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**Competing endogenous RNAs network and gastric cancer**

Guo LL *et al*. ceRNA network of gastric cancer

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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” hypothesis. Long non-coding RNAs (lncRNAs) are supposed to play important roles in pathological cancer. While Compelling evidence suggests that lncRNAs can interact with miRNAs and regulate the expression of miRNAs as competitive endogenous RNAs (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 ceRNAs regulatory networks including mRNAs, miRNAs, lncRNAs and circular RNAs may play critical roles in tumorigenesis, and the perturbations of ceRNETs may contribute to pathogenesis of GC.

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

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**Core tip:** Competitive endogenous RNAs (ceRNAs) share microRNA (miRNA) response elements and compete common miRNAs, thereby regulating each other’s expressions. The ceRNAs 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 pathogenesis of gastric cancer.

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**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](#_ENREF_1)]. Since the carcinogenesis in GC is a complex process with etiological factors, genetic and epigenetic alterations involved[[2](#_ENREF_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 and lncRNAs were involved in the initiation and progression of GC[[3](#_ENREF_3)], but the pathogenic mechanism 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 microRNAs (miRNAs) and lncRNAs, both of which play important roles in the post-transcriptional regulation[[4](#_ENREF_4)]. In fact, miRNAs have been extensively studied in the field of oncological research, and emerging evidences suggest that miRNA-mediated regulation plays crucial roles in tumor cell biological processes, such as cell proliferation, migration and invasion[[5](#_ENREF_5)]. Furthermore, aberrantly expressed miRNAs have been discovered in diverse diseases including GC.

The ceRNA hypothesis postulates that RNAs that share miRNA response elements(MREs) in their 3' UTRs can influence the expression miRNA, inducing gene silencing[[6](#_ENREF_6)]. While recently several studies have demonstrated that lncRNAs can harbor MREs and interact with other RNA transcripts as ceRNAs[[7](#_ENREF_7),[8](#_ENREF_8)]. The complex crosstalks of ceRNAs have been found in many different cancers including GC. Above all, functional interactions and disequilibrium of ceRNA networks (ceRNETs) may contribute to disease pathogenesis[[9](#_ENREF_9)]. This review discusses the features of ceRNETs and overviews the functional roles and regulatory interactions of ceRNETs in the development of GC.

**FEATURES OF CERNA NETWORKS**

In view of competing endogenous RNA (ceRNA) hypothesis, Three studies were reported in 2011 from Columbia University, Harvard Medical School and the University of Roma La Sapienza, which made to verify the hypothesis of ceRNA from many aspects and further confirmed the establishment of regulation mechanism based on ceRNAs[[10](#_ENREF_10)]. The discovery of ceRNA mechanism provocatively subverts traditional meaning of the mRNA function, which means mRNA not only has the functions of encoding proteins, but also participate in the gene regulation processes[[11](#_ENREF_11),[12](#_ENREF_12)]. Transcriptional regulatory networks based on ceRNAs, notonly enrich the biological pathway in the existing networks, also expand function of the human genome. Regulation members of ceRNETs consist of mRNAs, miRNAs, lncRNAs and circular RNAs etc. Notably, miRNA and MREs are considered as two important elements in the ceRNA hypothesis. The former is core motivation, while the latter are structural foundations.

***Protein coding genes***

So far, the number of protein coding genes in human genome has been found to be approximately 20000[[13](#_ENREF_13)]. And most of mRNAs are covered in MREs[[14](#_ENREF_14),[15](#_ENREF_15)]. Recently researches have demonstrated that many mRNAs are validated as ceRNAs, so mRNAs play essential role in ceRNETs.

