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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](javascript:void(0);) *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](javascript:void(0);). 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](javascript:void(0);) 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](javascript:void(0);) [study](javascript:void(0);) 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](javascript:void(0);) 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 [play](javascript:void(0);)s [a](javascript:void(0);) [part](javascript:void(0);).

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](javascript:void(0);) 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, r[esearch](javascript:void(0);) [technique](javascript:void(0);)s 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.

**REFERENCES**

1 **Catalano V**, Labianca R, Beretta GD, Gatta G, de Braud F, Van Cutsem E. Gastric cancer. *Crit Rev Oncol Hematol* 2009; **71**: 127-164 [PMID: 19230702 DOI: 10.1016/j.critrevonc.2009.01.004]

2 **Crew KD**, Neugut AI. Epidemiology of gastric cancer. *World J Gastroenterol* 2006; **12**: 354-362 [PMID: 16489633]

3 **Chang WJ**, Du Y, Zhao X, Ma LY, Cao GW. Inflammation-related factors predicting prognosis of gastric cancer. *World J Gastroenterol* 2014; **20**: 4586-4596 [PMID: 24782611 DOI: 10.3748/wjg.v20.i16.4586]

4 **Li PF**, Chen SC, Xia T, Jiang XM, Shao YF, Xiao BX, Guo JM. Non-coding RNAs and gastric cancer. *World J Gastroenterol* 2014; **20**: 5411-5419 [PMID: 24833871 DOI: 10.3748/wjg.v20.i18.5411]

5 **Tan JY**, Marques AC. The miRNA-mediated cross-talk between transcripts provides a novel layer of posttranscriptional regulation. *Adv Genet* 2014; **85**: 149-199 [PMID: 24880735 DOI: 10.1016/B978-0-12-800271-1.00003-2]

6 **Salmena L**, Poliseno L, Tay Y, Kats L, Pandolfi PP. A ceRNA hypothesis: the Rosetta Stone of a hidden RNA language? *Cell* 2011; **146**: 353-358 [PMID: 21802130 DOI: 10.1016/j.cell.2011.07.014]

7 **Arvey A**, Larsson E, Sander C, Leslie CS, Marks DS. Target mRNA abundance dilutes microRNA and siRNA activity. *Mol Syst Biol* 2010; **6**: 363 [PMID: 20404830 DOI: 10.1038/msb.2010.24]

8 **Wang P**, Ning S, Zhang Y, Li R, Ye J, Zhao Z, Zhi H, Wang T, Guo Z, Li X. Identification of lncRNA-associated competing triplets reveals global patterns and prognostic markers for cancer. *Nucleic Acids Res* 2015; **43**: 3478-3489 [PMID: 25800746 DOI: 10.1093/nar]

9 **Ergun S**, Oztuzcu S. Oncocers: ceRNA-mediated cross-talk by sponging miRNAs in oncogenic pathways. *Tumour Biol* 2015; **36**: 3129-3136 [PMID: 25809705 DOI: 10.1007/s13277-015]

10 **Karreth FA**, Pandolfi PP. ceRNA cross-talk in cancer: when ce-bling rivalries go awry. *Cancer Discov* 2013; **3**: 1113-1121 [PMID: 24072616 DOI: 10.1158/2159-8290.cd-13-0202]

11 **de Giorgio A**, Krell J, Harding V, Stebbing J, Castellano L. Emerging roles of competing endogenous RNAs in cancer: insights from the regulation of PTEN. *Mol Cell Biol* 2013; **33**: 3976-3982 [PMID: 23918803 DOI: 10.1128]

12 **Su X**, Xing J, Wang Z, Chen L, Cui M, Jiang B. microRNAs and ceRNAs: RNA networks in pathogenesis of cancer. *Chin J Cancer Res* 2013; **25**: 235-239 [PMID: 23592905 DOI: 10.3978/j.issn.1000-9604.]

