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Current Advancement of the miR-17-92 Cluster in Gastrointestinal Cancers

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Abstract

Gastrointestinal (GI) cancers, especially including esophageal, gastric and colorectal cancer, are common types of cancer with high morbidity and mortality worldwide. Despite great advances having been made for these cancers, current treatments including surgery, Radiotherapy (RT) and Chemotherapy (CT) are still far from satisfactory as these cancers are usually discovered in advanced stages that are associated with short longevity and poor outcomes. MicroRNAs (miRNAs) are short noncoding strands of RNA that regulate gene expression, affecting proliferation, development, differentiation, apoptosis, metabolism and Epithelial-mesenchymal Transition (EMT). The miR-17-92 cluster was detected as "oncomir-1", which is involved in the onset and progression of numerous human cancers. This review presents the recent developments in knowledge about miR-17-92 clusters for diagnosing and treating GI cancers based on genetic functions, biological phenotypes, related mechanisms, biomarkers and therapeutic perspectives, which could provide a wider horizon for future use.

Keywords: miR-17-92, miRNA, Gastrointestinal cancer, Biomarker, Gastric cancer, Esophageal cancer, Colorectal cancer

Introduction

Gastrointestinal cancer (GI cancer) arises from the combination of the esophagus, stomach, liver, biliary system, pancreas, small intestine, large intestine, rectum and anus, and it is related to malignant conditions of the gastrointestinal tract (GI tract) and digestive tract associated organs [1]. Among these cancers, esophageal, gastric and colorectal cancers are three common types of cancer that exhibit significant morbidity and mortality worldwide. As the International Agency for Research on Cancer (IARC) estimates, malignant tumors of the gastrointestinal system cause nearly 30% of cancer-related morbidity and approximately 40% of cancer-related mortality worldwide [2]. Without any obvious or specific symptoms, GI cancers usually cannot be detected in early stages. Additional means of detection of early stage cancer are urgently needed to improve the survival of patients with GI cancer.

miRNAs are endogenous noncoding regulatory RNAs

that regulate gene expression at the post-transcriptional level. The miR-17-92 cluster was originally detected as "oncomir-1" in human B-cell lymphoma (lacking miR-92a), which indicates new functions in tumorigenesis [3]. The miR-17-92 cluster is located in C13orf25 (chromosome 13 open reading frame 25) and comprises seven miRNAs, including miR-17-3p, miR -17-5p, miR-18a-5p, miR-19a-3p, miR-19b-3p, miR-20a-5p and miR-92a-3p [4]. These highly conserved microRNAs are characterized by similar structural features, demonstrate diverse expression patterns and participate in a broad spectrum of physiological procedures including but not limited to developmental processes, proliferation, apoptosis, metabolism, differentiation, and epithelial-mesenchymal transition (EMT), and they are involved in the initiation and progression of various human cancers.

In this review, the functions of the miR-17-92 cluster as oncogene and suppressive regulator are profiled in gastrointestinal cancer. The mechanisms are identified, involving cell proliferation and chemoresistance, metastasis and EMT and so on. Moreover, biomarkers and targeted therapy are discussed in this paper, which provide a reference for the diagnosis and therapy of gastrointestinal cancer.

The potential oncogenic and suppressive effect of the miR-17-92 cluster on GI cancers

According to Wu's research, miR-17-92 is upregulated during esophageal adenocarcinoma development [5]. In gastric cancer cells, the miR-17-92 cluster acts as an oncogene, mainly regulating cellular proliferation and apoptosis, as Liu et al. elucidated [6]. They pointed out that the miR-17-92 cluster regulated and was regulated by the development, progression and aggressiveness of GI cancers, which was associated with the occurrence of epithelial-mesenchymal transition (EMT). To better understand the expression pattern of the miR-17-92 cluster in the progression of colon cancer, Knudsen et al. examined miRNA in models from mucosal polyps to adenocarcinomas using chromogenic in situ hybridization [7]. The expression of miR-17, miR-19b, miR-20a, and miR-92a increased in the transitional zone in the adenomatous tissue developing in normal tissue, but miR-17 was predominant. The expression of miR-17-92 is altered early in the normal-adenoma-adenocarcinoma sequence and is involved in the development of colon cancer. In addition, the upregulation of miR-18a is related to the occurrence and development of gastric cancer and increases cyclin D1 by regulating the PTEN-PI3K-AKT-mTOR signal axis, promoting cell proliferation, and affecting chemoresistance of esophageal cancer [8]. The microRNAs 19a and 19b may represent the most important miRNAs as oncomiRs as shown in some research [9]. In gastric cancer, they participated in fundamental functions such as facilitating cell migration, and in colorectal cancer, they decreased apoptosis and increased cell proliferation, migration, and invasion [10,11]. The carcinogenesis role of miR-92 is reported in Duan's and Liu's research [12,13]. Compared with adjacent normal tissues, the level of miR-92 was upregulated in gastric cancer tissues. Furthermore, miR-92 mimics promoted gastric cancer cell proliferation and invasion in both gain or loss-of-function in vitro while its antisense oligos inhibited the related functions in this experiment. However, another study found that miR-92a regulated the migration and invasion but not the apoptosis and proliferation of esophageal squamous cell carcinoma cells in vitro [14].

