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The Role of ceRNA Networks in the Development and Progression of Gastric Cancer

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Abstract

MicroRNAs or miRNAs bind to miRNA Response Elements (MREs), a location on target transcripts, causing either transcript destruction or translational inhibition. NcRNAs with MREs can compete with mRNA as a miRNA sponge and are involved in a complex regulatory network that regulates the transcription of mRNAs through miRNAs competitive binding. According to the ceRNA hypothesis, ncRNAs, including lncRNAs, circRNAs, and pseudogenes, contend against mRNAs in binding to miRNAs *via* miRNAs' MRE. MicroRNA is the most important part of the ceRNA network and ncRNAs and mRNAs are other components of the ceRNA network. LncRNAs, circRNAs, and pseudogenes have been demonstrated to play a key role in cellular processes like cell proliferation, cell growth, apoptosis, and differentiation. CeRNA networks are involved in many cancers, including liver, breast, lung, and Gastric Cancer (GC). Therefore, the study of the ceRNA network in GC will help to understand how the disease develops and progresses, as well as identify new therapeutic approaches.

Keywords: Apoptosis, Cell proliferation, MicroRNAs, Pseudogenes, Response elements, Circular, Competitive endogenous, Long noncoding, Stomach neoplasms

Introduction

Non-coding RNAs (ncRNAs) can not encode proteins, but are widely expressed in organisms (1). Based on their length, they are sorted into two main groups: small ncRNAs (less than 200 nucleotides) and long ncRNAs (lncRNAs, more than 200 nucleotides). Small ncRNAs include several subtypes such as microRNAs (miRNAs), small nuclear RNAs (snRNAs), transfer RNAs (tRNAs), PIWI-interacting RNAs (piRNAs), small nucleolar RNAs (snoRNAs), circular RNAs (circRNAs), and QDE-2-interacting RNAs (qiRNAs) (2). Among these, miRNAs, typically about 22 nucleotides long, regulate gene expression at both the transcriptional and post-transcriptional levels. They bind to complementary sequences on the target transcripts called miRNA Response Elements (MREs), resulting in transcript degradation or translational repression (3,4). According to the competing endogenous RNA (ceRNA) theory, proposed in 2011, various transcripts including lncRNAs, circRNAs, pseudogenes, and mRNAs can act as miRNA sponges by competing for shared miRNAs through common MREs, thereby influencing each other's expression levels (5,6). Some types of cancer, such as the stomach, liver, breast, and lung, are only a few of the cancers that are affected by ceRNAs (5).

Globally, Gastric Cancer (GC) is a prevalent cancer and a significant cancer-related mortality all over the world (5). LncRNAs, circRNAs, and pseudogenes, like ceRNAs, have been revealed to play a key role in biological processes like stomach cancer proliferation, differentiation, and drug resistance. Therefore, it is anticipated that more research on the ceRNA network in GC will offer fresh perspectives on how the disease develops and arises, as well as pave the right path for identifying novel therapeutic targets (5).

Gastric cancer (GC)

GC is the third leading cause of cancer fatality all over the world. It's a malignancy that emanates from the mucosal epithelium of the stomach (7,8). Increase in age, excessive salt consumption, lack of fruit and vegetable consumption, and *Helicobacter pylori* infection are all risk factors for stomach malignancy. Additionally recognized risk factors include drinking alcohol and actively smoking (9). Clinically, few patients with GC stages exhibit overt symptoms, and those who do, often struggle to get enough attention because of symptoms like nausea, vomiting, or upper gastrointestinal symptoms that resemble ulcers. Therefore, the majority of patients suffering from GC are diagnosed at advanced stages (5,7).

The prognosis and diagnosis of cancers are determined by the stages of the tumor and disease. Since primary GC has vague symptoms, the majority of sick persons only receive an advanced diagnosis. Advanced computed tomography and endoscopic biopsy are the gold standard for diagnosing GC. New clinical biomarkers are required for early tumor diagnosis, monitoring of therapy response, and prognosis because early detection of tumor and diagnosis are crucial to lowering GC-related mortality (5,8).