13 **Baltimore D**. Our genome unveiled. *Nature* 2001; **409**: 814-816 [PMID: 11236992 DOI: 10.1038/35057267]

14 **Friedman RC**, Farh KK, Burge CB, Bartel DP. Most mammalian mRNAs are conserved targets of microRNAs. *Genome Res* 2009; **19**: 92-105 [PMID: 18955434 DOI: 10.1101/gr.082701.108]

15 **Lee DY**, Jeyapalan Z, Fang L, Yang J, Zhang Y, Yee AY, Li M, Du WW, Shatseva T, Yang BB. Expression of versican 3'-untranslated region modulates endogenous microRNA functions. *PLoS One* 2010; **5**: e13599 [PMID: 21049042 DOI: 10.1371/journal.pone.0013599]

16 **Poliseno L**, Pandolfi PP. PTEN ceRNA networks in human cancer. *Methods* 2015; **77-78**: 41-50 [PMID: 25644446 DOI: 10.1016/j.ymeth.2015.01.013]

17 **Zhang X**, Park JS, Park KH, Kim KH, Jung M, Chung HC, Rha SY, Kim HS. PTEN deficiency as a predictive biomarker of resistance to HER2-targeted therapy in advanced gastric cancer. *Oncology* 2015; **88**: 76-85 [PMID: 25300346 DOI: 10.1159/000366426]

18 **Karreth FA**, Tay Y, Perna D, Ala U, Tan SM, Rust AG, DeNicola G, Webster KA, Weiss D, Perez-Mancera PA, Krauthammer M, Halaban R, Provero P, Adams DJ, Tuveson DA, Pandolfi PP. In vivo identification of tumor- suppressive PTEN ceRNAs in an oncogenic BRAF-induced mouse model of melanoma. *Cell* 2011; **147**: 382-395 [PMID: 22000016 DOI: 10.1016/j.cell.2011.09.032]

19 **Tay Y**, Rinn J, Pandolfi PP. The multilayered complexity of ceRNA crosstalk and competition. *Nature* 2014; **505**: 344-352 [PMID: 24429633 DOI: 10.1038/nature12986]

20 **Busuttil RA**, Zapparoli GV, Haupt S, Fennell C, Wong SQ, Pang JM, Takeno EA, Mitchell C, Di Costanzo N, Fox S, Haupt Y, Dobrovic A, Boussioutas A. Role of p53 in the progression of gastric cancer. *Oncotarget* 2014; **5**: 12016-12026 [PMID: 25427447]

21 **Fricke E**, Keller G, Becker I, Rosivatz E, Schott C, Plaschke S, Rudelius M, Hermannstädter C, Busch R, Höfler H, Becker KF, Luber B. Relationship between E-cadherin gene mutation and p53 gene mutation, p53 accumulation, Bcl-2 expression and Ki-67 staining in diffuse-type gastric carcinoma. *Int J Cancer* 2003; **104**: 60-65 [PMID: 12532420 DOI: 10.1002/ijc.10879]

22 **Chu CM**, Chen CJ, Chan DC, Wu HS, Liu YC, Shen CY, Chang TM, Yu JC, Harn HJ, Yu CP, Yang MH. CDH1 polymorphisms and haplotypes in sporadic diffuse and intestinal gastric cancer: a case-control study based on direct sequencing analysis. *World J Surg Oncol* 2014; **12**: 80 [PMID: 24684952 DOI: 10.1186/1477-7819-12-80]

23 **Sugimoto S**, Yamada H, Takahashi M, Morohoshi Y, Yamaguchi N, Tsunoda Y, Hayashi H, Sugimura H, Komatsu H. Early-onset diffuse gastric cancer associated with a de novo large genomic deletion of CDH1 gene. *Gastric Cancer* 2014; **17**: 745-749 [PMID: 23812922 DOI: 10.1007/s10120-013-0278-2]

24 **Inada R**, Sekine S, Taniguchi H, Tsuda H, Katai H, Fujiwara T, Kushima R. ARID1A expression in gastric adenocarcinoma: clinicopathological significance and correlation with DNA mismatch repair status. *World J Gastroenterol* 2015; **21**: 2159-2168 [PMID: 25717252 DOI: 10.3748/wjg.v21.i7.2159]