A novel study found that the expression of the miR-17-92 cluster could be controlled to regulate the progression of colon cancer. This study showed that medium levels of miR-17-92 could promote tumor metastasis, but inhibition could happen at high levels. In parallel, the inhibition by miR-17-5p may have tumor suppressive effects on gastric cancer and colorectal cancer and enhance its chemosensitivity [15,16]. One study showed that the overexpression of miR-18a had a negative effect on tumor growth and angiogenesis in gastric tumor cells using flow cytometry and Transwell-Matrigel assays [17]. In addition, this paper paid attention to the role of miR-18a under hypoxic conditions. The same results were found for miR-92a. To investigate the functional role of miR-92a on cell viability, Shin et al. transfected the miR-92a mimic into five gastric cancer cell lines. The results showed that overexpression of miR-92a significantly induced growth retardation, which implicated miR-92a as playing an inhibitory role in the growth of gastric cancer [18]. Similar results were reported in Ahmadi's study in colorectal cancer [19].

An increasing body of evidence showed that miRNAs are responsible for cell migration, morphology, cell cycle arrest and apoptosis in each stage of cancer progression. The miR-17-92 cluster not only has an oncogenic function in GI cancer progression, such as cell proliferation, invasion, and metastasis, but also has a positive effect on promoting apoptosis, decreasing cell migration, altering cell morphology and so on. Understanding the dual mechanism of action of the miR-17-92 cluster could provide novel ideas for the treatment of GI cancers.

miR-17-92 signatures for biological phenotypes and mechanisms of GI cancer

The implications of miR-17-92 clusters in gastrointestinal malignancies as well as their potential utility to serve as oncogenes and suppressor genes have been depicted in detail. However, to better understand the pathogenesis of the gastrointestinal malignancies, we need to fully interpret the mechanisms that are involved in the regulation of miR-17-92 at the transcriptional and posttranscriptional level.

The functions and mechanisms of miR-17-92 implicated in chemoresistance and proliferation: Cancer stem cells (CSCs) that possess the ability to self-renew are highly chemoresistant and represent a cellular source for malignancy relapse. In the stem cell literature, miRNAs have been associated with key cell-fate regulators. However, what role the miR-17-92 cluster plays in CSCs chemoresistance still needs definite elucidation. A sequence of evidence showed that particular miRNA alterations are associated with tumor initiation, progression and recurrence [20]. Cioffi et al. [21] observed that miR-17-92 cluster was upregulated in bulk cancer tissue including pancreatic cancer while downregulated in chemoresistant CSCs. Of note, overexpression of miR-17-92 in cancer stem cells resulted in abrogation of stem-like features including self-renewal via miR-17-92/NODAL-ACTIVIN-TGF-β1/p21 Tbx3 axis. However, the process promoted proliferation which resulted in exhaustion of normally slow-cycling CSCs and increased sensitivity to chemotherapeutics. In addition to the abovementioned studies, a study observed that miR-17-92 served as a link between DNA methylation and cancer stem cells, which could provide a rationale to improve the poor outcome of malignancy [22].

Understanding the mechanisms implicated in chemoresistance and metastasis is critical to finding prognostic factors and therapeutic targets and improving patient outcomes. To find novel strategies to reverse drug resistance, Awan et al. established an integrated model of the miR-17-92 cluster and crosstalk of two signaling pathways (EGFR and IL-6) to evaluate the relationships of critical targets of miR-17-92 involved in sorafenib resistance [23]. Zhu and Zhou demonstrated that drug resistance is related to higher expression of the miR-17-92 cluster in some types of cancers [24,25]. This cluster played a key role in cellular proliferation, apoptosis and chemoresistance through suppressing the inhibitor of the AKT signaling pathway and subsequently activating this pathway. Similar effects happen for miR-92a, which acts as a tumor suppressor to inhibit cellular proliferation and invasion and is apoptosis-inducing through the NF-κB-EP4/Notch 1 pathway in gastric cancer [18]. The sensitivity to rapamycin could be restored by inhibition of members of the miR-17-92 clusters [26]. Wang et al. [27] demonstrated that miR-19a/b are also important members in regulating multidrug resistance in gastric cancer cells by targeting PTEN, which provides a therapeutic aspect for failure of gastric cancer chemotherapy. Mastropasqua et al. [16] concluded that TRIM8, via controlling p53 and its regulator miR-17-5p, participates in cellular proliferation via p53, miR-34a and N-MYC, which plays a pivotal role in drug responsiveness of cancers.

