding RNAs (ncRNAs) refer to a class of RNAs with no protein-coding function that are widely expressed in organisms, including small ncRNAs such as miRNAs and lncRNAs, both of which play important roles in the post-transcriptional regulation[4]. In fact, miRNAs have been extensively studied in the field of oncology, and emerging evidence suggests that miRNA-mediated regulation plays crucial roles in tumor cell biological processes, such as cell proliferation, migration and invasion[5]. Furthermore, aberrantly expressed miRNAs have been discovered in diverse diseases including GC.

The competing endogenous RNA (ceRNA) hypothesis postulates that RNAs that share miRNA response elements (MREs) in their 3'-untranslated regions (UTRs) can influence the expression of miRNAs, inducing gene silencing[6]. While recent several studies have demonstrated that lncRNAs can harbor MREs and interact with other RNA transcripts such as ceRNAs[7,8]. The complex crosstalks of ceRNAs have been found in many different cancer types including GC. Above all, functional interactions and disequilibrium of ceRNA networks (ceRNETs) may contribute to disease pathogenesis[9]. This review discusses the features of ceRNETs and the functional roles and regulatory interactions of ceRNETs in the development of GC.

FEATURES OF CERNETS

In view of ceRNA hypothesis, three studies were reported in 2011 from Columbia University, Harvard Medical School and the University of Roma La Sapienza, which verified the ceRNA hypothesis from many aspects and further confirmed the establishment of regulatory mechanism based on ceRNAs[10]. The discovery of ceRNA mechanism provocatively subverts traditional meaning of the mRNA function, which means that mRNAs not only have the function of encoding proteins, but also participate in the gene regulation processes[11,12]. Transcriptional regulatory networks based on ceRNAs, not only enrich the biological pathway in the existing networks, but also expand the function of the human genome. Regulation members of ceRNETs consist of mRNAs, miRNAs, lncRNAs and circular RNAs (circRNAs). Notably, miRNAs and MREs are considered two important elements in the ceRNA hypothesis. The former is core motivation, while the latter is structural foundation.

Protein coding genes

So far, the number of protein coding genes in human genome has been found to be approximately 20000[13]. And most of mRNAs are covered in MREs[14,15]. Recent studies have demonstrated that many mRNAs are validated as ceRNAs, so mRNAs play an essential role in ceRNETs.

The function of miRNAs can be influenced by their target mRNAs for limited MREs within each cell. For a given mRNA, its upregulation can lead to the increasing number of MREs, which exceeds their targeting miRNAs. So each mRNA can act as an inhibitor for shared miRNAs. To date, *PTEN* that competes with various ceRNAs has been widely validated in a variety of advanced and metastatic cancers[16]. This tumor suppressor gene is involved in the regulation of cell proliferation, migration and apoptosis. The occurrence of *PTEN* inactivation was closely related to GC stage[17]. Recently, a study has successfully validated that a protein-coding transcript ZEB2 plays a role as a PTEN ceRNA in melanoma, which suggests that ZEB2 is involved in regulation of PTEN expression in an miRNA-dependent manner[18]. In another study, Tay *et al*[19] have validated that endogenous protein-coding transcripts VAPA and CNOT6L possessing tumor-suppressive properties could regulate *PTEN* through the disturbance of the PI3K/AKT signaling pathway.

Studies utilizing high-throughput technologies such as microarray and NGS for gene expression profiling have increased the discovery of predictive and treatment biomarkers. So far, numerous driver genes have been involved in gastric tumorigenesis. *P53* mutations, which were observed in a large proportion of tumors, had a crucial and early role in gastric carcinogenesis of intestinal type[20,21]. E-cadherin gene (*CDH1*) inactivating mutations were identified in diffuse GC and carriers with *CDH1* mutation(s) were more likely to have an increased risk of developing GC[22,23]. Furthermore, previous studies found that frequent *ARID1A* alterations were detected by exome sequencing in two specific molecular subtypes of GC[24,25]. In addition to the previously known mutations, a recent study of whole-genome sequencing (WGS)[26] has identified new driver genes of gastric adeno-

carcinoma. *MUC6*, which encodes gastric mucin, was significantly mutated. And *RHOA* mutations were observed in diffuse-type GC. These emerging drivers, together with other genes including *CTNNA2, GLI3,* and *RNF43*, are potential players in the perturbed pathways of GC. Although dozens of genes have been found, their roles in tumorigenesis in GC remain to be elucidated. Concurrently, these driver genes could be ceRNAs, which act as mediators, involved in the regulation of ceRNETs.