25 **Yamamoto H**, Watanabe Y, Maehata T, Morita R, Yoshida Y, Oikawa R, Ishigooka S, Ozawa S, Matsuo Y, Hosoya K, Yamashita M, Taniguchi H, Nosho K, Suzuki H, Yasuda H, Shinomura Y, Itoh F. An updated review of gastric cancer in the next-generation sequencing era: insights from bench to bedside and vice versa. *World J Gastroenterol* 2014; **20**: 3927-3937 [PMID: 24744582 DOI: 10.3748/wjg.v20.i14.3927]

26 **Wang K**, Yuen ST, Xu J, Lee SP, Yan HH, Shi ST, Siu HC, Deng S, Chu KM, Law S, Chan KH, Chan AS, Tsui WY, Ho SL, Chan AK, Man JL, Foglizzo V, Ng MK, Chan AS, Ching YP, Cheng GH, Xie T, Fernandez J, Li VS, Clevers H, Rejto PA, Mao M, Leung SY. Whole-genome sequencing and comprehensive molecular profiling identify new driver mutations in gastric cancer. *Nat Genet* 2014; **46**: 573-582 [PMID: 24816253 DOI: 10.1038/ng.2983]

27 **Calin GA**, Croce CM. MicroRNA-cancer connection: the beginning of a new tale. *Cancer Res* 2006; **66**: 7390-7394 [PMID: 16885332 DOI: 10.1158/0008-5472.CAN-06-0800]

28 **Ebert MS**, Sharp PA. MicroRNA sponges: progress and possibilities. *RNA* 2010; **16**: 2043-2050 [PMID: 20855538 DOI: 10.1261/rna.2414110]

29 **Ebert MS**, Sharp PA. Emerging roles for natural microRNA sponges. *Curr Biol* 2010; **20**: R858-R861 [PMID: 20937476 DOI: 10.1016/j.cub.2010.08.052]

30 **Hong L**, Yang Z, Ma J, Fan D. Function of miRNA in controlling drug resistance of human cancers. *Curr Drug Targets* 2013; **14**: 1118-1127 [PMID: 23834156]

31 **Wang Z**, Cai Q, Jiang Z, Liu B, Zhu Z, Li C. Prognostic role of microRNA-21 in gastric cancer: a meta-analysis. *Med Sci Monit* 2014; **20**: 1668-1674 [PMID: 25230738 DOI: 10.12659/MSM.892096]

32 **Si ML**, Zhu S, Wu H, Lu Z, Wu F, Mo YY. miR-21-mediated tumor growth. *Oncogene* 2007; **26**: 2799-2803 [PMID: 17072344 DOI: 10.1038/sj.onc.1210083]

33 **Xu LF**, Wu ZP, Chen Y, Zhu QS, Hamidi S, Navab R. MicroRNA-21 (miR-21) regulates cellular proliferation, invasion, migration, and apoptosis by targeting PTEN, RECK and Bcl-2 in lung squamous carcinoma, Gejiu City, China. *PLoS One* 2014; **9**: e103698 [PMID: 25084400 DOI: 10.1371/journal.pone.0103698]

34 **Yang SM**, Huang C, Li XF, Yu MZ, He Y, Li J. miR-21 confers cisplatin resistance in gastric cancer cells by regulating PTEN. *Toxicology* 2013; **306**: 162-168 [PMID: 23466500 DOI: 10.1016/j.tox.2013.02.014]

35 **He XJ**, Ma YY, Yu S, Jiang XT, Lu YD, Tao L, Wang HP, Hu ZM, Tao HQ. Up-regulated miR-199a-5p in gastric cancer functions as an oncogene and targets klotho. *BMC Cancer* 2014; **14**: 218 [PMID: 24655788 DOI: 10.1186/1471-2407-14-218]