There are a few studies showing that apoptotic or antiapoptotic roles of the miR-17-92 cluster have been identified by repression of PTEN, Bim, MYCN, HDAC8, and the E2F family as its targets [28]. In recent years, the mechanisms of maintaining neoplastic status have been shown to be modulated by MYC associated with miRNAs. Through miR-17-92, the expression of specific chromatin regulatory genes (Sin3b, Hbp1, Suv420h1, Btg1, and Bim) was regulated to sustain autonomous proliferation, self-renewal, and survival [29]. There is a lack of complete understanding of drug resistance, so further investigation of miRNAs and miRNA-related pathways are urgently needed to broaden our horizon on the mechanisms implicated in drug resistance.

The functions of miR-17-92 in GI cancer metastasis and EMT: Epithelial-mesenchymal transition(EMT) is a complex process involved in the conversion of an epithelial (E) cell into a mesenchymal (M) cell, and it plays significant roles in inducing and maintaining stemness properties(cancer stem cells transition) and increasing tumorigenicity [30]. Specifically, the process is in relation to every stage involved in the progression of initiation, primary tumor growth, invasion, and spread to colonization as well as treatment-resistance.

Although epithelial-mesenchymal transition is rarely completed in tumor cells, a partial activation by epithelial-mesenchymal transition transcription factor (EMT-TFs) increases cancer cell motility for invasion and dissemination. EMT-TF, a factor that activates epithelial-mesenchymal transition in most types of tumors including nonepithelial tumors, is often described as tissue-specific in that you can discern differences, for example between pancreatic and breast carcinoma [31-33]. Previous

research has shown that miR-200 participates in the EMT process associated with miRNA regulation of pancreatic cancer stem cells [34]. Subsequent studies on miR-17-92 clusters and EMT in carcinoma metastasis have provided promising targeted therapy in the progression of cancer [32,33]. A research team observed that upregulation of the miR-17-92 cluster remarkably enhanced the abilities of metastasis and invasion of gastric cancer cells, which was associated with the occurrence of epithelial-mesenchymal transition [6]. Specifically, another study identified the influence of different levels of miR-17-92 influence for tumor metastasis in colon tumor [35]. They analyzed EMT-associated markers in control and cell lines with different level of miR-17-92 and found an increase of mesenchymal markers and transcriptional factors in the cell line with medium levels of miR-17-92 while decreased in cell line with high levels of miR-17-92. Meanwhile, medium levels of miR-17-92 activate Wnt/β-catenin mediated EMT and promote tumor metastasis whereas EMT inhibited in those cells with high levels of miR-17-92.

In summary, a better understanding of how miRNAs, especially the miR-17-92 cluster, function in GI cancer could provide novel strategies for the development of therapeutics and diagnostics. Given the few studies involving EMT and the miR-17-92 cluster in GI cancer, the specific mechanism still needs to be explored.

The direct or indirect impact of the miR-17-92 cluster on GI cancer immune response: In 2004, miRNAs (miR-142a, miR-181a and miR-223) were first found to regulate immune responses in immune cells. Since the initial observation, miRNAs, including the miR-17-92 cluster, have been described as being implicated in various immune responses including infections, tumors, and autoimmunity [36]. To better understand the meaning of the miR-17-92 cluster in the immune response and to provide a new approach to improve clinical outcomes, we will review several main areas implicating esophageal, gastric and colorectal cancer.

Gastroesophageal reflux disease (GERD), Barrett's esophagus (BE) and obesity are important proinflammatory factors in the pathogenesis of EAC [37,38]. The hypothesis has been toppled that establishment of BE comes from augment of Body Mass Index (BMI) and GERD. Several studies suggest that obesity does not increased acid exposure [39]. Obesity could increase plasma levels of C - reactive protein (CRP), interleukin-6 (IL-6), tumor necrosis factor-alpha (TNF-α) and leptin which represent a chronic proinflammatory state fueling carcinogenesis [40]. Under the stimulation of long-lasting inflammatory insults, Barrett's esophagus developed to low- and high-grade dysplasia (LGD/HGD) and to adenocarcinoma. Therefore, inflammation is regarded as a hallmark which can promote tumor progression and increase cancer risk. miRNAs were pinpointed to regulate esophageal mucosa metaplastic (and neoplastic) transformation during the inflammation. However, there are little article on miR-17-92 and GERD and BE regarding immune response.

Inflammation contributes to the accumulation of both genetic and epigenetic alterations including DNA methylation in gastric epithelial cells which plays a key role in the development of gastric carcinogenesis. microRNAs have been recognized as an important factor in the process of regulation of inflammatory pathways. miRNAs regulate the transcription and expression of related genes to affect the immune host response to Helicobacter pylori (H.pylori). Vacuolating cytotoxin A (VacA), one of virulence factors of H. pylori, suppress proliferation of T and B-lymphocytes, deregulating the host immune response, inducing apoptosis of host cells, finally lowering the threshold for neoplastic transformation [41,42]. Cytotoxin-associated gene A (CagA) could also affect inflammatory responses through multiple signaling pathways like nuclear factor-kappa B (NF-κB pathway) [43]. On the other hand, several tumor-suppressor miRNAs were reported to be silenced by aberrant DNA methylation involved in several inflammatory mediators, such as TNF-α, IL-1ß and reactive oxygen species (ROS) in the epithelial reconstruction [44-48].