MiRNAs

MiRNAs are small noncoding RNAs that regulate the expression of various genes by inhibiting or degrading target mRNAs[27]. It is estimated that 30% of genes in the human genome were regulated by miRNAs[28,29]. MiRNAs containing MREs are shared by all ceRNAs. Accumulating evidence supports that a new layer of regulation of ceRNETs produces a tendency to be mediated by miRNAs. Multiple miRNAs can regulate different MREs in mRNA transcripts, and each miRNA can inhibit hundreds of transcripts, so miRNAs act as mediators in huge transcriptional and signaling networks[30]. This regulatory mechanism constitutes the basis of ceRNA interplay networks.

Emerging evidence suggests that aberrant miRNAs participate in the pathogenesis of GC, mainly by regulating the expression of oncogenes and tumor suppressors. Overexpression of miR-21, a known oncogenic miRNA, could enhance cell proliferation and inhibit apoptosis in cancer patients[31,32]. The target genes of miR-21 such as TMP1, PTEN and RECK were confirmed in several studies by different technological methods[33,34]. These findings support that miR-21 that function *via* the regulation of target genes mediates oncogenic processes in GC. Dysregulated miRNAs (miR-125a, miR- 199a, and miR-100) were considered to be important factors in the regulation of GC[35-37], suggesting that they may play different functions in different sites.

Gastric carcinogenesis is a multi-stage process, in which molecular expression and signaling pathway disturbances are involved[38]. Chronic inflammation is a driving factor promoting the malignant transformation. Specifically, *Helicobacter pylori* (HP)-induced gastritis is a risk factor for GC. The expression of certain miRNAs including miR-21, miR-155, miR-194, miR196, miR-218, and miR-223 has been found to be increased in GC with HP infection. Saito *et al*[39] noted that the overexpressed miR-155 acting as an important negative regulator modulates the inflammatory responses in GC induced by HP infection. Additionally, Wang *et al*[40] reported that a great dependence was confirmed between miR-106a and lymph node metastasis in GC. Another study also[41] discovered that HP infection could lead to decreased expression of Let-7, which increases the expression of oncogene *Ras*. As stated above, aberrant miRNAs play central roles in ceRNETs by regulating target genes.

LncRNAs

LncRNAs play regulatory roles and are dysregulated in a variety of tumors. However, the potential mechanisms of how lncRNAs alter in GC remain largely undefined. An increasing number of lncRNA transcripts emerged recently as ceRNAs have been implicated in GC.

In the research of GC, some lncRNAs are upregulated and act as oncogenic genes, including H19 and HOTAIR, while others are downregulated and function as suppressor genes, such as growth arrest-specific transcript 5 (GAS5) and maternally expressed gene 3 (MEG3). H19, a typical onco-lncRNA, was dysregulated in many cancers[42-44]. Park *et al*[45] reported that upregulated H19 can promote the development of GC by regulating the activity of *P53*. Recently, several studies[46] have demonstrated that HOTAIR may participate in the progression and metastasis of GC, and can be used as a therapeutic target for GC. GAS5, another famous lncRNA, plays a tumor-suppressive role in tumor formation. Significant downregulation of GAS5 could promote tumor cell proliferation by regulating expression of p21 and E2F1 proteins[47]. In addition, MEG3 was frequently studied in GC. Decreased expression of MEG3 could regulate cell proliferation and differentiation by interacting with *p53, Rb,* and *VEGF*[48]. Additionally, MEG3 may be associated with poor prognosis of GC by increasing the spread of cancer cells[49].

The key step in cancer research is to discover lncRNAs associated with specific diseases. At present, the screening of lncRNAs *via* chip analysis is a quick and accurate method. Song *et al*[50] demonstrated that 135 lncRNAs were dysregulated in GC tissues by microarray analysis, and H19 and uc001lsz were markedly expressed. The use of qRT-PCR also confirmed that the overexpression of H19 was closely related to GC, and uc001lsz might be a potential diagnostic marker for early GC. By means of expression profile analysis, Cao *et al*[51] identified 88 abnormally expressed lncRNAs including LINC00152, SNHG3, GAS5 and LINC00261. Additionally, Park *et al*[52] detected 31 differentially expressed lncRNAs using transcriptomics data, which further suggested that down-regulated BM742401 was closely related to poor survival of GC, and could be used as a therapeutic target to improve the prognosis of GC.