36 **Xu Y**, Huang Z, Liu Y. Reduced miR-125a-5p expression is associated with gastric carcinogenesis through the targeting of E2F3. *Mol Med Rep* 2014; **10**: 2601-2608 [PMID: 25231560 DOI: 10.3892/mmr.2014.2567]

37 **Shi DB**, Xing AY, Gao C, Gao P. [Expression of microRNA-100 in human gastric cancer]. *Zhonghua Bing Li Xue Za Zhi* 2013; **42**: 15-19 [PMID: 23611267 DOI: 10.3760/cma.j.issn.0529-5807.2013.01.004]

38 **Piazuelo MB**, Correa P. Gastric cáncer: Overview. *Colomb Med (Cali)* 2013; **44**: 192-201 [PMID: 24892619]

39 **Saito Y**, Suzuki H, Tsugawa H, Imaeda H, Matsuzaki J, Hirata K, Hosoe N, Nakamura M, Mukai M, Saito H, Hibi T. Overexpression of miR-142-5p and miR-155 in gastric mucosa-associated lymphoid tissue (MALT) lymphoma resistant to Helicobacter pylori eradication. *PLoS One* 2012; **7**: e47396 [PMID: 23209550 DOI: 10.1371/journal.pone.0047396]

40 **Wang Z**, Liu M, Zhu H, Zhang W, He S, Hu C, Quan L, Bai J, Xu N. miR-106a is frequently upregulated in gastric cancer and inhibits the extrinsic apoptotic pathway by targeting FAS. *Mol Carcinog* 2013; **52**: 634-646 [PMID: 22431000 DOI: 10.1002/mc.21899]

41 **Hayashi Y**, Tsujii M, Wang J, Kondo J, Akasaka T, Jin Y, Li W, Nakamura T, Nishida T, Iijima H, Tsuji S, Kawano S, Hayashi N, Takehara T. CagA mediates epigenetic regulation to attenuate let-7 expression in Helicobacter pylori-related carcinogenesis. *Gut* 2013; **62**: 1536-1546 [PMID: 22936674 DOI: 10.1136/gutjnl-2011-301625]

42 **Zhu M**, Chen Q, Liu X, Sun Q, Zhao X, Deng R, Wang Y, Huang J, Xu M, Yan J, Yu J. lncRNA H19/miR-675 axis represses prostate cancer metastasis by targeting TGFBI. *FEBS J* 2014; **281**: 3766-3775 [PMID: 24988946 DOI: 10.1111/febs.12902]

43 **Berteaux N**, Lottin S, Monté D, Pinte S, Quatannens B, Coll J, Hondermarck H, Curgy JJ, Dugimont T, Adriaenssens E. H19 mRNA-like noncoding RNA promotes breast cancer cell proliferation through positive control by E2F1. *J Biol Chem* 2005; **280**: 29625-29636 [PMID: 15985428 DOI: 10.1074/jbc.M504033200]

44 **Yang F**, Bi J, Xue X, Zheng L, Zhi K, Hua J, Fang G. Up-regulated long non-coding RNA H19 contributes to proliferation of gastric cancer cells. *FEBS J* 2012; **279**: 3159-3165 [PMID: 22776265 DOI: 10.1111/j.1742-4658.2012.08694.x]

45 **Park IY**, Sohn BH, Choo JH, Joe CO, Seong JK, Lee YI, Chung JH. Deregulation of DNA methyltransferases and loss of parental methylation at the insulin-like growth factor II (Igf2)/H19 loci in p53 knockout mice prior to tumor development. *J Cell Biochem* 2005; **94**: 585-596 [PMID: 15543560 DOI: 10.1002/jcb.20263]

46 **Endo H**, Shiroki T, Nakagawa T, Yokoyama M, Tamai K, Yamanami H, Fujiya T, Sato I, Yamaguchi K, Tanaka N, Iijima K, Shimosegawa T, Sugamura K, Satoh K. Enhanced expression of long non-coding RNA HOTAIR is associated with the development of gastric cancer. *PLoS One* 2013; **8**: e77070 [PMID: 24130837 DOI: 10.1371/journal.pone.0077070]