Chemotherapy combined with operation is still the first-line cure for GC. Drug resistance in chemotherapy is a significant matter that needs to be addressed despite progression in surgical procedures, radiotherapy, and chemotherapy treatment (10). This is since the tumoral cells will develop a mechanism to neutralize the impact of drugs in chemotherapy, which will finally result in more clones, increased aggression, and a weak prognosis (10). Resistance to chemotherapy may be inherited or acquisitive, and it is a complex phenomenon containing DNA damage responses, acquired mutations, and the dysregulation of important signaling pathways (10).

Therefore, a research concentration has always been on examining the pathophysiology and searching for important components to direct diagnosis and treatment. The onset, progression, and pathophysiology of GC are multi-stage and multi-factor processes. According to recent studies, it frequently occurs in association with aberrant transcription. This anomaly involves faults in the regulatory capacity of the genome's ncRNAs, in addition to aberrant protein-coding RNA (mRNA) levels (11). Based on many studies, one of the primary causes of cancer therapy failure is the Cancer Stem Cell (CSC). Stem cell preservation depends heavily on the expression of miRNAs. The start and development of gastric cancer are directly correlated with the dysregulation of miRNAs in Gastric Cancer Stem Cells (GCSCs) (11).

Competing endogenous RNA (CeRNA)

Salmana *et al* first presented the concept of ceRNA in 2011 and explained that there was another mode of gene expression regulation called RNA-miRNA-mRNA in addition to the standard mode of miRNA-RNA (11-13). In this context, the term "ceRNA" refers to a regulatory mechanism rather than a specific RNA (11-13). According to the ceRNA hypothesis, transcripts such as lncRNAs, circRNAs, pseudogenes, and mRNAs can regulate each other by competing for shared miRNA Response Elements (MREs) through miRNA binding (Figure 1) (14,15). This competitive binding is also referred to as miRNA sponge activity (14,15). Any RNA molecules that share MREs may act as a ceRNA. The most important part of the ceRNA network is miRNA, and its other components include lncRNAs, mRNAs, and pseudogenes (7). Also, lncRNAs, circRNAs, and pseudogenes have dual functions concerning development of tumors in an organ such as the stomach, meaning they can cause tumors as well as prevent their progression (16). miRNAs will be mature when a series of processing stages occur sequentially in the nucleus and cytoplasm; then, mature miRNAs combine with Argonaute (Ago) family proteins to make the RNA-Induced Silencing Complex (RISC) (16). The location component of target transcripts which are known as MREs is the complement of the miRNA sequences; miRNAs detect them particularly and conduct the RISC toward target transcripts (16).

Competitive mechanisms of endogenous RNA include two states: a) where ceRNA is silent, *i.e.*, a pseudogene remains transcriptionally silent and b) in which ceRNA is active when the pseudogene is transcriptionally activated with competing target sites. In the first case, mRNA after transcription is transported to the cytoplasm, where it is targeted by the miRNA-mediated silencing complex (miRNA-RISC). As a result, translation is blocked, mRNAs are rapidly degraded, and gene expression is reduced (15). In the second case, there will be competition for miRNA targeting and binding to the RISC complex, reducing miRNA inhibition. The miRNA-RISC complex dissociates from the gene, leading to increased gene expression (15).