CircRNAs

CircRNAs are a special kind of endogenous RNAs featuring stable structure and high tissue-specific expression[53]. Instead of nonlinear RNAs, circRNAs are more common features[54]. So far, thousands of circRNAs have been found in human cells. The newly discovered circular RNAs can act as ceRNAs that affect the regulation of gene expression.

At present, studies on circRNAs are relatively few. CircRNAs functioning as miRNA sponges may play an important role at the level of miRNA fine tuning[55]. Hansen *et al*[56] suggested that CDR1 (cerebellar degeneration-related protein 1), known as ciRS-72011, was perceived as a ceRNA. Unlike other transcripts, CDR1 containing more than 70 MREs plays a role in regulation by interacting with miRNAs. By functional approaches, CDR1 was found to be overexpressed as a ceRNA that bound miRNAs, thus inhibiting the activity of miR-7[57]. Additionally, the study also discovered that 16 MREs were shared between miR-138 and a circRNA transcript derived from the testis determining gene (sex-determining region Y, Sry), which could have an miRNA sponge effect in regulating gene expression by inhibiting the activity of miR-138. In general, circRNAs are difficult to be degraded by enzyme for the feature of stable configuration and high abundance, which brings the regulatory function of cirRNA into full play.

Currently, circRNAs have been involved in several types of diseases[58,59] including GC. A study discovered that a typical circRNA, hsa_ circ_002059, is significantly downregulated and may be a potential diagnostic marker in GC[60]. Given the fact that the interactions between circRNA and miRNA may be very common, with the recognition of more molecules, circRNAs research is likely to have a giant leap, which will make contributions to tumor biology.

PREDICTION OF CERNETS

The availability of transcriptome data of diverse cancers, together with bioinformatic tools and computational approaches, enables the prediction of ceRNETs. At present, research on ceRNETs is certainly in its infancy, but still has made some progress.

By a novel multivariate analysis method, a huge miR-mediated ceRNET including 248000 crosstalks was first observed in glioblastoma[61]. Based on a special algorithm, a recent study has constructed a breast cancer-specific ceRNET using the expression profiles of miRNAs and mRNAs[62]. Similarly, a computational approach[63] was explored to predict miRNA- mediated sponge interactions (MMI-networks) based on both normal and breast cancer expression data, separately. This study also found that ceRNETs may be significantly altered between normal and pathological breast tissues and lncRNA PVT1 was a key factor in the tumorigenesis of breast cancer. Interestingly, based on lncRNA microarray data of GC, Xia *et al*[64] first constructed a ceRNA regulatory network including 8 lncRNAs and 9 miRNAs using bioinformatics methods and confirmed this network using the data from six types of other cancers. Additionally, Basia *et al*[65] proposed to analyze the equilibrium and non-equilibrium properties of ceRNETs based on a stochastic model, while emphasizing the robustness and response-time to external perturbations of the network.
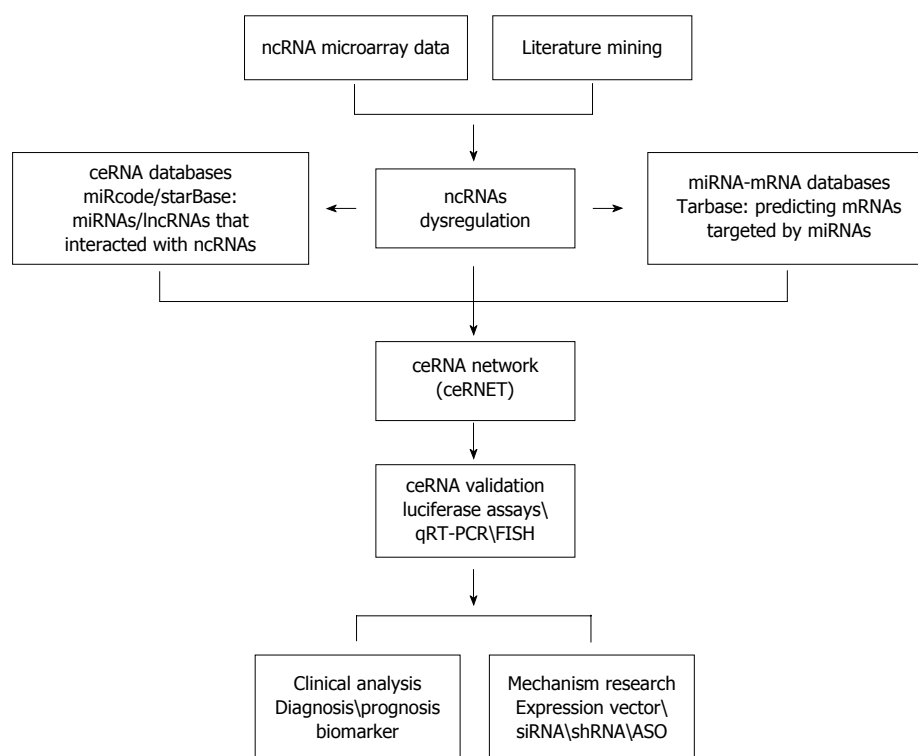
CeRNA database

