

2016 Colorectal Cancer: Global view

MicroRNAs as diagnostic and prognostic biomarkers in colorectal cancer

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Abstract

MicroRNAs (miRNAs) are key regulators involved in various tumors. They regulate cell cycle, apoptosis and cancer stemness, metastasis and chemoresistance by controlling their target gene expressions. Here, we mainly discuss the potential uses of miRNAs in colorectal cancer (CRC) diagnosis. We also shed light on the important corresponding miRNA targets and on the major regulators of miRNAs. Furthermore, we discuss miRNA activity in assessing the prognosis and recurrence of CRC as well as in modulating responsiveness to chemotherapy. Based on the various pro-oncogenic/anti-oncogenic roles of miRNAs, the advantages of a therapeutic strategy based on the delivery of miRNA mimics are also mentioned. Together, miRNA seems to be an excellent tool for effectively monitoring and targeting CRC.

Key words: MicroRNA; Diagnosis; Prognosis; Colorectal cancer; Biomarkers

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Core tip: MicroRNAs (miRNAs) regulate oncogenesis, metastasis and chemotherapy by controlling corresponding target gene expressions. Here, we shed light on the diagnostic and prognostic value of some miRNAs in colorectal cancer and potential miRNA-based therapy was also discussed. We hope that this review will offer useful information for researchers who work in a related field.

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INTRODUCTION

MicroRNAs (miRNAs) are endogenous short non-coding RNAs that downregulate target gene expressions by binding to their 3'-UTR^[1]. MiRNAs function as regulators in a broad biological process. Dysregulation of miRNAs exerts a strong influence in disease progression by changing target gene expressions in various tumors^[2,3]. More and more data have suggested that miRNAs could be potential biomarkers of early-stage colorectal cancer (CRC) since they are unable to be degraded easily and their expression levels in colorectal polyps, blood and stool may give a hint of the occurrence of the disease. CRC accounts for 10% of new cancer cases and is one of the leading causes of death worldwide (over 1.23 million deaths per year)^[4]. To date, the common methods for CRC early diagnosis are computed tomography (CT), colonoscopy and fecal occult blood test (FOBT)^[5]. However, CT has a low sensitivity for the diagnosis of early CRC and could result in a large radiation exposure^[6]. Colonoscopy is also expensive and increases the risk of morbidity or mortality due to perforation of the gut^[7], although it can effectively detect neoplastic occurrence and allow for the removal of polyps when found. FOBT is commonly used but other digestive diseases such as ulcerative colitis and hemorrhoids may also cause blood in stool^[8] so the detection of FOBT is not a sensitive test for an early diagnosis. Taken together, current methodologies for early detection are neither sensitive nor specific. Differential miRNA expression in CRC individuals vs normal individuals is a common event and may be pivotal for tumor onset and progression. What's more, some dysregulated miRNAs are associated with progression and grade malignancy of CRC. Multiple studies have identified the values of miRNAs in CRC diagnosis. Some reports indicated that changed expression levels of miRNAs correlate closely with cancer progression and prognosis^[9-11]. Here, we review the literature to summarize the association of some important miRNAs with early-stage diagnosis, prognosis and recurrence of CRC and to discuss some miRNAs that might give a hint to guide treatment decisions (Table 1).

MiR-21

MiR-21 is one of the most extensively investigated oncogenic miRNAs whose expression is frequently upregulated in CRC^[12-14]. Overexpression of miR-21 is closely correlated with CRC cell proliferation, invasion, lymph node metastases and advanced clinical stage, all of which are the main prognostic factors for CRC. MiR-21 can downregulate several tumor suppressor genes, including PTEN and RECK. The tumor suppressor protein PTEN acts as a lipid phosphatase to dephosphorylate phosphatidylinositol 3,4,5-trisphosphate (PIP3), antagonizing the PI3K/Akt pathway^[15]. This pathway has an important effect on numerous biological functions, such as cell proliferation, adhesion, angiogenesis, migration, invasion, metabolism and anti-apoptosis^[16]. Besides, the key action of RECK (reversion-inducing cysteine rich protein with kazal motifs) is to suppress the cell metastasis by

inhibiting matrix metalloproteinases (MMPs) involved in the breakdown of the extracellular matrix (ECM)^[17]. All of these suggest the oncogenic role of miR-21 in CRC.