The miRNAs’function can be influenced by its target mRNAs for limited MREs within each cell. For a given mRNA,the upregulation can lead to the increasing number of MREs, which exceeds their targeting miRNAs. So each mRNA can act as a inhibitor for shared miRNAs. To date, *PTEN* that compete with various ceRNAs has been widely validated in a variety of advanced and metastatic cancers[[16](#_ENREF_16)]. And 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 development staging[[17](#_ENREF_17)]. Recently, a study has successfully validated that a protein-coding transcript ZEB2 play a role as a PTEN ceRNA in melanoma, which suggest that ZEB2 is involved in regulation of PTEN expression in a miRNA-dependent manner[[18](#_ENREF_18)]. In another study, Tay *et al*[[19](#_ENREF_19)] have validated that endogenous protein-coding transcripts VAPA and CNOT6L possessing tumor-suppressive properties could regulate *PTEN* through the disturbance of PI3K/AKT signaling pathway.

Researches by high-throughput technologies such as microarray and NGS for gene expression profiles 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](#_ENREF_20),[21](#_ENREF_21)]. E-cadherin gene (*CDH1*) inactivating mutations were identified in diffuse GC and carriers with *CDH1* mutation were more likely to increase the risk of developing GC[[22](#_ENREF_22),[23](#_ENREF_23)]. Furthermore, previous studies found that frequent *ARID1A* alterations were detected by exomesequencing in two specific molecular subtypes of GC[[24](#_ENREF_24),[25](#_ENREF_25)]. In addition to the previously known mutations, a recent study of Whole-genome sequencing (WGS)[[26](#_ENREF_26)] have identified new driver genes of gastric adenocarcinoma. *MUC6*, which encoded gastric mucin, was significantly mutated. And *RHOA* mutations were observed in diffuse-type of GC. These emerging drivers together with other genes including *CTNNA2, GLI3, RNF43* were potential players in the perturbed pathways of GC. Although dozens of genes have been found, they are insufficient to elucidate the tumorigenesis in GC. 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](#_ENREF_27)]. According to the inference, 30% genes of human genome were regulated by microRNAs[[28](#_ENREF_28),[29](#_ENREF_29)]. MiRNAs containing miRNA response element (MREs) are shared by all ceRNAs. Accumulating evidences support that a new layer regulation of ceRNETs produce a tendency to be mediated by the 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](#_ENREF_30)]. This regulatory mechanism constitute the basis of ceRNA interplay networks.

Emerging evidences suggest 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 the apoptosis in patients with cancers[[31](#_ENREF_31),[32](#_ENREF_32)]. The target genes of miR-21 such as TMP1, PTEN and RECK were confirmed in several studies by different technological methods[[33](#_ENREF_33),[34](#_ENREF_34)]. These evidences support that miR-21 that function *via* the regulation of target genes mediate oncogenic processes in GC. Dysregulated miRNAs (miR-125a, miR- 199a, miR-100) were considered to be important factors in the regulation of GC[[35-37](#_ENREF_35)], suggesting that they may play different functions in different sites.

The incidence of GC is a multi-stage process, in which molecular expression and signaling pathway disorders were involved[[38](#_ENREF_38)]. And chronic inflammation is a driving factor that promoting the malignant transformation. Specifically, *Helicobacter pylori* (HP)-induced gastritis is a risk factor for GC. The expressions of certain miRNAs including miR-21, miR-155, miR-194, miR196, miR-218, and miR-223 have been found to be increased in GC with HP infection. Saito *et al*[[39](#_ENREF_39)] noted that the overexpressed miR-155 acting as an important negative regulator modulate the inflammatory responses in GC induced by HP infection. Additionally, wang *et al*[[40](#_ENREF_40)] reported that a great dependence was confirmed between miR-106a and lymph nodemetastasis in GC. Another study also[[41](#_ENREF_41)] discovered that Hp infection could lead to a dereased expression of Let-7, which increase the expression of oncogene *Ras*. As stated above, aberrated miRNAs play central roles in ceRNETs by regulating target genes.

***Long noncoding RNAs***

LncRNAs played regulatory roles and were dysregulated in a variety of tumors. However, the potential mechanism and function of how lncRNAs altered in GC remain largely undefined. An increasing number of lncRNA transcripts emerged recently as ceRNAs have been impliated in GC.