At present, the most effective way to reveal ceRNAs' function is constructing ceRNETs. As increasing attention has focused on ceRNA research, ceRNA databases are constantly established. Sarver *et al*[66] developed a putative human ceRNA database ceRDB, which aimed to predict specific miRNA target genes related to ceRNAs. In ceRDB, the competing mRNAs were sorted by an interaction score based on the number of shared MREs among ceRNAs. The higher the score was, the more likely to be affected by ceRNAs the target mRNAs were. However, unlike the ceRDB database, which excluded information about lncRNAs. lnCeDB[67] provided a database of human lncRNAs that could potentially act as ceRNAs by computing a ceRNA score, which was a novel algorithm. Noteworthily, lncRNA-mRNA pairs with common shared miRNAs were available in this database. Additionally, based on ceRNA hypothesis, a web resource Linc2GO database[68] was established to provide comprehensive function annotations for human lincRNAs. starBase v2.0[69] stored the information about regulatory networks based on broadest experimental support, and this database provided potential interactions between miRNAs, mRNAs and lncRNAs. A newly developed database miRcode[70] was described to collect putative microRNA target sites based on complete GENCODE gene annotations and was used to predict the targets of miRNAs, including mRNAs and lncRNAs. The latest version of this database contained 10419 lncRNA genes. DIANA-LncBase database[71] attempted to depict putative miRNA-lncRNA interactions, providing annotations of miRNA targets on lncRNAs. Furthermore, ChIPBase[72] database platform aimed to unravel transcriptional regulatory relationships between lncRNAs/lincRNAs and miRNAs through the integration of ChIP-Seq data. In short, the effective use of these databases will help us seek for biomarkers, avoiding the blindness in practice (Table 1).

Conditions that ceRNETs work

It is well-known that ceRNETs play a role in cell culture. Recently, some conditions required for ceRNETs have been found. First, the concentration of the ceRNAs should be strongly emphasized. Expression changes of ceRNAs should be large enough to effectively eliminate or weaken the inhibition of miRNAs to ceRNAs. Second, the effectiveness of ceRNETs always depends on the number of shared miRNAs. It can be speculated that, in a network, the ceRNA having more binding preference to the shared miRNA will have more profound ceRNA effect on the components with less binding preference. In addition, taking tissue specificity into account, ceRNETs would also rest on density and subcellular distribution of RNAs in the cell[73]. The balance between shared miRNAs and targeted ceRNAs is critical for ceRNA activity and disruption of this balance can trigger internal crosstalks in ceRNETs. In general, alterations of one ceRNA may lead to joint

Table 1 Competitive endogenous RNA related databases

Database	Website	Ref.
ceRDB	http://www.oncomir.umn.edu/cefinder/	[66]
lnCeDB	http://gyanxet-beta.com/lncedb/	[67]
Linc2GO	http://www.bioinfo.tsinghua.edu.cn/~liuke/Linc2GO/index.html	[68]
starBase v2.0	http://starbase.sysu.edu.cn/	[69]
miRcode	http://www.mircode.org/	[70]
DIANA-LncBase	http://diana.imis.athena-innovation.gr/DianaTools/index.php?r=lncBase/index	[71]
ChIPBase	http://deepbase.sysu.edu.cn/chipbase/	[72]

Figure 1 Flow chart for studying competing endogenous RNA network in cancers. ncRNA: Non-coding RNA; ceRNA: Competing endogenous RNA; shRNA: Short hairpin RNA.

consequences in huge ceRNETs and thus promote cancer.

