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Review

Non-coding RNAs in regulating gastric cancer metastasis

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ABSTRACT

Gastric cancer is one of the leading causes of cancer-related deaths worldwide, and mortality remains high, especially in East Asia. At present, the main method to diagnose gastric cancer is pathological biopsy. At the time of diagnosis, most patients have been diagnosed with advanced cancer and metastasis. The treatment of gastric cancer patients is mainly radical surgical resection and chemoradiotherapy, while patients with metastatic tumor have great challenges to radical surgery and are prone to drug resistance. Metastasis is an important factor affecting tumor development. In addition, evidence accumulated in the literature indicates that non-coding RNA plays a key role in tumor metastasis. This article reviews the role of ncRNAs in gastric cancer metastasis and discusses the regulatory mechanism in the development and treatment of gastric cancer.

1. Introduction

Gastric cancer (GC) is a typical malignant tumor of the gastrointestinal tract. The number of GC deaths is increasing year by year in the world, especially in East Asia [1]. One of the reasons for this high mortality rate is that most GC patients have been diagnosed with advanced stage and cancer metastasis, losing the optimal time for treatment [2]. At present, with the advancement of pathological biochemical diagnostic techniques and surgical resection techniques, the success rate of cancer treatment and postoperative survival rate of patients have been significantly improved. However, metastatic patients are less effective in surgical treatment, more resistant to drug therapy, and have lower survival rates [3].

Metastatic cancer is a huge challenge for current cancer treatment, and there is currently no effective treatment for metastatic cancer. Metastasis involves multiple sequential steps, and is characterized by increased invasion and proliferation of cancer cells, an important feature of malignant progression of cacner. Epithelial-mesenchymal transition (EMT) is the key to tumor metastasis. During the biological process of EMT, epithelial cells lose their polarity, lose the connection with the basement membrane, and reduce the intercellular adhesion. More “free” tumor cells enter the blood circulation, proliferate, spread and metastasize at new sites, tumor cells are more likely to evade drug treatment [4]. Metastasis is often the leading cause of cancer treatment failure.

Recently, non-coding RNAs (ncRNAs) have attracted more attention. In addition to traditional disease auxiliary diagnostic indicators, ncRNAs can also participate in the occurrence and development of tumors and affect the treatment of disease. Due to the temporal and spatial specificity of ncRNAs expression, there is an urgent need to study the association between ncRNAs dysregulation and metastatic pathways in GC. However, the number of studies is still limited. With the development of ncRNA-based therapies, it is necessary to summarize the role of ncRNAs in tumor metastasis, particularly in GC. In this review, we will overview the current research status of ncRNAs in GC metastasis, and discuss the potential clinical application value of ncRNAs in GC.

2. ncRNAs in diagnosis

Liquid biopsy, as a non-invasive method, can provide auxiliary value for early diagnosis and prognosis monitoring of diseases [5–7]. With the emergence of new technologies and methods, the advantages of liquid biopsy in tumor research are becoming more and more obvious [6]. Initially, liquid biopsy was performed on blood [8], but now a variety of body fluids (urine, saliva, digestive fluids,etc.) are available for clinical testing [9–11].

Plasma is the liquid part of the blood, which doesn't include all cellular components, and is the transport medium for nutrients and metabolites to various organs of the body [12]. It also plays a vital role in maintaining normal blood pressure. The main difference between serum and plasma is the lack of coagulation factors in serum, which mainly contains fibrinogen, whose main function is to provide necessary nutrients for the body and maintain the normal properties of blood

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[13]. Plasma and serum contain a variety of proteins [14], hormones, growth factors, etc., which can better reflect the physical condition and is an ideal “liquid biopsy” marker. In our previous study, we found a new lncRNA CTC-497E21.4 in the TCGA database and GEO database using bioinformatics analysis, which was highly expressed in GC tissues and correlated with patient survival. By collecting serum from 110 patients with GC and 84 normal people, we used qPCR technology to detect the relative expression level of lncRNA CTC-497E21.4. Combined with the clinical information of patients, we confirmed that high expression of lncRNA CTC-497E21.4 was positively correlated with tumor metastasis and patient prognosis [15].