NF-κB signaling pathway is a key factor of inflammation which has been implicated in the carcinogenic process [49]. Several miRNAs have been reported to influence the NF-κB signaling pathway through either targeting members of the NF-κB family or upstream signaling molecules [50]. In colon cancer, activation of the NF-κB classical pathway and associated inflammation in intestinal epithelial cells have been implicated in tumor formation [51]. A novel study has been systematically evaluated the co-regulatory functions of NF-κB signaling pathway and miRNAs in colorectal cancer. They found miR-20b-5p was matching with four genes (BTK, CSNK2A2, PLCG1, TNFRSF11A) while miR-92a-3p was associated with five gene (CSNK2A2, TRAF5, PLCG1, TRFRSF11A, BCL2L1) [52].

In conclusion, the immune response is regulated by upregulation of genes that are pro-inflammatory

and promotion of downregulation of genes that have a positive role of immune response in gene expression. The balance of two factors implicated the gene regulation by miRNAs is important for immune response in cancers. The associations between immune response and miRNAs should be further detected to get a better understanding of future immunotherapy.

The miR-17-92 cluster as a potential discriminative biomarker in the diagnosis and prognosis of GI cancers

GI cancers cannot generally be detected in early stages because their clinical manifestation is not obvious. The conventional blood biomarkers including carcinoembryonic antigen (CEA), cancer antigen 125 (CA125), cancer antigen 199 (CA199), and squamous cell carcinoma (SCC) are simple and noninvasive technology, but the low sensitivity and specificity of these available biomarkers limits their utility particularly in distinguishing between aggressive and indolent tumors [53]. However, apart from all of the aforementioned biomarkers used for GI cancers, microRNAs (miRNAs) are quite stable, can be isolated from plasma or serum and have shown great promise as potential prognostic and diagnostic biomarkers for GI cancers [54,55].

Esophageal cancer: Precancerous lesions are actually in various sequential stages from dysplasia to malignancy in histopathology and are high-risk factors for the origin of cancer [56]. Fassan et al. [57] mentioned that the expression of hsa-miR-18a in microRNA profiling was progressively down regulated in the phenotypic sequence from squamous to gastric-type to intestinal-type mucosa samples. This provides proof of the changes of progression-related miRNAs in GI cancer. miR-17, miR-18a, miR-19a, and miR-92a are expressed at higher levels in esophageal squamous cell carcinoma tissues than normal tissues as shown in many studies [14,58,59]. Through univariate and multivariate analysis, they indicated that expression of miR-18a and miR-92a in particular are related to clinical stage. In addition, miR-18a has diagnostic and preventive potential and may be significantly correlated with survival time. miR-19a was reported to be associated with lymph node metastasis and clinical stage in esophageal squamous cell carcinoma, the same as miR-92a [14]. A study analyzed the tissue-associated miRNAs differentially expressed in esophageal adenocarcinoma; hsa-miR-92a-1 was one of 113 upregulated miRNAs, and hsa-miR-18a was the one of five miRNAs correlated with survival time [60] (Table 1).

Hirajima et al. [61] designed a clinical study confirming that miR-18a was expressed at higher levels in primary esophageal squamous cell carcinoma tissues and cells in a Japanese report. To evaluate the expression pattern of miR-18a in the plasma, the investigators selected 106 patients with esophageal squamous cell carcinoma to detect the level of miR-18a in pre/postoperative and healthy volunteers using qRT-PCR. They found that miR-18a was reduced significantly in postoperative patients. Subsequently, Komatsu et al. further confirmed that the expression of miR-18a in serum/plasma was higher in esophageal cancer than in healthy controls [62]. In addition, some researchers established a multiple miRNA combination model to distinguish esophageal adenocarcinoma (ECA), especially Barrett's esophagus (BE) [63,64].

Gastric cancer: miR-19a and miR-19b were reported to be over expressed in gastric cancer cells and strongly correlated with metastasis [9]. To authenticate related miRNAs in gastric carcinogenesis, Lee et al. compared the expression of miRNAs between cancerous and noncancerous gastric mucosa and found that miR-18a-5p was upregulated in cancer tissue [65]. Chen et al. [66] validated the role of miR-18a in gastric adenocarcinoma tissue and adjacent non-tumor tissues by in situ hybridization, and inhibiting miR-18a was found to markedly decrease cell proliferation, migration and invasion in gastric cancer cells. Zhang et al. [67] investigated the level of miR-17 and miR-20a in human gastric cancer tissue and found it was significantly higher than that in surrounding normal mucosa. Some studies showed that miR-92a expression was downregulated in tissues of gastric cancer, but more studies reported that high levels of miR-92a were an important predictor of shorter survival in stage II and stage III gastric cancer [18]. A tissue microarray analysis of 180 patients with gastric cancer who were undergoing radical resection showed that high levels of miR-92 were a negative prognostic factor, similar to tumor stage, tumor status, node status, and tumor size, for predicting overall survival of patients with gastric cancer [68] (Table 2).