47 **Sun M**, Jin FY, Xia R, Kong R, Li JH, Xu TP, Liu YW, Zhang EB, Liu XH, De W. Decreased expression of long noncoding RNA GAS5 indicates a poor prognosis and promotes cell proliferation in gastric cancer. *BMC Cancer* 2014; **14**: 319 [PMID: 24884417 DOI: 10.1186/1471-2407-14-319]

48 **Benetatos L**, Vartholomatos G, Hatzimichael E. MEG3 imprinted gene contribution in tumorigenesis. *Int J Cancer* 2011; **129**: 773-779 [PMID: 21400503 DOI: 10.1002/ijc.26052]

49 **Sun M**, Xia R, Jin F, Xu T, Liu Z, De W, Liu X. Downregulated long noncoding RNA MEG3 is associated with poor prognosis and promotes cell proliferation in gastric cancer. *Tumour Biol* 2014; **35**: 1065-1073 [PMID: 24006224 DOI: 10.1007/s13277-013-1142-z]

50 **Song H**, Sun W, Ye G, Ding X, Liu Z, Zhang S, Xia T, Xiao B, Xi Y, Guo J. Long non-coding RNA expression profile in human gastric cancer and its clinical significances. *J Transl Med* 2013; **11**: 225 [PMID: 24063685 DOI: 10.1186/1479-5876-11-225]

51 **Cao WJ**, Wu HL, He BS, Zhang YS, Zhang ZY. Analysis of long non-coding RNA expression profiles in gastric cancer. *World J Gastroenterol* 2013; **19**: 3658-3664 [PMID: 23801869 DOI: 10.3748/wjg.v19.i23.3658]

52 **Park SM**, Park SJ, Kim HJ, Kwon OH, Kang TW, Sohn HA, Kim SK, Moo Noh S, Song KS, Jang SJ, Sung Kim Y, Kim SY. A known expressed sequence tag, BM742401, is a potent lincRNA inhibiting cancer metastasis. *Exp Mol Med* 2013; **45**: e31 [PMID: 23846333 DOI: 10.1038/emm.2013.59]

53 **Memczak S**, Jens M, Elefsinioti A, Torti F, Krueger J, Rybak A, Maier L, Mackowiak SD, Gregersen LH, Munschauer M, Loewer A, Ziebold U, Landthaler M, Kocks C, le Noble F, Rajewsky N. Circular RNAs are a large class of animal RNAs with regulatory potency. *Nature* 2013; **495**: 333-338 [PMID: 23446348 DOI: 10.1038/nature11928]

54 **Zlotorynski E**. Non-coding RNA: Circular RNAs promote transcription. *Nat Rev Mol Cell Biol* 2015; **16**: 206 [PMID: 25714680 DOI: 10.1038/nrm3967]

55 **Hansen TB**, Jensen TI, Clausen BH, Bramsen JB, Finsen B, Damgaard CK, Kjems J. Natural RNA circles function as efficient microRNA sponges. *Nature* 2013; **495**: 384-388 [PMID: 23446346 DOI: 10.1038/nature11993]

56 **Hansen TB**, Wiklund ED, Bramsen JB, Villadsen SB, Statham AL, Clark SJ, Kjems J. miRNA-dependent gene silencing involving Ago2-mediated cleavage of a circular antisense RNA. *EMBO J* 2011; **30**: 4414-4422 [PMID: 21964070 DOI: 10.1038/emboj.2011.359]

57 **Hansen TB**, Kjems J, Damgaard CK. Circular RNA and miR-7 in cancer. *Cancer Res* 2013; **73**: 5609-5612 [PMID: 24014594 DOI: 10.1158/0008-5472.can-13-1568]

58 **Peng L**, Yuan XQ, Li GC. The emerging landscape of circular RNA ciRS-7 in cancer (Review). *Oncol Rep* 2015; **33**: 2669-2674 [PMID: 25873049 DOI: 10.3892/or.2015.3904]