Urine is a fluid that is excreted by the body through the urinary system and urinary tract and is used for the metabolic needs of humans or vertebrates. Urine production is dependent on glomerular filtration, absorption and secretion of renal tubules and collecting tubes [16]. Therefore, urine tests can reveal many diseases. Kao HW and his colleagues collected and detected the expression levels of miR-21-5p in preoperative and postoperative urine samples of GC patients, and found that high expression of miR-21-5p was significantly associated with cancer and survival [17].

Saliva is a colorless and thin liquid. Secreted mainly by salivary glands, which lubricates the oral mucosa, dissolves food and facilitates swallowing, and protects the oral mucosa from biological and chemical factors [18]. Because saliva composition is very similar to serum, changes in saliva composition also reflect disease and health conditions. At present, methods for determining health status and diagnosing diseases using saliva components and their changes have been widely developed [18]. Saliva test is also very popular with doctors and patients because it is convenient and painless. Li F et al. confirmed a group of miRNAs (miR-140-5p, miR-301a) as potential biomarkers for the diagnosis of GC by studying the saliva of GC patients [19]. Similar studies have also demonstrated the existence of other ncRNAs in saliva, which can serve as important markers for cancer diagnosis [20,21].

At present, a number of ncRNAs detection and research techniques have been established (Table 3), and each method has its own advantages and disadvantages. In order to make the detection and research of ncRNAs become an important means of human disease screening, we need to make the detection method meet certain conditions. For example, 1) high sensitivity. Detection can still be carried out in the case of fewer objects to be tested. 2) high specificity. It can detect the target gene specifically and is not easily disturbed by other substances. 3) economy. It doesn't require expensive reagents or equipments, and it doesn't require a lot of manpower and material resources.

2.1. Northern blotting

Northern blot uses electrophoresis to distinguish different RNA molecules according to their molecular weight, and then hybridizes them with probes that are complementary to specific genes to detect the target fragment [22]. The advantage of Northern blot is that it can detect the size of the target segment, whether there is variable shear, and allow partial mismatch of the probe, but it is expensive and takes time and energy [22,23]. In addition, the commonly used labeling marker fo NB detection is the radioisotopes(^{32}P), which causes many safety problems to researchers and the envieronment [24]. Despite many shortcomings, NB is the only way to provide RNA sequences and lengths [25]. Therefore, this technique is still widely used in RNA detection [25–27].

2.2. Real-time fluorescence quantitative PCR

RT-qPCR is a method to determine the total amount of products after each polymerase chain reaction cycle using fluorescence chemicals in DNA amplification reaction. Quantitative analysis of a specific DNA sequence in a sample by internal or external methods. A large number of recent reports on the use of PCR technology in cancer research have proved that this method has great advantages [28,29].

2.3. Fluorescence in situ hybridization

FISH technique is to hybridize the nucleic acid probe directly or indirectly labeled with fluorescein and the nucleic acid sequence in the sample to be tested in accordance with the principle of complementary pairing of bases. After washing, the probe is directly observed under the fluorescence microscope. This technology has advantages in qualitative, quantitative, integration, expression and other aspects of genes, and has been widely used in genetic disease diagnosis, virus infection analysis, prenatal diagnosis, tumor genetics and genomics research and other fields, and has played an important role in gene research [30–32].

3. ncRNAs in metastasis

Cancer metastasis is a huge challenge in treating diseases. Early diagnosis of diseases and detection of cancer metastasis have potential significance for treatment. Currently, clinical screening indicators lack specificity and accuracy, such as CEA, CA19-9, etc., have a low diagnostic efficiency [33]. Therefore, it is urgent to study new effective predictive indicators. However, since the discovery of ncRNAs, many studies have demonstrated that ncRNAs can serve as a potential cancer diagnostic markers [25,34,35]. Meanwhile, mechanism studies have confirmed that ncRNAs can also regulate tumor progression and prognosis [36–38]. Here, we discuss the various mechanisms involved in the regulation of ncRNAs.