CRC tissue has been extensively reported on, as discussed in head and neck squamous cell carcinoma (HNSCC), non-small-cell lung cancer (NSCLC) and carcinomas of the digestion system^[18,19]. Moreover, some but not all polyps end up as malignant tumors through a string of increased genetic events. Therefore, it is important for early diagnosis to determine which polyp has the potential to become invasive carcinoma and then to remove it early. Accumulating studies show that miR-21 is correlated with the malignant progression of polyps and is highly expressed in CRC^[20-22]. Yamamichi *et al.*^[23] evaluated the expression of miR-21 during CRC progress in 39 surgically excised colorectal tumors and 34 CRC endoscopically resected colorectal polyps using nucleic acid *in situ* hybridization and found that miR-21 keeps increasing from precancerous polyps to early cancer, further increasing from the early to advanced stage of CRC. MiR-21 from CRC tissues may also be used to identify prognosis. Oue *et al.*^[12] used formalin-fixed, paraffin-embedded (FFPE) tumor tissues from 301 CRC patients at different TNM stages to discuss the relationship between miR-21 and prognosis and found that high miR-21 expression is significantly associated with poor survival. Furthermore, a meta-analysis of miR-21 expression level in 1174 CRC tissues suggested that increased miR-21 can be predictive of poor survival; however, CEA level shows no correlation with miR-21 expression^[24]. The relationship between Pcd4 (programmed cell death 4) and miR-21 is of great interest as well because miR-21 posttranscriptionally regulates Pcd4 and Pcd4 suppresses invasion and intravasation by suppressing the expression of the invasion-related urokinase receptor (*u-PAR*) gene *via* the transcription factors Sp1/Sp3^[25]. More importantly, Pcd4 was revealed by Asangani *et al.*^[26] to be a novel and independent prognostic factor in CRC. All of these suggested that miR-21 may be a poor prognostic biomarker. Consistently, the expression of miR-21 in a Japanese cohort ($n = 156$) and a German cohort ($n = 145$) was measured and analyzed by Harris's group. Elevated expression of miR-21 is correlated with poor prognosis in both stage II/III Japanese and stage II German cohorts^[12]. Similar results were also observed in another Japanese cohort^[11], American^[13], Hong Kong^[13], Czech^[27] and Danish^[28,29] cohorts of CRC patients.

In addition, the prognostic significance of miR-21 level was investigated in 306 patients with CRC at each Dukes' stage. However, a significant prognostic impact is not demonstrated in the analysis of Dukes' stage A patients, which may be due to the low rate of recurrence and death. This study showed that high miR-21 expression indicates poor overall survival (OS) and disease-free survival (DFS) in patients of Dukes' stage B, C and D^[30]. The prognostic value of miR-21 was also assessed for TNM stage. The TNM system describes a degree to which the tumor has invaded the