Research methods of ceRNETs

Although ceRNA research is in its infancy, the current progress has gained much attention. The availability of RNA-seq data, along with bioinformatics tools, enables the prediction of ceRNETs. As show in Figure 1, we display a way to research ceRNETs.

First, multiple strategies can be applied to obtain differentially expressed ncRNAs in cancers, including literature mining and microarray analysis. Then by means of computational algorithm and public data-bases, we can predict potential connections in ceRNETs. Some miRNA target prediction databases such as Tarbase, TargetScan and miRecords can provide experi-mentally verified miRNA-gene interactions, which are stable foundation for ceRNETs. As a supplement, the CLIP-Seq datasets come in handy. These ceRNA databases encompass information about miRNA,

mRNA, lncRNA, circRNA and pseudogene associations. Taken together, ceRNETs including lncRNAs, miRNAs, and mRNAs are constructed by invoking bioinformatics analysis.

Second, the precondition to study ceRNETs should be expression correlations, regulatory relationships, and shared MREs of ceRNA pairs. The validation of ceRNETs is considered to be an experimental framework for the biochemical method of ceRNA interactions. Based on the ceRNETs, the differentially expressed ceRNAs could be confirmed by qRT-PCR or fluorescence *in situ* hybridization (FISH).

Finally, functional studies should be conducted to investigate the dysregulation of ceRNAs in car-cinogenesis. In brief, the effect of overexpression/interference expression among ceRNAs was assessed by function gain/deficit experiments such as siRNAs, shRNAs, and antisense oligonucleotides (ASO). Fur-thermore, these experimentations for validating the perturbation of ceRNAs should be investigated in

mouse models to get confirmed correlations.

CROSSTALKS BETWEEN CERNAS IN GC

In recent years, the mechanism of ncRNAs in tumors has become a hot research topic. At the same time, increasing evidence has indicated that ncRNAs can regulate each other and affect their function by binding to MREs of shared miRNAs[74]. Like the role of ceRNAs in GC, the disturbance of interactions between ceRNAs also plays a part.

Due to the ceRNA theory, the competition between lncRNAs and miRNAs makes indirect regulation possible. In light of the role in regulating target genes, miRNAs can exercise the similar function to negatively regulate the expression of lncRNAs, and thus exert a series of biological effects in GC. Yan *et al*[75] reported that MEG3 expression level was markedly reduced in both tissues and cell lines of GC, and further experiments found that transfection of MEG3 siRNA into cells could diminish the suppression of proliferation induced by overexpression of miR-148a, which suggested that miR-148a might decrease the expression of MEG3 by modulation of DNMT-1. Furthermore, another study[76] found that upregulated H19 could promote the proliferation of GC cells by binding miR-675, which inversely inhibited the tumor suppressor gene RUNX1. The interaction between H19/miR-675 and RUNX1 may serve as novel targets in the tumorigenesis of GC.

In addition to indirect regulation of ceRNAs, lncRNAs can have a direct interaction by invoking the "endogenous miRNA sponge" (miRNA sponge) to inhibit the activity of mRNAs, thus affecting the occurrence and development of tumors. Xu *et al*[77] discovered that upregulated lncRNA AC130710 played a crucial role during GC progression by targeting miR-129-5p. Liu *et al*[78] reported that the expression levels of upregulated HOTAIR and HER2 had a positive correlation in GC. And subsequent luciferase and RIP assays confirmed that HOTAIR served as an endogenous "sponge" to regulate the expression of HER2 by sinking miR-331-3p. These results indicate that possible crosstalks in ceRNETs may provide new clues for the mechanism of GC.

CONCLUSION

Recently, increasing evidence suggests that the dysregulation of ceRNA interactions including miRNAs and lncRNAs has been involved in disease etiology, including gastric cancer. In this review, we present and discuss the features of ceRNETs and crosstalks in GC, as well as the methods in the study of ceRNETs.

CeRNAs that function as key regulators have been implicated in many biological processes and the perturbation of ceRNETs may contribute to carcinogenesis. Given the complexity of ceRNETs, future works should focus on identifying the hubs that have significant influence on network balance or tumorigenesis. Despite some improvements in research field, the mechanisms of ceRNA crosstalks are still not fully elucidated. And there are still several considerations limiting the applications of ceRNETs. With the development of computational methods, research techniques and abundance of all components in ceRNETs, we anticipate that ceRNETs will provide a new avenue for the research of GC, and shed light on complex mechanisms underlying malignant processes.

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