3.1. ncRNAs regulate metastasis through EMT

Transcription factors Snail, Twist, and ZEB are the initiation factors of EMT induction. They can regulate the expression of EMT-related molecular labels, thereby interfering with the EMT process and affecting the occurrence and development of tumors [39]. At present, many studies have proved that ncRNAs can directly or indirectly participate in the regulation of the expression of transcription factors, thus affecting the EMT process (Fig. 1). Wu et al. found that lncRNA TRERNA1 could act as an enhancer of Snail and regulated the expression of CDH-1, suppress the expression of E-cadherin, thus promoting the metastasis of GC cells [40]. Similarly, overexpression of lncRNA XLOC-010235 could increase the mRNA and protein level of Snail [41]. Yu et al. validated that low expression of miR-491-5p in GC was obviously correlated with tumor metastasis. In vitro cell experiments showed that increasing miR-491-5p could enhance the level of Snail and promote EMT [42]. Dual luciferase reporter assay demonstrated that miR-124 could also bind Snail, and low expression of miR-124 was negatively correlated with tumor metastasis [43]. Another study showed that Snail can inhibit the expression of miR-128, thereby increasing the expression of Bim-1 through the PI3K/AKP pathway and promoting the EMT process of tumor [44]. miR-34a and miR-185 in GC tissues were positively correlated with GKN1, and the increased expression of GKN1 could reduce the expression of mesenchymal marker Snail and inhibit EMT [45]. In addition, according to the EMT models in vitro, miR-204 could inhibit Snail by increasing the TGF-β1, thereby inhibiting cancer metastasis [46]. Twist is a member of transcription factor family, which is up-regulated in a variety of tumors. Mechanism studies have shown that Twist can play an important role in tumor development by influencing apoptosis, inducing EMT, and participating in tumor resistance and metastasis [47,48]. Studies have found that Twist can act on the upstream of E-cadherin and inhibit its expression, thus promoting the metastasis of cancer cells [49]. miR-13a-3p and miR-16-1-3p was negatively correlated with the expression of Twist and plays a role in cancer inhibition [50]. Conversely, overexpression miR-2392 have the ability to affect mastermind-like 3 (MAML3) and wolf-hirschhorn 1 (WHSC1), thereby reducing the expression of Twist and ultimately inhibiting the metastasis of GC cells [51]. ZEB (Zinc finger E-