Table 1 Overview of functions of microRNAs in colorectal cancer

MiRNA	Disease progression	Biomarker	Treatment
MiR-21	Increased miR-21 correlated with CRC cell proliferation, invasion, lymph node metastases and advanced clinical stage ^[11,23,24] MiR-21 keeps increasing during the process from precancerous polyps to early cancer ^[20] High expression of miR-21 associated with poor progress in the stage II / III Japanese ^[11,21] and stage II German cohorts ^[21] , Hong Kong ^[25] , Czech ^[26] and Danish ^[27,28] cohorts of CRC patients	Increased miR-21 as an indicator for poor OS and DFS in patients of Duke stage ^[29] Elevated miR-21 as a marker for lymph metastasis in patients of TNM stage ^[30] MiR-21 in serum ^[33] as a noninvasive marker to detect early stage of CRC	Decreased miR-21 sensitizes CRC cells to 5-FU-treatment ^[21]
MiR-29	Elevated miR-29a is significantly correlated with metastasis, especially liver metastasis ^[38,39,42] Upregulation of miR-29a associated with a better outcome at 12 mo ^[43,44] High miR-29b expression associated with higher 5-yr DFS and OS ^[48]	MiR-29a as a biomarker for early detection of CRC and prediction of survival ^[38,43,44] MiR-29b as a biomarker for 5-yr DFS and OS (stage III CRC) ^[48]	
MiR-34a	Downregulation of miR-34a associated with CRC development ^[57] MiR-34a predicates recurrence of CRC patients ^[59] Increased miR-34b/c observed in more advanced tumors and associated with poor prognosis ^[60]	MiR-34a as a biomarker to predict recurrence of stage II and stage III CRC patients ^[59]	Increased miR-34a sensitizes CRC cells to 5-FU-treatment ^[58]
MiR-124a	High frequency of methylation of miR-124a in chronic inflammation and CRC ^[65,66] Methylation of miR-124a is emerging during oncogenesis in UC patients and could be used to estimate individual risk for cancer ^[71]	The methylation level of miR-124a as a factor for evaluating the risk of carcinogenesis in UC patients ^[71]	
MiR-130b	High level of miR-130b in advanced tumor stages (III-IV), miR-130b-PPAR γ axis plays a novel role in progressing towards more invasive CRC ^[77] MiR-130b inhibits CRC cells migration ^[75]	Increased miR-130b in advanced tumor stages ^[77]	
MiR-139-3p	Decreased miR-139-3p in CRC tissues ^[82,83] Downregulation of miR-139-3p associated with poor survival, especially in patients with TNM stages I and II ^[82]	MiR-139-3p as a marker for poor survival ^[82] MiR-139-3p in plasma used for predicting occurrence of CRC ^[84]	
MiR-155	High expression correlated with an advanced TNM stage and metastasis ^[85] Increased expression of postoperative miR-155 correlated with recurrence and metastasis of CRC ^[87]	MiR-155 as a prognostic maker for OS and DFS of CRC patients ^[11,86]	
MiR-224	Increased expression of miR-224 associate with tumor growth ^[89] and metastasis of CRC ^[90] MiR-224 inhibits CRC cells migration ^[95]	MiR-224 as a predictor for the short-time relapse and shorter metastasis-free survival ^[90-93]	Suppression of miR-224 sensitizes CRC to chemoradiotherapy ^[94]
MiR-378	MiR-378 is up-regulated in CRC samples ^[96,97] and promotes cell survival, invasion, and angiogenesis ^[98,99] Expression of miR-378 is increased in plasma of CRC patient, and rapidly goes down within 4-6 mo after surgery ^[103] Decreased miR-378 in CRC tissues and cell lines is associated with increased the size of tumor, metastasis and short OS ^[104,105]	MiR-378 in plasma used to predict the occurrence of CRC ^[103] Reduction of miR-378 in CRC tissues as a predictor for short OS ^[104]	

UC: Ulcerative colitis; CRC: Colorectal cancer; OS: Overall survival; DFS: Disease-free survival.

intestinal wall and spread to the regional lymph nodes as well as distant organs. Compared to T1, T2 and T3 cases, Harris's group found that miR-21 expression level is significantly elevated in T4 cases. A similar result was also observed in the comparison of N1 to N0^[12]. Besides, patients with a high level of miR-21 expression are insensitive to 5-FU therapy, while decreasing miR-21 enables patients to achieve a better response to 5-FU. Recently, anti-miRNA based therapies have achieved primary progress in treatment of patients with chronic hepatitis C infection^[31]. Hence, anti-miR-21 based therapies seem to be promising for the future.

More importantly, the prognostic value of miR-21 in serum and stool of CRC patients has also been extensively investigated. Due to the ineffectiveness of a

direct amplification method, the importance of circulating miR-21 was vague^[32]. Recently, TaqMan assays as an effective approach was used by Kanaan *et al.*^[33] and they found dramatically upregulated plasma miR-21 in patients with CRC. Toiyama *et al.*^[14] systematically investigated the expression of miR-21 in medium collected from 2 CRC cell lines and serum from 12 CRC patients and 12 healthy volunteers and concluded that miR-21 is a secretory miRNA. They further expanded verification of circulating miR-21 expression in 246 CRC cases, 53 controls and 43 patients with polyps. They also tested whether serum miR-21 reflects that of CRC tissues in 166 matched CRC specimens. MiR-21 significantly increases in serum from patients with precancerous polyps and CRCs. Notably, its expression decreases in patients' serum after surgery.