Su et al. examined the expression of miR-18a using a TaqMan real-time quantitative PCR (TaqMan PCR) assay in 82 patients with gastric cancer and 65 healthy controls. The expression of miR-18a was upregulated in the plasma of gastric cancer patients with a 0.907 Area Under the Curve (AUC). The sensitivity and specificity were 80.5% and 84.6%, respectively, in discriminating gastric cancer from healthy controls [62]. Cox analysis showed that miR-18a is related to disease-free survival

and could serve as a biomarker in diagnosing gastric cancer and prognostication [69]. Wang et al. [70] detected that exosome miR-19b-3p was associated with lymphatic metastasis and clinical staging in gastric cancer. Some researchers also demonstrated that the miR-17-92 cluster in the serum of the intestinal metaplasia was higher than in the normal group [71]. The miR-17-92 cluster not only participates in the progression of gastric cancer but also could be used to monitor therapeutic utility. Fan et al. tested the expression of the miR-17-92 cluster in the plasma of gastric cancer patients undergoing traditional chemotherapy with oxaliplatin/capecitabine (XELOX) [72]. The results showed that the miR-17-92 cluster was expressed at higher levels in advanced gastric cancer and was downregulated after chemotherapy. Numerous studies have shown that circulating miR-17-5p, miR-20a, and miR-18 expression are significantly lower after surgery. These miRNAs are correlated with the degree of malignancy and disease survival. miR-17 can also be a predictor of postoperative outcomes [73-75]. There are different points in Shin's study. They found that miR-92a is underexpressed in tissues and plasma. miR-92a served as an inhibitor in cell proliferation and invasion and induced apoptosis when overexpressed in cancer cells [18].

Interestingly, researchers have paid attention to the peritoneal fluid since peritoneal metastasis is the most frequent type of recurrence and is associated with a poor prognosis in gastric cancer, although it has low sensitivity [76]. There are a few studies of the miR-17-92 cluster in fecal and urine samples from patients with gastric cancer. Similar to circulating miRNA, further studies on test approaches urgently need to be established for the clinical utility of body fluid testing of miRNAs. We need to attain both high sensitivity and specificity of these miRNAs in the future, which could provide inexpensive approaches and widespread use of miRNAs for patients.

Colorectal cancer: In 2015, there was a study that reported that the level of miR-17 increased from normal to adenomatous tissue. miR-19b, miR-20a, and miR-92a followed the same expression pattern, but miR-17 was the most upregulated member during early colon cancer evolution [7]. Overexpressed miR-92a was associated with biopathologic features in colorectal cancer (CRC), such as TNM stage, lymph node and distant metastases and poor survival of the patients [77]. Multivariate analysis showed that miR-92a may act as a prognostic marker and disease progression marker for CRC. miR-20a-5p was included in a prognostic and predictive microRNA model for stage II colon cancer [78] (Table 3).

The differential expression of microRNAs in the circulation has the potential to diagnose precancerous lesions and colorectal cancer [79]. miR-19b and miR-18a are highly expressed in IBD and polyps, respectively [80]. miR-17, miR-19 and miR-20a are highly expressed in CRC. Similar studies have shown that plasma miR-17, miR-18a, and miR-92a are abnormally expressed in patients with colorectal adenomas [81-83]. Furthermore, compared to patients, miR-17-3p, miR-17-5p, and miR-18a-5p were screened in plasma and found to be overexpressed in patients with colorectal cancer [63,84,85]. The high expression of circulating miR-17 and miR-92 is associated with the pathological stage and grade involved in the progression of colorectal cancer [86]. Apart from their diagnostic value, miR-17, miR-92a or miR-19a can be used to monitor the dynamics during chemotherapy and surgery and predict recurrence of colorectal cancer [87-92]. Similar results showed that the expression of miRNA was downregulated after treatment. Kral et al. [93] investigated the correlation between miRNA profiles and treatment outcomes. Plasma samples were collected repeatedly over a period of 1 year to reflect the patient's response to treatment. Finally, they identified RC (rectal cancer)-specific miRNA signals, including members of the miR-17-92 cluster that distinguished responders to adjuvant chemotherapy from nonresponders. Upregulation of miR-17-92 in tumors has a correlation with a higher risk of tumor relapse. Azizian et al. [94] also found that downregulated miR-18a and miR-20a in plasma were associated with negative lymph nodes after surgery. However, a study from the Czech Republic showed that miR-17-3p and miR-92a in serum had no significant differences between colorectal cancer and health controls [95]. They were also not correlated with staging. This provided evidence that miR-17-92 is not suitable for the diagnosis of colorectal cancer.