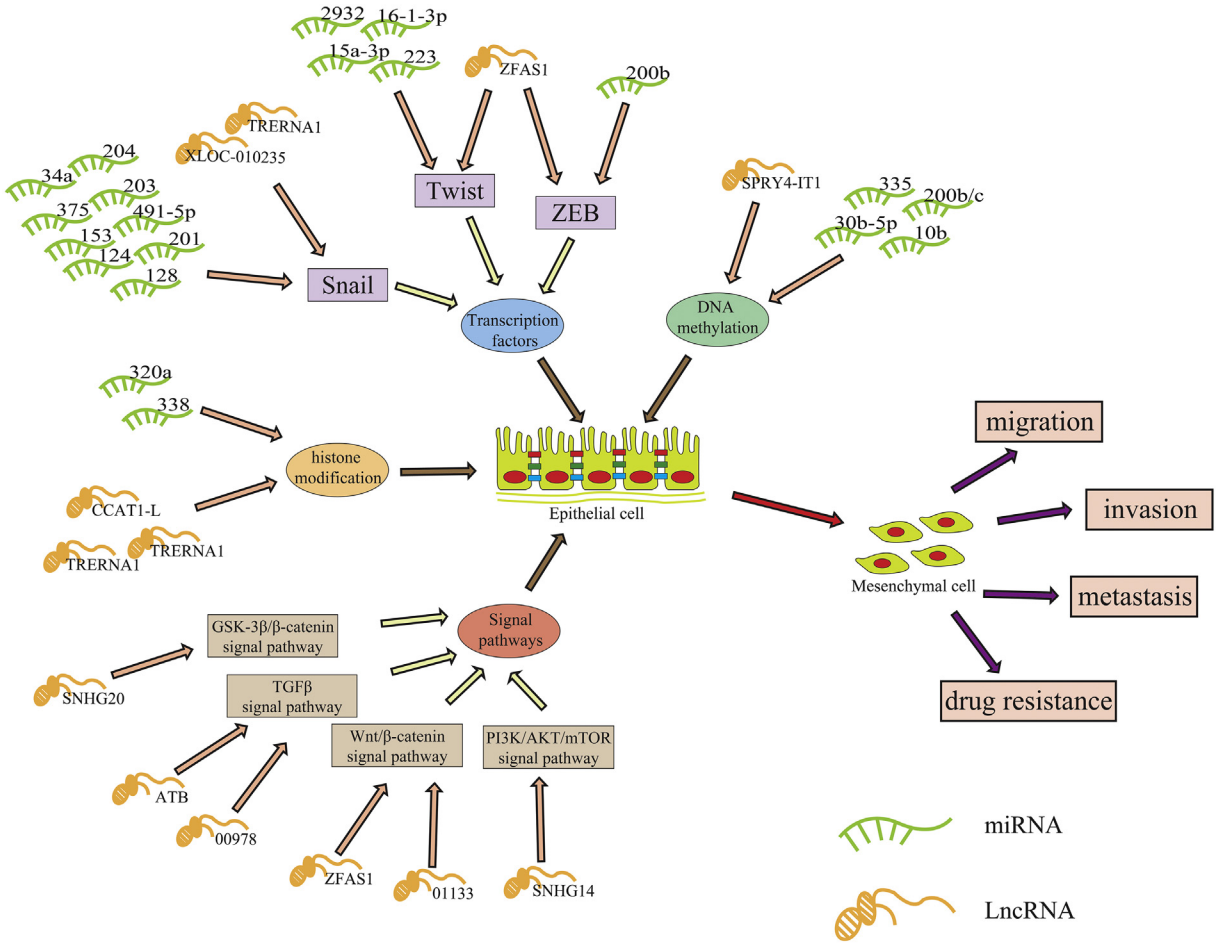

Fig. 1. The complex network of lncRNAs and miRNAs in regulating EMT. Different ncRNAs regulate EMT through diverse signaling pathway by targeting relevant genes which ultimately result in different outcomes.

box-binding protein) has two similar structures, including ZEB1 and ZEB2. Highly expressed ZEB is closely related to tumor metastasis and development [52]. Studies have confirmed that ZEB can promot the metastasis of tumor cells [53]. lncRNA ZFAS1 has also been shown to regulate the process of EMT by inhibiting another transcription factor, ZEB1 [54].

Other studies have confirmed that the EMT process is not only regulated by transcription factors, but also by DNA methylation and histone modification [55–59]. lncRNA SPRY4-IT1 was confirmed to have CpG island in its promoter region, and inhibition of DNA methyltransferase1 (DNMT1) can increase the expression of SPRY4-IT1, thus promoting the metastasis of cancer [60]. The low expression of miR-335 in GC was significantly related to LNM, while the PLAUR and CDH11 target genes were significantly increased in GC tissues. Mechanism studies have demonstrated that miR-335-DNA methylation may be a potential noninvasive method for the treatment of GC [61]. Similar studies have shown that abnormal methylation of miR-335 can also promote the invasion and migration of GC cells. The expression level of miR-335 can be enhanced through demethylation, thus inhibiting the occurrence and development of cancer [62]. The level of miR-30b-5p can be increased by DNA demethylation, while the highly expressed miR-30b-5p can promote the migration of tumor cells and and accelerate the progress of cancer [63]. The level of miR-10b was decreased in GC, and the level of CpG island methylation in the promoter region was increased, which inhibited the level of miR-10b, while the high level of miR-10b could significantly inhibit the proliferation and migration of tumor cells, playing a role in tumor inhibition [64]. Overexpression of mir-200b/c can directly target DNMT3A, DNMT3B and SP1 (a trans-activator of the DNMT1 gene), thereby reducing the protein level of these DNA methyltransferases and inhibiting the growth and invasion of tumor cells [65].

Histone modification refers to the process of methylation, acetylation, phosphorylation and ubiquitination of some enzymes in the body, among which histone methylation take important regulatory part in the process of EMT [66]. lncRNA TRERNA1 can recuit the enhancer of zeste homolog2 (EZH2) as a molecular sponge, and then inhibit the expression of CDH1 through H3K27me3 in the promoter region, thereby inhibiting cancer metastasis [40]. Studies have proved that lncRNA HOXA-AS2 can induce H3K27me3 by binding to EZH2, thus exogenously inhibiting p21, PLK3 and DDIT3, leading to the occurrence of GC metastasis [67]. Similar studies have shown that lncRNA CCAT1-L expression is significantly increased in GC. When lncRNA CCAT1-L is knocked out, it can significantly inhibit tumor growth, improve the survival time of nude mice, increase the expression of E-cadherin, and inhibit tumor metastasis [68]. Ubiquitin-specific protease 14 (USP14) can interact with vimentin to cause its deubiquitination. Studies have shown that miR-320a can bind to the 3′UTR of USP14 and vimentin, suppressing the expression of these proteins and ultimately inhibiting tumor metastasis [69]. As the upstream regulator of NRP1, miR-338 directly acts on NRP1 and inhibits the migration and metastasis of GC cells [70].