Moreover, serum miR-21 expression shows an apparent difference between patients with precancerous polyps and controls. Accumulated miR-21 level is correlated with tumor size, metastasis and poor survival. Thus, miR-21 in serum could be an ideal noninvasive biomarker to detect CRC early and evaluate the prognosis. Additionally, the expression of miR-21 in stool samples is different in healthy individuals compared to CRC individuals. Link *et al*^[34] found higher expression of miR-21 in stool from 29 patients with CRC compared to 8 healthy individuals. A similar result was also revealed by Wu *et al*^[35] from 88 patients with CRC and 101 healthy controls. Furthermore, miR-21 in later TNM carcinoma stages was reported to exhibit a more pronounced expression^[36]. To sum up, miR-21 expression could be a promising biomarker to predict the outcome of CRC patients.

MiR-29 family

MiR-29 family consists of three members: MiR-29a, miR-29b and miR-29c. Members of this family have been shown to be dysregulated in many different types of cancers. MiR-29 family members exert function by targeting genes involved in cell proliferation, senescence and metastasis at genetic and epigenetic levels, which makes them effective regulators of tumorigenesis and cancer progression^[37].

MiR-29a: Huang *et al*^[38] analyzed 100 CRC samples and 59 controls and found that the expression levels of miR-29a in plasma are significantly upregulated. The authors further investigated the diagnostic significance of plasma miR-29a in 37 early lesions of CRC and found an obvious increase in miR-29a expression compared to that of the control, suggesting the plasma miR-29a appears to be a novel biomarker for early detection of CRC^[38]. In addition to serving as a noninvasive tool to detect the CRC earlier, the prognostic value of miR-29a can also be applied to the early detection of CRC metastasis. Tang *et al*^[39] analyzed the expression levels of miR-29a and KLF4 mRNA in 85 cases using quantitative real-time polymerase chain reaction (qRT-PCR). Because KLF4 has been identified as a novel target of miR-29a, KLF4 inhibits metastasis through inhibition of MMP2 and upregulation of E-cadherin^[40,41]. Tang *et al*^[39] found that low KLF4 mRNA expression is correlated with metastasis. More importantly, a correlation between miR-29a expression and metastasis was observed in this study, with elevated miR-29a indicating metastasis and worse survival of CRC patients. Wang *et al*^[42] recruited a total of 114 participants, including 58 liver metastatic patients and 56 non-metastatic CRC patients, into their study since colorectal liver metastasis is most common. They discovered that the expression of miR-29a in the serum is significantly elevated in colorectal liver metastatic patients. Besides, the significantly elevated expression of miR-29a was found in CRC patients with advanced tumor T stage, while miR-29a shows a non-significant elevation in patients with advanced tumor N stage. Consequently,

they discovered that miR-29a can serve as a promising non-invasive, economic screening tool for early detection of colorectal liver metastasis^[42]. In conclusion, high expression of miR-29a is associated with poor prognosis and metastasis.

With regards to the prediction of CRC early recurrence, Kuo *et al*^[43] found that both miR-29a and miR-29c show significantly decreased expression levels in 43 patients with early recurrence compared to 35 patients of non-early recurrence. Increased miR-29a or increased miR-29c suggests a better outcome at 12 mo. However, only miR-29a can be used as a predictor of the early recurrence. That miR-29c fails to predict the early recurrence may be due to a short follow-up or a small sample size^[43]. Furthermore, the prognostic value of miR-29a was also found in stage II CRC. Weissmann-Brenner *et al*^[44] examined the microRNA array expression profile in 51 stage I and 59 stage II CRC samples and then 903 miRNA expressions were verified by qRT-PCR. The authors defined poor prognosis as recurrence within 3 years after surgery. Their data revealed that in stage II, miR-29a solely shows an obvious difference between patients with good prognosis and those with poor prognosis. However, in stage I, there are no miRNA with different expressions between the two groups. The result showed the prognostic value of miR-29a on the recurrence in patients with stage II. They also concluded that higher expression of miR-29a is associated with a longer DFS^[44].