Fecal miRNAs could also serve as potential noninvasive markers for detection of colorectal cancer. Through analyzing exfoliated colonocytes, the miR-17-92 cluster was expressed higher in CRC patients than in healthy controls, which could be used in colorectal cancer screening [96]. After removal of tumors and advanced adenomas, the expression of miR-18a, miR-19b, miR-20a and miR-92a showed a declining trend in a different paper [97-99]. Specifically, the use of antibiotics did not influence stool miRNA-18a levels. Based on current evidence, their diagnostic effectiveness still needs to be validated in large clinical trials.

Table 1: Tissue-related and circulation-related miR-17-92 cluster in esophageal cancer.

Year	miRNA	Cancer	Source	Effect	Samples	Analysis methods	Cancer malignant pheno-types	Implication	Reference
2011	miR-92a	ESCC	Tissue	Up	107 ESCC	qRT-PCR	lymph node metastasis and TNM stage, tumor initiation and progression	Prognosis	[14]
2013	miR-18a	BE	Tissue	Down	10BE	qRT-PCR	risk evaluation	Prognosis	[57]
2014	miR-17 miR-18a miR-19a	ESCC	Tissue	Up	105 ESCC	RT-qPCR	TNM stage, tumor size, lymph node metastasis, progres-sion-free survival and overall survival	Prognosis	[58]
2013	miR-18a-5p	ESCC	Tissue	Up	52 ESCC	RT-PCR Western blotting	TNM stage, tumor differentiation	Prognosis	[59]
2015	miR-18a miR-92a-1	ESCC	Tissue			Data analysis	survival time	Prognosis	[60]
2013	miR-18a	ESCC	Plasma	Up	106ESCC 54NC	quantitative RT-PCR	detection and monitoring of ESCC	Diagnosis	[61]
2014	miR-18a	ESCC	Plasma/ Serum	Up		Review	detection of ESCC	Diagnosis	[62]
2017	miR-18a, miR-20a	ESCC	Plasma	Up	101ESCC, 133NC	qRT-PCR	diagnosis of ESCC	Diagnosis	[63]
2015	miR-17-5p	ECA	Serum	Up	19NC, 10BE, 18ECA	TaqMan OpenArray miRNA Profiling	detection of ECA	Diagnosis	[64]

Notes: ESCC: Esophageal squamous cell carcinoma; NC: Normal control; ECA: Esophageal adenocarcinoma.

The molecular biological therapeutic perspective of the miR-17-92 cluster

Therapeutics is based on the mechanism of microRNA in cancer, which could target or mimic miRNAs involved in cancer development, EMT and metastasis. The generation of mature miRNAs is a complex process from long primary miRNAs with hundreds to thousands of nucleotides to mature strand miRNAs. miRNAs regulate the mRNA degradation or expression of protein-coding genes through binding the 3′-UTR or 5′-UTR or other regions of messenger RNA (mRNA) [100]. The whole process is significantly important in the treatment of cancer. For instance, the transcription of the miR-17-92 cluster could be mediated by histone deacetylase inhibitors (HDACi) to regulate tumor cell growth and enhance the sensitivity of tumor cells to natural killer cell-mediated lysis in HCC [101]. In addition, miRNAs could also modulate the expression of transcription factors to regulate the function of cells. For example, miR-18a was detected to be upregulated and could trigger cell proliferation by increasing cyclin D1 through the PTEN-PI3K-AKT-mTOR signaling pathway. This could provide a potential treatment for patients with esophageal squamous cell carcinoma by using inhibitors of AKT-mTOR signaling to regulate the miR-17-92 cluster [102]. Additionally, targeting the miR-20a /miR-17–FBXO31–cyclinD1 axis is an effective therapy method that may help to control the progression of gastric cancer [68]. It has been reported that overexpression of miR-19a and miR-19b-1 promoted EMT and reduced lung cancer cell adhesion through regulating epithelial proteins [35]. The migration and invasive abilities of these cells will decrease after silencing the endogenous miR-19.

On the other hand, targeted tumor-associated miRNAs are suitable for intervention therapeutics. miRNA replacement therapy is increasingly concerned with the tumor suppressor miRNAs (mimics) miR-34 and miR-16, which have shown great progress in the treatment of liver cancer and mesothelioma in phase I clinical trials [103-105]. An inhibitor of pri-miR-17-92 named MIR17PTi was developed by Morelli to induce MIR17HG

Table 2: Tissue-related and circulation-related miR-17-92 cluster in gastric cancer.