3.2. ncRNAs regulate metastasis through the microenvironment

Tumor metastasis is not only regulated by key genes and mechanisms, but also closely related to the microenvironment of tumor cell

Table 1
lncRNAs and drug resistance in digestive system cancers.

ncRNAs	Gene type	Targets	Mechanisms	Ref.
Linc00460	Oncogene		Lymph node metastasis	[90]
lncRNA SLC25A5-AS1	Tumor suppressor	MiR-19a-3p	PTEN/PI3K/AKT signal pathway	[91]
LncRNA SNHG17	Oncogene		Lymph node metastasis	[92]
LncRNA DUSP5P1	Oncogene	C8orf76	MAPK/ERK signal pathway	[93]
LncRNA ZEB2-AS1	Oncogene	MiR-143-5P HIF-1α		[94]
LncRNA PCGEM1	Oncogene	SNAI1	Hypoxia induce	[95]
Linc01939	Tumor suppressor	miR-17-5p EGR2	ceRNA	[96]
Linc02465	Oncogene		PI3K/AKT signal pathway	[97]
LncRNA SNHG20	Oncogene	MiR-495-3p ZFX	ceRNA	[98]
Linc00707	Oncogene	HuR	VAV3/F11R	[99]
LncRNA DGCR5	Tumor suppressor	BTG1	PTEN signal pathway	[100]
LncRNA UCA1	Oncogene	MiR-203 ZEB2	ceRNA	[101]
Linc00165	Oncogene	PRC2 STAT3	EMT	[102]
LncRNA GMAN	Oncogene	Ephrin A1 GMAN-AS	Competitively bind	[25]
LncRNA HOTAIR	Oncogene	PRC2	H3K27me3 EMT	[103]
LncRNA MALAT1	Oncogene	miR-125a-3p IL-21R	ceRNA	[104]
LncRNA GCAWKR	Oncogene	WDR5 KAT2A	Lymph node metastasis	[105]
LncRNA SNHG17	Oncogene	P15 P57	Lymph node metastasis	[106]
Linc01606	Oncogene	JW74	Wnt/β-catenin signal pathway	[107]
Linc01133	Tumor suppressor	miR-106a-3p APC	Wnt/β-catenin signal pathway	[108]
LncRNA LSINCT5	Oncogene	E2F1	EMT	[109]
LncRNA SNHG6	Oncogene	EZH2	JNK pathway	[32]
LncRNA RP11-789C1.1	Oncogene	E-cadherin miR-5003	ceRNA	[110]
LncRNA UCA1	Oncogene	MiR-590-3p CREB1	ceRNA	[111]
Linc01410	Oncogene	MiR-532 NCF2	NK-κB signal pathway	[112]
LncRNA HOTAIR	Oncogene	Runx3 Mex3b	Ubiquitination	[113]
Linc01234	Oncogene	MiR-204-5P CBFB	ceRNA	[114]
LncRNA BC005927	Oncogene	EPHB4	Hypoxia	[115]
LncRNA SMARCC2	Oncogene	miR-551b-3p TMPRSS4	ceRNA	[116]
Linc00261	Oncogene		EMT	[117]
LncRNA AK023391	Oncogene	BCL-6	PI3K/AKT signal pathway	[118]
Linc00675	Oncogene	Ser83 Vimentin	phosphorylation	[119]
LncRNA TRERNA1	Oncogene	SNAI1 EZH2	EMT	[40]
LncRNA SNHG6	Oncogene	miR-101-3p p27	EMT	[120]
LncRNA XLOC010235	Oncogene	Snail1	EMT	[41]
LncRNA HOXA11-AS	Oncogene	KLF2 EZH2		[121]
LncRNA HNRNPKP2	Oncogene	DC-SIGNR CXCR4		[122]

Table 2
miRNAs and drug resistance in digestive system cancers.