MiR-29b: As a member of the miR-29 family, miR-29b is the most highly expressed in the miR-29 family and is found at two genomic loci^[45]. MiR-29b can inhibit proliferation and induce apoptosis in CRC cells and mediate the inhibition of epithelial-mesenchymal transition (EMT), which is closely related to the prognosis of CRC. Moreover, Yuan *et al*^[46] performed qRT-PCR to test miR-29b in 41 matched-paired CRC samples and reported that miR-29b is significantly decreased in CRC, suggesting that miR-29b is associated with tumor size, advanced clinical stage and lymph node metastasis of CRC^[46,47]. Furthermore, Inoue *et al*^[48] analyzed miR-29b expression in 245 patients with CRC. The patients were divided into two groups: Those under the median (low) and those above the median (high) of miR-29b expression. Their analysis revealed that high miR-29b expression is significantly associated with higher 5-year DFS and OS. In sub-analyses by each stage, they found that miR-29b expression has a prognostic impact on 5-year DFS solely in patients with stage III CRC, which showed that low miR-29b expression is an independent predictor of a reduced 5-year DFS. In addition, low miR-29b expression is predictive of lymph node metastasis and a pathological T classification, indicating the prognostic value of miR-29b in stage III CRC^[48]. Hence, the dysregulation of miR-29a and miR-29b can serve as a biomarker to predict early recurrence and shorter DFS in CRC.

MiR-34

The miRNA-34 family (miR-34a, miR-34b and miR-34c) has been reported to be a tumor suppressor regulated by the TP53 and DNA hypermethylation. The miR-34 family influences a series of cancer cell activities, such as stemness, metastasis and chemoresistance^[49]. It is well known that miR-34 is directly regulated by p53 at transcriptional level and miR-34 exerts p53 downstream effects through targeting c-MET, CDK6 and c-MYC to regulate proliferation arrest and to induce apoptosis^[50]. MiR-34a treatment results in downregulation of NOTCH1 and induction of apoptosis^[51]. The expression level of miR-34a is crucial for CRC cells to self-renew or divide. In addition, the NOTCH signaling regulates asymmetric division of stem cells. High miR-34a levels downregulate NOTCH signaling and suppress symmetric division, thus reducing the production of colon cancer stem cells (CCSC)^[52,53].

Proteinase activated receptor 2 (PAR2) is positively correlated with tumor progression in CRC. Ma *et al.*^[54] described that miR-34a is inhibited by PAR2, resulting in the upregulation of Cyclin D1 and TGF- β in CRC cells. MiR-34a promoter methylation in CRC tissues is associated with metastasis. Consistently, in 101 of 111 CRC tissues and in 9 of 9 cell lines, the miR-34 family is epigenetically silenced; hence, the authors pointed out that the methylation of miR-34a promotes motility and metastasis^[55,56]. In another study, the downregulation of miR-34a was noticed in some CRC patients, indicating the role of miR-34a in CRC development^[57].

The potential treatment value of miR-34a was also tested. In 5-FU-resistant CRC DLD-1 cells, low levels of miR-34a were observed. The restoration of miR-34a significantly sensitizes cells to 5-FU treatment and inhibits cell growth^[58]. Furthermore, miR-34a as a recurrence biomarker has been investigated. In two independent cohorts of 268 CRC patients, miR-34a expression is positively associated with DFS survival and can serve as a prognostic factor for recurrence of CRC. In addition, compared to patients with p53-negative expression, miR-34a is much higher in those with p53-positive expression. The authors concluded that miR-34a inhibits cell growth and invasion of CRC in a p53-dependent manner and predicts recurrence in stage II and III CRC patients^[59].

Most recently, the effects of the miR-34 family on prognosis was also systematically surveyed in CRC and an increased miR-34b/c predominantly expressed in stromal tissues was revealed to be associated with poor prognosis in CRC^[60]. The relationship between miR-34b/c and the development of disease was investigated in CRC samples from 159 American and 113 Chinese by qRT-PCR. They found that miR-34b/c was accumulated in advanced tumors and associated with poor cancer-specific mortality in two independent cohorts. TP53 regulates the expression of miR-34b/c at transcriptional level. Moreover, compared with epithelial tissue, miR-34b/c is enhanced greatly in cancer stroma. Collectively, miR-34 b/c may contribute to cancer-stromal interaction associated with CRC progression. All data presented

above revealed that the miR-34 family might be an ideal tool to predict the prognosis and recurrence in CRC.