59 **Bachmayr-Heyda A**, Reiner AT, Auer K, Sukhbaatar N, Aust S, Bachleitner-Hofmann T, Mesteri I, Grunt TW, Zeillinger R, Pils D. 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 DOI: 10.1038/srep08057]

60 **Li P**, Chen S, Chen H, Mo X, Li T, Shao Y, Xiao B, Guo J. Using circular RNA as a novel type of biomarker in the screening of gastric cancer. *Clin Chim Acta* 2015; **444**: 132-136 [PMID: 25689795 DOI: 10.1016/j.cca.2015.02.018]

61 **Sumazin P**, Yang X, Chiu HS, Chung WJ, Iyer A, Llobet-Navas D, Rajbhandari P, Bansal M, Guarnieri P, Silva J, Califano A. An extensive microRNA-mediated network of RNA-RNA interactions regulates established oncogenic pathways in glioblastoma. *Cell* 2011; **147**: 370-381 [PMID: 22000015 DOI: 10.1016/j.cell.2011.09.041]

62 **Zhou X**, Liu J, Wang W. Construction and investigation of breast-cancer-specific ceRNA network based on the mRNA and miRNA expression data. *IET Syst Biol* 2014; **8**: 96-103 [PMID: 25014376 DOI: 10.1049/iet-syb.2013.0025]

63 **Paci P**, Colombo T, Farina L. Computational analysis identifies a sponge interaction network between long non-coding RNAs and messenger RNAs in human breast cancer. *BMC Syst Biol* 2014; **8**: 83 [PMID: 25033876 DOI: 10.1186/1752-0509-8-83]

64 **Xia T**, Liao Q, Jiang X, Shao Y, Xiao B, Xi Y, Guo J. Long noncoding RNA associated-competing endogenous RNAs in gastric cancer. *Sci Rep* 2014; **4**: 6088 [PMID: 25124853 DOI: 10.1038/srep06088]

65 . Modelling Competing Endogenous RNA Networks. *PLoS One* 2013; **8**: e66609 [PMID: 23840508 DOI: 10.1371/journal.pone.0066609]

66 **Sarver AL**, Subramanian S. Competing endogenous RNA database. *Bioinformation* 2012; **8**: 731-733 [PMID: 23055620 DOI: 10.6026/97320630008731]

67 **Das S**, Ghosal S, Sen R, Chakrabarti J. lnCeDB: database of human long noncoding RNA acting as competing endogenous RNA. *PLoS One* 2014; **9**: e98965 [PMID: 24926662 DOI: 10.1371/journal.pone.0098965]

68 **Liu K**, Yan Z, Li Y, Sun Z. Linc2GO: a human LincRNA function annotation resource based on ceRNA hypothesis. *Bioinformatics* 2013; **29**: 2221-2222 [PMID: 23793747 DOI: 10.1093/bioinformatics/btt361]

69 **Li JH**, Liu S, Zhou H, Qu LH, Yang JH. starBase v2.0: decoding miRNA-ceRNA, miRNA-ncRNA and protein-RNA interaction networks from large-scale CLIP-Seq data. *Nucleic Acids Res* 2014; **42**: D92-D97 [PMID: 24297251 DOI: 10.1093/nar/gkt1248]

70 **Jeggari A**, Marks DS, Larsson E. miRcode: a map of putative microRNA target sites in the long non-coding transcriptome. *Bioinformatics* 2012; **28**: 2062-2063 [PMID: 22718787 DOI: 10.1093/bioinformatics/bts344]

71 **Paraskevopoulou MD**, Georgakilas G, Kostoulas N, Reczko M, Maragkakis M, Dalamagas TM, Hatzigeorgiou AG. DIANA-LncBase: experimentally verified and computationally predicted microRNA targets on long non-coding RNAs. *Nucleic Acids Res* 2013; **41**: D239-D245 [PMID: 23193281 DOI: 10.1093/nar/gks1246]