ncRNAs	Gene type	Targets	Mechanisms	Ref.
MiR-502-5P	Oncogene	CircDLST	NRAS/MEK1/ERK1/2 signal pathway	[123]
MiR-106b	Oncogene	ALEX1	JAK1/STAT3 signal pathway	[30]
MiR-577	Oncogene	TGF-β SDPR	ERK/NF-κB signal pathway	[124]
MiR-296-5p	Oncogene	CircPSMC3 PTEN	ceRNA	[125]
MiR-7	Oncogene	RelA P65	NF-Kb signal pathway	[126]
miR-149-5p	Oncogene	AKT1 mTOR	EMT	[127]
MiR-520b	Oncogene	GATA6 CREB1		[128]
miR-133a-3p	Oncogene	GABARAPL1 ATG13	Autophagy-mediated glutaminolysis	[129]
miR-371a-3p	Oncogene	TOB1		[130]
miR-338-3p	Tumor suppressor	N-cadherin MMP	Hypermethylation	[131]
miR-130a	Oncogene	C-MYB	Exosome	[132]
miR-589	Oncogene	LIFR c-Jun	PI3K/AKT signal pathway	[133]
miR-17	Tumor suppressor	DEDD	EMT	[134]
miR-129-5p	Tumor suppressor	ADAM9		[135]
miR-423-5p	Oncogene	SUFU	Exosome	[136]
miR-1236-3p	Tumor suppressor	MTA2	PI3K/AKT signal pathway	[137]
miR-375	Oncogene	YAP1 TEAD4 CTGF	Hippo signal pathway	[138]
miR-302b	Tumor suppressor	EphA2	Wnt/β-catenin/EMT signal pathway	[139]
miR-599	Tumor suppressor	EIF5A2	EMT	[140]
miR-335-5p	Tumor suppressor	PLAUR CDH11		[61]
miR-200a	Tumor suppressor	Toosendanin	β-catenin signal pathway	[141]
miR-599	Tumor suppressor	EIF5A2	EMT	[140]
miR-130a-3p	Tumor suppressor	TBL1XR1	EMT	[142]
miR-182	Tumor suppressor	RUNX3 HOXA9		[143]

growth. Microenvironment includes cell growth factors, macrophages, stem cells, etc. ncRNAs can also regulate metastasis by regulating tumor microenvironment.

Vascular endothelial growth factor (VEGF) has the ability to continuously induce angiogenesis. Tumor growth often requires adequate nutrition and oxygen. Su et al. showed that resistin can down-regulate miR-186 through the c-Src signal pathway, thereby inducing VEGF-C-dependent lymphangiogenesis [71]. lncRNAs MEG3 has been proved to be a molecular sponge of miR-494 in HAs cells, and miR-494 can inhibit the function of MEG3 with regulating PTEN/PI3K/AKT pathway, which is negatively correlated with the expression of VEGF [72]. Angiogenesis can aggravate GC progression. High expression of lncRNA PVT1 can activate STAT3 signal pathway, improve VEGFA expression level, stimulate angiogenesis, and patients with GC show poor prognosis [73].

The main immune cells of the body are M2 macrophages. Zheng et al. found that M2 macrophages treated with PMA/IL-4 could induce the expression of MALAT1 in PCa cell lines, and the mechanism study showed that M2 macrophages activated the STAT3 signaling pathway by secreting IL-8 [74]. Chen et al. found that LNMAT1 can activate CCL2 by recruiting hnRNPL to the promoter region of CCL2 and stimulate the secretion of VEGF-C by macrophages to promote lymphatic metastasis [75]. In addition, the plasticity of macrophages enables the dynamic transformation between the M1 and M2 phenotypes. Studies have shown that inhibition of lncRNA cox-2 can reduce the immune effect of M1 macrophages on tumor cells and enhance the cancer

Table 3
Established methods for the detection of ncRNAs.

Methods	Advantage	Limitation	Ref.
Northern blot	Gold standard, High specificity Cheap	Poor sensitivity, Poor efficiency, Radioactivity	[144,145]
RT-PCR	High sensitivity, Quantifiability	Low thoughput, Vulnerable to pollution	[146]
Microarray	High throughput	Expensive, Low specificity	[147]
FISH	High specificity, Localizable	Low thoughput, Low sensitivity, Expensive	[148]

promoting effect of M2 macrophages [76].

Cancer stem cells (CSCs) is a kind of self-renewing and pluripotent cell, which has great influence on the development of tumor and treatment [77]. In vitro studies confirmed that miR-940 can target ARHGAP1 and FAM134A and promote mesenchymal stem cell differentiation [78]. Similar studies demonstrated that miR-34a can target C22ORF28 to inhibit breast cancer stem cells [79]. In addition, mesenchymal stem cells can promote the progression and metastasis of liver cancer through the interaction of lncRNA MUF with ANXA2 and miR-34a [80].