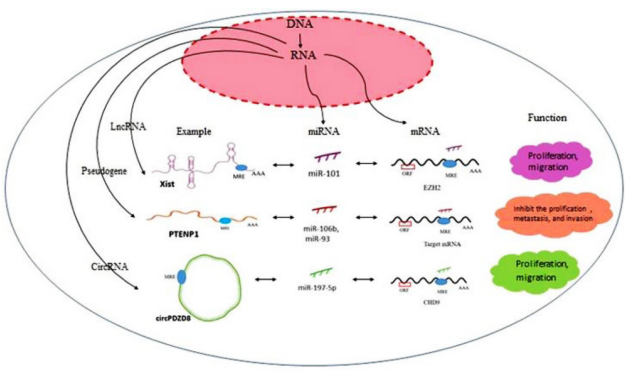

Figure 1. CeRNA network. Three ncRNAs including lncRNA, circRNA and pseudoRNA are involved in stomach cancer as ceRNA, which competitively target miRNAs.

Despite abundant studies on the effects of ceRNA networks in cancer, some limitations remained in ceRNA theory. First, genes interactions in ceRNA networks were predicted by bioinformatics studies and should be verified by some experimental studies. Second, because of compete in target pool of the miRNA, optimal concentration of ceRNA activity that is computed by mathematical models, might not be achieved in experimental studies (17,18).

LncRNAs

LncRNAs are a type of RNA molecule that have over 200 nucleotides, but do not encode proteins. The largest type of ncRNAs is lncRNAs that are sorted in subclasses based on various characteristics, the most widespread of which are pseudogenes, long intergenic ncRNA (lincRNA), antisense RNA (asRNA), and circular RNA (circRNA) (3). LncRNAs were formerly assumed to be side products of RNA polymerase II transcription that have no biological role (19). Although LncRNAs were once assumed to have no biological role, but recent researches have revealed that they are important regulators in cancer progression (8,19). LncRNAs have been discovered in the nucleus and cytoplasm that are mostly involved in epigenetic, transcriptional, and post-transcriptional regulation, respectively (19,20). Anomalous alterations in the expression of lncRNAs have been discovered in nearly all kinds of cancers, demonstrating their significant functions in the expansion and cancer progression (19). LncRNAs play a diversity of biological functions through interaction with proteins, DNA, and RNAs (19). Cell proliferation, metastasis, metabolism, and apoptosis can all be impacted by unusually produced lncRNAs,

that play a role as a ceRNA to regulate miRNAs (8). When lncRNAs act as endogenous miRNA sponges, they compete with mRNAs for the binding of MREs to miRNAs, thus regulating the expression of target gene transcripts (5,8). There are some LncRNAs such as Xist, H19, HOTAIR, and MALAT1 that function as competitive platforms for both miRNAs and mRNAs (Table 1) (14).

lncRNA X-inactive specific transcript (lncRNA Xist)

There is a long noncoding RNA called lncRNA *Xist* (lncRNA X-inactive specific transcript) on the X chromosome that is 17 *kb* and takes part in cell growth and proliferation (21). *Xist* has also a function as a ceRNA, by sponging different miRNAs from various protein-coding genes that participate in the development of tumor and other human illnesses (21). According to some researches, *Xist* is inappropriately expressed in GC and exerted its function as a ceRNA in the progression of GC (5,21). Current studies have illustrated that the *Xist* acts as a miRNA sponge, working on several miRNAs like miR-101, miR-497, miR-185, miR-132, miR-let-7b, and miR-337 to promote GC (21). Among these interactions, the XIST/miR101/EZH2 axis has been particularly well characterized (3). *EZH2* overexpression has been associated with tumor proliferation, invasion, and metastasis in gastric cancer (22,23). In GC tissues and cell lines, *Xist* is significantly up-regulated, while miR101 is down-regulated, showing a negative correlation between them. *Xist* acts as a molecular sponge for miR101, preventing it from inhibiting *EZH2* expression (24). As a result, *EZH2* levels increase, promoting malignant behaviors (22,23). Knockdown of *Xist* has been shown to suppress GC cell proliferation and invasion *in vitro*, and reduce tumor growth and metastasis *in vivo*, *via* downregulation of *EZH2* mediated by miR101. These findings underscore the oncogenic role of the *Xist*/miR101/*EZH2* regulatory loop, and its potential as a therapeutic target in gastric cancer (24).