72 **Yang JH**, Li JH, Jiang S, Zhou H, Qu LH. ChIPBase: a database for decoding the transcriptional regulation of long non-coding RNA and microRNA genes from ChIP-Seq data. *Nucleic Acids Res* 2013; **41**: D177-D187 [PMID: 23161675 DOI: 10.1093/nar/gks1060]

73 **Kartha RV**, Subramanian S. Competing endogenous RNAs (ceRNAs): new entrants to the intricacies of gene regulation. *Front Genet* 2014; **5**: 8 [PMID: 24523727 DOI: 10.3389/fgene.2014.00008]

74 **Jalali S**, Bhartiya D, Lalwani MK, Sivasubbu S, Scaria V. Systematic transcriptome wide analysis of lncRNA-miRNA interactions. *PLoS One* 2013; **8**: e53823 [PMID: 23405074 DOI: 10.1371/journal.pone.0053823]

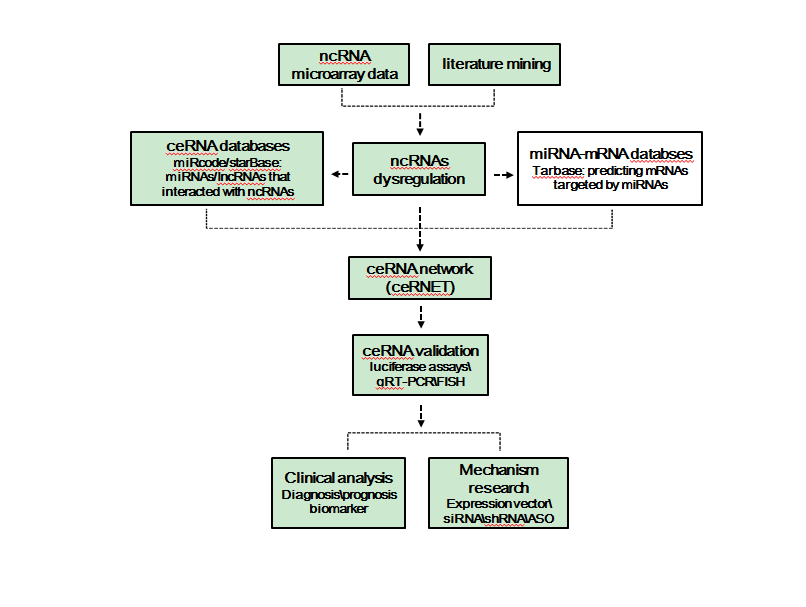
75 **Yan J**, Guo X, Xia J, Shan T, Gu C, Liang Z, Zhao W, Jin S. MiR-148a regulates MEG3 in gastric cancer by targeting DNA methyltransferase 1. *Med Oncol* 2014; **31**: 879 [PMID: 24515776 DOI: 10.1007/s12032-014-0879-6]

76 **Li H**, Yu B, Li J, Su L, Yan M, Zhu Z, Liu B. Overexpression of lncRNA H19 enhances carcinogenesis and metastasis of gastric cancer. *Oncotarget* 2014; **5**: 2318-2329 [PMID: 24810858]

77 **Xu C**, Shao Y, Xia T, Yang Y, Dai J, Luo L, Zhang X, Sun W, Song H, Xiao B, Guo J. lncRNA-AC130710 targeting by miR-129-5p is upregulated in gastric cancer and associates with poor prognosis. *Tumour Biol* 2014; **35**: 9701-9706 [PMID: 24969565 DOI: 10.1007/s13277-014-2274-5]

78 **Liu XH**, Sun M, Nie FQ, Ge YB, Zhang EB, Yin DD, Kong R, Xia R, Lu KH, Li JH, De W, Wang KM, Wang ZX. Lnc RNA HOTAIR functions as a competing endogenous RNA to regulate HER2 expression by sponging miR-331-3p in gastric cancer. *Mol Cancer* 2014; **13**: 92 [PMID: 24775712 DOI: 10.1186/1476-4598-13-92]

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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] |