3.3. ncRNAs regulate metastasis through exosomes

Exosomes is a small vesicle with a diameter of 40-100 nm, containing RNA, protein, etc., which can be absorbed and secreted by exosomes and transported in vivo through exosomes. Unlike cell-shedding microbubbles, exosomes are released by the cells themselves. Exosomes can enhance substance exchange between cells, enhance signal transduction, and affect cell biological processes. However, stable and effective material exchange and transfer remains a key obstacle to exosome research. More and more research evidence shows that exosomes can play an important role in regulating the metastasis of cancer cells and cancer treatment by transferring and exchanging ncRNAs.

Wang et al. found that the expression level of miR-27a in exosomes secreted by GC cells was significantly higher. In vivo and in vitro functional tests proved that the overexpression of miR-27a could promote cancer-associated fibroblasts (CAFs) and malignant behaviors of GC cells, such as enhanced proliferation and metastasis [81]. In addition, it has been found that the exosomes secreted by GC cells contain a large amount of EGFR, which can enter the liver through exosomes, bind to the stromal cells of the liver, inhibit the expression of miR-26a/b, enhance the expression of hepatocyte growth factor (HGF), and promote the metastasis of GC cells to the liver [82]. Similarly, exosomes-mediated transfer of lncRNA-ZFAS1 promotes GC metastasis [54].

4. ncRNAs regulate metastasis and affect therapy

Although radical resection and radiotherapy have made great progress in the treatment of cancer patients, there is still no satisfactory treatment for advanced and metastatic cancer. The main reason is that tumor cells with metastatic characteristics are prone to “escape” the targeted effects of drugs. At present, many studies have confirmed that ncRNAs can regulate certain key genes of tumor cells, promote or inhibit the process of tumor cell metastasis, thus improving the therapeutic effect.

CD44 is one of the markers of GC stem cells, which is involved in regulating the self-renewal and pluripotency of cells. Lee et al. found that in $CD44^+$ GC cells, miR-193a-3p expression was increased and cisplatin resistance was observed [83]. Similar studies showed that GC cell lines with high lncRNA XLOC_006753 expression could promote the metastasis of GC cells by activating the PI3K/AKT/mTOR pathway, so as to generate drug resistance [84]. Zhang et al. found that overexpression of miR-939 can activate Raf/MEK/ERK pathway, thereby inhibiting the growth of GC cells and enhancing the sensitivity of GC cells to 5-FU [85]. Studies have shown that lncRNA LEIGC can inhibit tumor growth and metastasis by inhibiting the EMT process, and at the same time improve the sensitivity of GC cells to 5-FU, which is conducive to the treatment of GC [86]. High expression of lncRNA ZFAS1 in GC cells can promote the growth and metastasis of GC cells, while silencing the expression of ZEFAS1 can inhibit the EMT process of GC cells and improve the sensitivity of cells to chemotherapy drugs [87]. miR-204 can directly target TGFBR2, thereby regulating the TGC-β-modulated EMT process. Low expressed miR-204 inhibit GC cell metastasis and enhance the sensitivity to 5-FU [88]. Similar studies have shown that overexpression of miR-30a can inhibit the EMT process of drug-resistant GC cells and make drug-resistant cells transform to epithelial phenotype, increasing the sensitivity to DDP, while knockdown of miR-30a shows the opposite effect [89].

5. Conclusion

In the past few years, the transcriptional noise of non-coding RNAs from the beginning has attracted the attention of many researchers, mainly because of their abnormal expression in cancer and their obvious correlation with the occurrence, development and treatment prognosis of tumors.

ncRNAs regulate the invasion and metastasis of GC based on different regulatory mechanisms and tumor microenvironment. Many studies have confirmed that ncRNAs can serve as a new potential target for prognosis and treatment. Here, we summarize the recent studies on the regulation of ncRNAs in GC metastasis (Tables 1, 2). In order to better apply non-coding RNA in clinical practice, there are still many challenges to overcome. In order to achieve this goal, we need to look for more and more meaningful non-coding RNA. Secondly, the specific mechanism of non-coding RNA regulating tumor cell metastasis needs to be further studied, and the individualized diagnosis and treatment of non-coding RNA is still our research direction and goal.

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Compliance with ethical standards

This article does not contain any studies with human participants or animals performed by any of the authors.

Declaration of Competing Interest

None.

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