Some researches indicated a negative correlation between *Xist* expression and miR-185, miR-101, and miR-let-7b (21). *Xist* can also act as a ceRNA to participate in the development of GC through different miRNA/gene axes, such as miR-185/*TGF-β1*, miR-497/*MACC1*, miR-101/*EZH2*, miR-337/*JAK2*, and 132/*PXN* axises (25-29).

H19-imprinted maternally-expressed transcript (lncRNA H19)

lncRNA H19 is located on human chromosome 11p15 and is close to the *IGF2* gene (5,30). H19 is inherited only from the maternal allel (5,30). During development and postnatal growth, it is highly expressed, but it is generally inhibited during adulthood (31). It is also known that the tumor suppressor p53 epigenetically inhibits H19 production (3). H19 dysregulation led to enhanced cell proliferation and partial p53 inactivation (1). H19 is a vital component in the emergence and advancement of cancer. It functions as a tumor suppressor gene in some cancers, while acting as an oncogene in others to mediate carcinogenesis (32,33). There is evidence that H19, in its RNA role,

Table 1. The function of LncRNA as ceRNAs in gastric cancer

LncRNA	MiRNA	Gene	Biological Functions	Ref
CNALPTC1	miR-6788-5p	*PAK1*	Invasion, proliferation, migration	(60)
LINC00205	miR-26a	*HMGA2, EZH2, and USP15*	Cell proliferation, migration, invasion	(61)
LINC00922	miR-204-5p	*HMGA2*	Cell proliferation, Apoptosis, migration, invasion	(62)
FAM225A	miR-206	*ADAM12*	Cell viability, migration, invasion	(63)
NKX2-1-AS1	miR-145-5p	*SERPINE1*	Angiogenesis	(64)
lncSLCO1C1	miR-211-5p, miR-204-5p	*SSRP1*	Cell proliferation, Apoptosis, migration	(65)
Loc100506691	miR-26a-5p, miR-330-5p	*CHAC1*	Cell growth	(66)

can deceive miRNA and enhance tumorigenesis (3). LncRNA H19 may be utilized as a ceRNA to take a part in the GC progression *via* different miRNA/gene axes, such as miR-let-7c/*HER2*, miR-22-3p/*Snail1*, miR-138/*E2F2*, miR-675/*FADD*, miR-675/*RUNX1*, and miR-141/*ZEB1* (34-39).

MiR-let-7c is an example of a negative correlation with the expression of H19, which acts as a tumor suppressor. When H19 is turned off, *HER2* expression is inhibited, so it can compete as ceRNA in GC (35). There is a positive corralation between H19 expression and miR-675 expression, which increases the occurrence and spread of GC *via* FADD/Caspase 8/Caspase 3 signaling pathway (34).

HOX transcript antisense intergenic RNA (lncRNA HOTAIR)

LncRNA HOTAIR was discovered in 2007 and called HOX antisense intergenic RNA (40). LncRNA HOTAIR is located on chromosome 12, which contains 2,158 nucleotides (41). *HOX* is an oncogene and has been reported to inhibit apoptosis and promote metastasis (1,41). *HOX*, as a member of ceRNA network, can promote carcinogenesis and progression of GC and affect the following axes: miR-126/*VEGFA*, miR-34a/PI3K/Akt, miR-34a/Wnt/β-catenin, miR-217/*GPC5* and *PTPN14*, miR-17-5p/*PTEN*, miR-454-3p/*STAT3*, miR-126/*CXCR4*, miR-618/*KLF12*, miR-1277-5p/*COL5A1*, miR-148b/*PCDH10*, and miRNA-206/*CCND1/CCND2* (31,42-50). In particular, the HOTAIR/miR-34a axis has been shown to play a crucial role in chemoresistance in gastric cancer. HOTAIR is overexpressed in GC and suppresses miR-34a, a known tumor suppressor (51). This suppression activates the PI3K/Akt and Wnt/β-catenin signaling pathways, both of which are involved in promoting cell proliferation, survival, and drug resistance. The PI3K/Akt pathway is essential for transmitting survival signals that protect cancer cells from apoptosis, while the Wnt/β-catenin pathway contributes to tumor growth and metastasis (52,53). Knockdown of HOTAIR leads to the upregulation of miR-34a, which in turn downregulates these signaling pathways, thereby reducing cisplatin resistance in GC cells. These findings indicate that HOTAIR may contribute to chemotherapy resistance through its regulatory effects on miR-34a and downstream oncogenic pathways (51).