In the research of GC, some lncRNAs are upregulated and exhibit oncogenic genes, including H19 and HOTAIR, while others are down-regulated 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](#_ENREF_42)]. Park *et al*[[45](#_ENREF_45)]reported that upregulated H19 can promote the development of GC by regulating the activity of *P53*. Recently, several studies[[46](#_ENREF_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, played 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](#_ENREF_47)]. In addition, MEG3 was frequently studied in GC. Decreased expression of MEG3 could regulate cell proliferation, differentiation by interacting with *p53, Rb, VEGF*[[48](#_ENREF_48)]. Additionlly, MEG3 may be associated with poor prognosis of GC by increasing the spread of cancer cells[[49](#_ENREF_49)].

The key step in cancer research is to discover specific diseases associated lncRNAs. At present, the screening of lncRNA *via* chip analysis is a quick and accurate method. Song *et al*[[50](#_ENREF_50)] demonstrated that 135 lncRNAs were dysregulated in gastric carcinoma tissues by microarray analysis. And H19 and uc001lsz were markedly expressed. While the use of qRT-PCR also confirmed that the overexpression of H19 was closely related to GC, and uc001lsz might be a early potential diagnosis marker. By means of expression profiles analysis, Cao *et al*[[51](#_ENREF_51)] identified 88 abnormal expression lncRNAs including LINC00152, SNHG3, GAS5 and LINC00261. Additionally, Park *et al*[[52](#_ENREF_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 carcinogenesis.

***Circular RNAs***

Circular RNAs (circRNAs) are a special kind of endogenous RNAs featuring stable structure and high tissue-specific expression[[53](#_ENREF_53)]. Instead of nonlinear RNA,cirRNAs are more common features[[54](#_ENREF_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.

Recently, researches on circRNA are relatively less. CircRNAs functioning as miRNA sponges may play an important role in the level of miRNA fine tuning[[55](#_ENREF_55)]. Hansen *et al*[[56](#_ENREF_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 played 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](#_ENREF_57)]. Additionally, the study also discoverd that 16 MREs were shared between miR-138 and a circRNA transcription derived from the testis determining gene (sex-determining region Y, Sry), which could play miRNA sponge effect on regulating the expression of genes 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](#_ENREF_58),[59](#_ENREF_59)] including GC. A study firstly discovered one typical circRNA, hsa\_ circ\_002059, is significantly downregulated and may be a potential diagnostic marker in GC[[60](#_ENREF_60)]. Given the fact that the interactions between circRNA and miRNA may be very common. With the recognition of more molecules, circRNAs researches are likely to bring out the leap development, which will make contribution to tumor biology.

**PREDICTION OF CERNA NETWORKS**

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

By a novel multivariate analysis method, a huge miR-mediated ceRNET including 248000 crosstalks was first observed in glioblastoma[[61](#_ENREF_61)]. Based on a special algorithm, a recent study has constructed a breast-cancer-specific ceRNA network using the expression profiles of miRNA and mRNA[[62](#_ENREF_62)]. Similarly, a computational approach[[63](#_ENREF_63)] was explored to predict miRNA- mediated sponge interactions (MMI-networks) based on both normal and brest 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 actor in the tumorigenesis of breast cancer. Interestingly, based on lncRNA microarray data of GC, Xia *et al*[[64](#_ENREF_64)] first constructed a ceRNA regulatory network including 8 lncRNAs and 9 miRNAs using bioinformatic methods and confirmed this network using the data from six types of other cancers. Additionally, Basia *et al*[[65](#_ENREF_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](#_ENREF_66)] developed a putative human ceRNA database ceRDB, which aimed to predict specific miRNA target genes related to ceRNA. 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](#_ENREF_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](#_ENREF_68)] was established to provide comprehensive function annotations for human lincRNAs. starBase v2.0[[69](#_ENREF_69)] stored the information about regulatory networks based on broadest experimental support, this database provided potential interactions between miRNAs, mRNA and lncRNAs. A newly developed database miRcode[[70](#_ENREF_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](#_ENREF_71)] attempted to depict putative miRNA-lncRNA interactions, providing annotations of miRNA targets on lncRNAs. Furthermore, ChIPBase[[72](#_ENREF_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 ceRNA networks work***