Year	miRNA	Cancer	Source	Effect	Samples	Analysis methods	Cancer malignant phenotypes	Implication	Reference
2014	miR-19a/b	GC	Cell	Up		gain or loss-of-function experiments	metastasis	Prognosis	[9]
2017	miR-18a	GAC	Tissue	Up	107 GC and NC	miRNA microarray	expression difference	Prognosis	[65]
2016	miR-18a	GC	Tissue	Up		in situ hybridization	cell proliferation, migration, and invasion	Prognosis	[66]
2014	miR-17 miR-20a	GC	Tissue	Up		qRT-PCR	prognosis	Prognosis	[67]
2018	miR-92a	GC	Tissue	Up		Data analysis	inhibited cell proliferation and invasion, and induced apoptosis	Prognosis	[18]
2016	miR-92a	GC	Tissue	Up	180 GC	in situ hybridization	tumor stage, tumor status, node status, tumor size, prognostic predictors for OS	Prognosis	[68]
2014	miR-18a	GC	Plasma	Up	82GC, 65NC	TaqMan quantitative RT-PCR	pathological grade, lymph node status, risk stratification and risk stratification	Prognosis	[69]
2013	miR-17 miR-18 miR-20	GC	Tissue	Up	32 GC and NC	Data analysis	diagnostic and/or prognostic factor	Diagnosis Prognosis	[70]
2017	miR-17-92	GC	Serum	Up	75GC, 104IM, 38NC	quantitative real-time PCR	early detection of GC	Diagnosis	[71]
2018	miR-17-92	GC	Plasma	Up	Advanced GC	quantitative RT-PCR	monitoring effectiveness of chemotherapy	Prognosis	[72]
2012	miR-17-5p miR-20a	GC	Plasma	Up	65,16,6 in pre-O, post-O, relapse GC. Paired-14 GC	real-time RT-PCR	differentiation status, TNM stages, pathological tumor progression, OS	Prognosis	[73]
2015	miR-18a	GC	Plasma	Up	104GC, 65NC	quantitative RT-PCR	screening GC and monitoring tumor dynamics	Prognosis	[74]
2018	miR-17-5pmiR-18a miR-19b-1 miR-20a	GC	Plasma	Up	323GC, 117NC	qPCR	predictive values of GC risk-DFS,OS	Prognosis	[75]

Notes: GC: Gastric cancer; NC: Normal control; OS: Overall survival; DFS: Disease-free survival; IM: Intestinal metaplasia.

primary transcripts and prevent biogenesis of miR-17-92 in Multiple Myeloma (MM) [36,106]. Of course, the inhibition and enhancement of miRNA activity could also be actualized by other small molecules, including RNA, DNA, DNA analogues, miRNA sponges, or miRNA mimics, such as synthetic mimics and those produced by plasmid or lentiviral vectors carrying miRNA sequences [107].

As mentioned earlier, the differential expression of miRNAs in response to surgery and chemotherapy indicated that miRNAs could also be used for monitoring the effectiveness of therapies. In summary, therapy for

Table 3: Tissue-related and circulation-related miR-17-92 cluster in colorectal cancer.

Year	miRNA	Cancer	Source	Effect	Samples	Analysis methods	Cancer malignant pheno-types	Implication	Reference
2015	miR-17	CRC	Tissue	Up (most)	24 ACP	in situ hybridization	development of CRC	Prognosis	[7]
2013	miR-92a	CRC	Tissue	Up	82CRC	RT-qPCR	clinical stage, lymph node metastases, distant metastases, OS	Prognosis	[77]
2013	miR-20a-5p	CRC	Tissue		138 stage II CRC	qRT-PCR	adjuvant chemotherapy man-agement and prog-nosis	Prognosis	[78]
2012	miR-17-3p miR-20a miR-92a	CRC	Tissue blood	Up	15CRC 5NC	PCR	TNM	Prognosis	[79]
2016	miR-17 miR-19a miR-20a	CRC	Serum	Up	30CRC 18IBD 18CP 24NC	PCR	diagnostic biomarkers for CRC	Diagnosis	[80]
2013	miR-18a	CRC	Plasma	Up	63CRC 60AAs 73NC	quantitative RT-PCR	identifying CRC	Diagnosis	[81]
2013	miR-92a	CRC	serum	Up	200CRC 50AAs 80NC	RT-PCR	poor survival, prognostic biomarker	Prognosis	[82]
2018	miR-17-5p (combina-tion)	CRC	serum		21CRC 19ade-noma 21NC	Fluidigm qPCR	distinguish CRC and adenoma	Diagnosis	[83]
2015	miR-17-3p	CRC	serum	Up	70CRC 70NC	QRT-PCR	diagnosis	Diagnosis	[84]
2018	miR-17-3p miR-18a-5p miR-18b-5p (panel)	CRC	plasma	Up	18CRC 18NC	qRT-PCR	CRC detection	Diagnosis	[85]
2018	miR-17-5p miR-92a-3p	CRC	serum	Up	29CRC 10NC	qPCR	pathologic stages and grades	Prognosis	[86]
2009	miR-92a	CRC	Plasma	Up	90CRC 20GC 20IBD 50NC		CRC screening	Prognosis	[87]
2017	miR-17 miR-18b miR-20a	CRC	plasma	Down (after-therapy)	111RC 47NC	Semi RT-PCR	monitoring of tumor response	Prognosis	[88]
2015	miR-17-3p	CRC	Serum	Up	20,20,20 in pre-O post-O and NC	TLDA	shorter DFS, prognostic indicators	Prognosis	[89]
2015	miR-17 miR-92	CRC	Serum	Up (recurred)	37CRC 7NC	RT-PCR	prognosis for recurred	Prognosis	[90]
2015	Exosomal miR-19a	CRC	Serum tissue	Up	90CRC 209	quantitative real-time RT-PCR	recurrence of CRC, prognostic biomarker	Prognosis	[91]