Metastasis-associated lung-adenocarcinoma transcript 1 (MALAT1)

MALAT1 is located on chromosome 11q13, which plays an important role in tumor growth, metastasis, apoptosis, epigenetic regulation, and cell signal transduction; it also acts as a ceRNA in GC (54-58). According to various studies, *MALAT1* interacts as a competitive endogenous RNA (ceRNA) with the microRNA/gene axis, such as miR-202/*Gli2*, miR-1297/*HMGB2*, miR-23b-3/*ATG12*, miR-30b/*ATG5*, miR-125a/*IL-21R*, miR-181a-5p/*AKT3*, miR-204/*LC3B*, miR-204/*TRPM3*, miR-22-3p/*ErbB3*, miR-22-3p/*ZFP91*, and miR-124-3p/*EZH2* (55-63).

CircRNAs as ceRNAs in GC

Single-stranded and closed RNAs (circRNAs) were first discovered in viroids, which are plant pathogens. CircRNAs lack the polyadenylic acid (poly A) tail structure at 3' and the cap structure at 5' (5, 64). CircRNAs exist in a variety of cells and have characteristics like stability and sequence conservation (65). It is known that they play roles in various biological processes, particularly cell cycle control and extracellular junctions (66). CircRNAs can be divided into four categories: tRNA intronic circRNAs (tricRNAs), exon-intron RNAs (EIciRNAs), circular intronic RNAs (ciRNAs), and Exonic circRNAs (ecircRNA) (67). There is increasing evidence that the dysregulation of circRNAs causes human disease, especially many types of cancer (66,67). There is evidence that circular RNAs play a role as ceRNAs in gastric cancer (Table 2) (5). In 2019, scientists detected a negative correlation between circCOL6A3 and miR-3064-5p (68). Overexpression of circCOL6A3 increases cell motility and apoptosis of GC cells (68). Patients with GC have a dismal prognosis for survival when circPDZD8 is significantly overexpressed (69). GC cells may not proliferate and migrate to other tissues as much if CircPDZD8 is knocked down (69). It was found that the expression of circPDZD8 was negatively correlated with MiR-197-5p and positively correlated with the *CHD9* gene (69). In 2021, it was reported by Tang Zhou *et al* that circ_0081143 could regulate miR-497-5p through its ceRNA activity of the miR-497-5p/*EGFR* axis. It is at least partially

Table 2. The function of circRNAs as ceRNAs in gastric cancer

Circular	MiRNA	Gene	Biological functions	Ref
CircCOL6A3	miR-3064-5p	*COL6A3*	Proliferation, migration, apoptosis	(71)
CircPDZD8	miR-197-5p	*CHD9*	Proliferation, migration	(72)
Circ_0081143	miR-497-5p	*EGFR*	Migration, invasion, EMT	(73)
Circ_0001789	miR-140-3p	*PAK2*	Cell migration, invasion and epithelial-mesenchymal transition	(74)
Circ0007360	miR-762	*IRF7*	Cell proliferation, migration	(75)
Circ_0001013,	miR-136	*TWSG1*	Migration, invasion, apoptosis, cell cycle	(76)
CircKIF4A	miR-144-3p	*EZH2*	Proliferation, migration, invasion, EMT	(77)
Hsa_circ_0044301	Hsa-miR-188-5p	*DAXX*	Proliferation, migration, invasion	(78)
Circ-0007707	miR-429	*PDGFD*	Tumor Microenvironment, Immune infiltration	(79)
CircRNA-0000081	hsa-miR-423-5p	*PDPK1*	Proliferation, migration, invasion	(80)

involved in improving migration and EMT caused by hypoxia in GC cells, and knockdown of circle 0081143 is mediated by miR-497-5 (70).