It is well-known that ceRNETs play a role in cell culture. Recently, some occurred conditions required for ceRNETs have been found. Firstly, the concentration of the ceRNAs should be strongly emphasized. Expression changes of ceRNA should be large enough to effectively eliminate or weaken the inhibition of miRNAs to ceRNAs. Secondly, the effectiveness of ceRNETs always depend 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, taken tissue specificity into account,ceRNETs would also rest on density and subcellular distribution of RNAs in the cell[[73](#_ENREF_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 consequences in huge ceRNETs and thus promote cancer.

***Research methods of ceRNA networks***

Although ceRNA research is in its infancy, the current progresses have gained a lot of 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.

Firstly, multiple strategies can be applied to get differentially expressed ncRNAs in cancers including literature mining, microarray analysis. Then by means of computational algorithm and public databases, we can predict potential connections in ceRNETs. Some miRNA target prediction databases such as Tarbase, TargetScan and miRecords can provide experimentally verified miRNA-gene interactions, which are stable foundation for ceRNETs. As a supplement, the CLIP-Seq datasets come in handy. These ceRNA databases encompass informations about miRNA, mRNA, lncRNA, circRNA and pseudogene associations. Taken together, ceRNETs including lncRNAs, miRNAs, mRNAs are constructed invoking bioinformatics analysis.

Secondly, the precondition to study ceRNETs should be expression correlations, regulatory relationships, 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 study should be conducted to investigate the dysregulation of ceRNAs in carcinogenesis. In brief, the effect of over- expression/ interference expression among ceRNAs was assessed by function gains/deficits experiment such as siRNA, shRNA, antisense oligonucleotides (ASO). Furthermore, these experimentations for validating the perturbation of ceRNAs should be investigated in mouse models to get confirmed correlations.

**CROSSTALKS BETWEEN ceRNAS in GASTRIC CANCER**

In recent years, the mechanism of ncRNAs in tumors has become hot spot. At the same time, increasing evidences have indicated that ncRNAs can regulate each other and affect their function by binding to MREs of shared miRNAs[[74](#_ENREF_74)]. Like ceRNA’role 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 play a series of biological effects in GC. Yan *et al*[[75](#_ENREF_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](http://link.springer.com/search?dc.title=siRNA&facet-content-type=ReferenceWorkEntry&sortOrder=relevance) 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](#_ENREF_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 be served as novel targets in the tumorigenesis of GC.

In addition to indirect regulation between ceRNAs, LncRNAs can play an direct interaction by invoking the "endogenous miRNA sponge" (miRNA sponge) inhibit the activity of mRNAs, thus affecting the occurrence and development of tumor. Xu *et al*[[77](#_ENREF_77)] discovered that upregulated LncRNA- AC130710 played a crucial role during GC progression by targeting miR-129-5p. Liu *et al*[[78](#_ENREF_78)]reported that the expression level between upregulated HOTAIR and HER2 proved to be a positive correlation in GC. And subsequent luciferase and RIP assays confirmed that HOTAIR that 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 have been involved in disease etiology, including gastric cancer. In this review, we presented and discussed the features of ceRNETs and crosstalks in GC, as well as the methods in the study of ceRNA networks.

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 gastric cancer, and shed light on complex mechanisms underlying malignant processes.

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**Figure 1 Flow chart for studying ceRNA network in cancers.**

**Table 1 Competitive endogenous RNA related databases**

|  |  |  |
| --- | --- | --- |
| **Database** | **Website** | **References** |
| 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] |