Year	miRNA	Cancer	Source	Effect	Samples	Analysis methods	Cancer malignant pheno-types	Implication	Reference
2013	miR-19a	CRC	Serum	Up (in resistance phase)	72CRC	reverse transcription and quantitative real- time PCR	predicted drug resistance, monitoring resistance	Prognosis	[92]
2018	miR-17-92	CRC	Plasma		100RC	PCR	tumor relapse, treatment response	Prognosis	[93]
2015	miR-18b miR-20a	CRC	Plasma		42RT	PCR	lymph node	Prognosis	[94]
2012	miR-17 miR-92a	CRC	serum		100CRC 30NC	qPCR	clinical stage, grade	Prognosis	[95]
2010	miR-17-92	CRC	Feces	Up	197CRC 119NC	quantitative real-time PCR	CRC screening	Prognosis	[96]
2015	miR-19b-3p miR-20a-5p miR-92a-3p	CRC	Feces	Up Down (surgery)	20CRC 20NC	RT-qPCR	CRC secondary prevention, CRC screening	Prognosis	[97]
2014	miR-18a	CRC	Stool	Up	198CRC 199CP 198NC	miRNA expression array	detection of CRC	Diagnosis	[98]
2012	miR-92a	CRC	Stool	Up	88CRC 57CP 101 NC	RT-qPCR	screening CRC and CP	Prognosis	[99]

Notes: CRC: Colorectal cancer; RC: Rectal cancer; NC: Normal control; OS: Overall survival; DFS: Disease-free survival; ACP: Adenocarcinomas developing in mucosal polyps; CP: Colorectal polyps; BE: Barrett's esophagus; IM: Intestinal metaplasia; GC/MS: Gas chromatography/Mass spectrometry; IBD: Inflammatory bowel disease; AAs: Advanced adenomas; TLDA: TaqMan Low-Density Array; PLF: Peritoneal lavage fluid; MA: Malignant ascites; CM: Culture supernatants (from GC cell lines).

malignancies is one avenue opened through research with miRNA, which provides a novel path to influence tumor progression and survival.

Conclusions and Future Perspectives

Malignancy has always been recognized as a complex process involving cell proliferation, differentiation and migration, especially in gastrointestinal cancer. In recent years, the discovery of miRNAs provided a new pattern of gene regulation for a better understanding of the pathogenesis of cancer. miRNAs serve as epigenetic controllers that target miRNA involved in distinct pathways to modulate various signaling pattern and exert opposing effects [108,109]. Interestingly, the miR-17-92 cluster, a key miRNA, has shown oncogenic and tumor suppressive properties. While miR-17-92 functioned as an oncogene in some cancers [110-112], overexpression of miR-17-92 has also related with cancer progression and poor outcome in osteosarcoma, breast cancer, esophageal squamous cell carcinoma, chronic lymphocytic leukemia and retinoblastoma [113-117]. Moreover, a tumour suppressive role of the miR-17-92 cluster has been verified in prostate tumor and in GI stromal tumours and in oral squamous carcinoma [118-120]. Thus, the duality of this cluster generates different tumor-modulatory effects, due to the complexities of tumor progression as well as the intricacies of the regulation network of miRNAs and their targets. Due to the special signature of miRNA in tissues and in circulation, methods of diagnosis and prediction in GIC or precancerous conditions are rapidly expanding. Along this line, treatment approaches involving molecular biology are reasonable to promote survival and monitor the progression of GI cancer patients. The role of miRNAs in the therapy of cancer is increasingly important with the development of replacement treatment.

Until now, the diagnosis of many GI malignancies including precancerous lesions has to depend on the gastrointestinal endoscope, which is not well tolerated and inconvenient. The miR-17-92 cluster in tissue and circulation has been detected and studied for less than ten years. The signature of expression will change but follows a pattern in various conditions of disease, which could provide a highly accurate diagnostic tool. The aberrant expression of miRNAs has been shown in a number of studies to play key roles in all aspects of GI cancer. Furthermore, miRNA is stable in the circulatory system (serum and plasma) at room temperature. Circulating miRNA detection is a promising method in the

future for the detection of early stage GI cancer. miRNAs have already been identified as novel targets for several diseases, including liver cancer, multiple myeloma(MM), lymphoma and so on. Several miRNA mimics have been tested in phase I clinical trials as a potential therapy for cancer and will transmit a better understanding in molecular therapy through targeting miRNAs. For the complex cellular functions that the miR-17-92 cluster is involved in, we believe that the miR-17-92 cluster has the potential to steer researchers in exciting directions of therapy. Hopefully, the rapid improvements of technique will provide a possibility for the application of the miR-17-92 cluster towards novel diagnostic, prognostic or therapeutic targets in GIC in the near future.

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