Pseudogenes

The pseudogenes are common in the human genome (approximately 11,000 pseudogenes); however, as previously thought, they are undesirable genes, known as "genomic fossils" (71-73).

Based on recent studies, pseudogenes take a significant regulatory role in a number of human diseases (71-73). Although pseudogenes do not encode functional proteins due to deleterious perturbations such as premature termination, deletions, insertions, or even mutations in their Open Reading Frames (ORFs), they take a major role in post-transcriptional regulation (71-73). These genes can act as miRNA sponges due to having an MRE similar to their original genes (70). Furthermore, pseudogenes can control gene expression by interacting with RNA-binding proteins (5). Pseudogenes can participate in the ceRNA regulatory network in the regulation of transcription of genes (5). *POU5F1B* is an example of pseudogenes that play a role in gastric cancer. Its overexpression not only causes cell proliferation and tumor growth, but also inhibits apoptosis (73).

One of the SUMO pseudogenes is *SUMO1P3* (SUMO small ubiquitin-like modifier 1 pseudogene 3), which induces lncRNA expression (73). According to a report by Mei *et al*, *SUMO1P3* is upregulated in GC. Upregulation of *SUMO1P3* is significantly related to various factors, including age, tumor size, and invasiveness. In addition, overexpression of *SUMO1P3* may be used for the diagnosis of GC as a biomarker (73).

OCT4 is a self-renewal gene in stem cells and is also called as *POU5F1*. *OCT4* is expressed in different cancer cell lines and embryonic stem cells as well as preliminary tumors (74). Based on some studies, *OCT4* pseudogenes are expressed differently in various types of cell lines. *POU5F1B*, which is also called *OCT4-pg1*, has many homologs with *OCT4* pseudogenes (74).

POU5F1B is situated on chromosome 8q24.21. This region is enhanced in different cancers. *POU5F1B* overexpression in GC cell lines has been illustrated by Pan *et al* (74). They showed that overexpression of *POU5F1B* not only causes tumorigenesis and cell proliferation, but also inhibits apoptosis. The *POU5F1B* pseudogene, by producing an active protein, can cause tumor development and is also considered as a prognostic factor in patients with advanced GC (73).

PTENP1 is situated on chromosome 9p13.3 and was the first ceRNA found in cancer cells of humans and causes tumor suppression (73,75). The *PTENP1* pseudogene and its ancestral gene, *PTEN*, have a highly conserved3′ UTR, and this pseudogene is

regulated by miR-106b and miR-93 in GC cells (76).

Conclusion

In summary, few studies have been done on the role of ceRNA in the diagnosis and treatment of GC. In this study, the role of non-coding RNAs (ncRNAs), including microRNA, long non-coding RNAs (lncRNAs), circular RNAs (circRNAs), and pseudogenes as a network of competing internal RNAs in regulating gene expression at the transcriptional level in GC, were presented. Non-coding RNAs, as ceRNAs, are involved in various biological processes, such as cell proliferation, apoptosis, invasion, and migration.

CeRNAs networks play a significant regulatory role in the progression of GC, and in the ceRNAs networks, ncRNAs competitively target miRNAs and play a role in the regulation of gastric cancer-related genes. Altogether, the study of the ceRNA network in GC can improve our knowledge on the disease development and progression, molecular signaling, prognosis, and diagnosis, as well as for identifying new therapeutic strategies for treating GC patients.

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Conflict of Interest

The authors declare that they have no conflicts of interest.

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