MiR-124a

MiR-124a is known as a tumor suppressor gene, which has been shown to downregulate oncogenic cyclin-dependent kinase 6 (CDK6) involved in carcinogenesis, resulting in cell-cycle arrest at the G1-S checkpoint^[61,62]. MiR-124a was reported to be expressed at low levels in CRC due to the methylation^[63]. On one hand, miR-124a is the most frequently methylated in CRC compared to other tumor types, indicating the methylation status of miR-124a may be a specific marker for CRC. As mentioned by Deng *et al.*^[64], the lower expression of miR-124a is associated with the methylation of it and the treatment with 5-aza-2'-deoxycytidine can induce the expression of miR-124a. Among CRC, cancer of the pancreas, stomach, liver, lung, breast, kidney and prostate and melanoma, they found that CRC shows the highest frequency of methylation of miR-124a and a high frequency of methylation of miR-124a was also observed in polyps^[65,66]. Together, the methylation of miR-124a may be an early event in all pathways of colorectal carcinogenesis. On the other hand, the transcription of miR-124a is controlled by DNA methylation of the promoter regions of three miR-124a isoforms (miR-124a-1, 2 and 3) in CRC^[61,62,67,68]. It was known that aberrant methylation of miR-124a is induced in chronic inflammation^[69]. In the colorectal mucosa of pediatric patients with ulcerative colitis (UC), miR-124a was reported to positively regulate the expression of signal transducer and activator of transcription 3 (STAT3), which is a major factor in inflammatory response^[70], indicating that silencing of miR-124a is related to the promotion of inflammation in colorectal mucosa through the STAT3 signaling pathway. Ueda *et al.*^[71] tested the miR-124a level in 40 UC patients without CRC, 4 patients with CRC or dysplasia, 8 sporadic CRC patients and 12 normal controls. They found that miR-124a-1, 2 and 3 genes are all methylated and cyclin-dependent CDK6, as the target of miR-124a, is elevated in neoplastic samples. The methylation level of miR-124a-3 is significantly higher in pancolitis than in HV and methylation levels in long-standing UC are higher than in short-term UC. Moreover, in contrast to patients without long-standing UC and pancolitis, the methylation level of patients with these risk factors shows a 7.4-fold increase. Collectively, methylation of miR-124a-3 is emerging during oncogenesis in UC patients and could be used to estimate individual risk for cancer.

MiR-130b

Previous studies demonstrated that miR-130b is significantly dysregulated in some tumors, such as CRC, clear cell renal cell cancer (ccRCC), liver cancer, osteosarcomas and pancreatic cancer, and contribute to the tumorigenesis^[72-76]. In 52 pairs of pancreatic cancer tissues, Zhao *et al.*^[72] showed that miR-130b is significantly downregulated, which is correlated with a worse prognosis, increased tumor size, late TNM stage,

lymphatic invasion and distant metastasis of pancreatic cancer. Wu *et al.*^[74] used the microarray technology to profile miRNA expression of 28 localized and metastatic ccRCC specimens and 78 benign tissues and samples from ccRCC patients who had at least 5 years follow-up if no metastasis developed. They speculated that miR-130b is associated with ccRCC metastasis and prognosis. However, in CRC, Colangelo *et al.*^[77] identified that miR-130b directly targets peroxisome proliferator-activated receptor γ (PPAR γ). Furthermore, they provided data that miR-130b exerts biological functions mostly through suppression of PPAR γ , leading to deregulation of E-cadherin, Snail, PTEN and VEGF. As the enhanced miR-130b was found in III-IV tumor stages of CRC, they proposed that the miR-130b-PPAR γ axis plays a novel role in progressing towards more invasive tumors. Thus, miR-130b-PPAR γ may be a promising biomarker to predict prognosis. On the other hand, we previously reported the inhibitory function of miR-130b in migration and invasion of CRC because it downregulates the expression of integrin β 1^[75], which mediates cell migration in a wide variety of human cancers. Blocking integrin β 1 can inhibit the transformation of human breast cancer cells^[78,79]. All of the above gave us a hint that miR-130b may have potential value in the prognosis of CRC.

MiR-139-3p

Previous studies reported the abnormal expression of miR-139-3p in some types of human cancers, such as adrenocortical cancer, clusters in bladder carcinoma and CRC^[80-82]. Accumulating evidence suggested the potent role of miR-139-3p as a molecular biomarker for CRC. Chen *et al.*^[83] screened the difference of miR-139-3p expression among CRC tissues, matched normal samples and celecoxib-treated HT-29 CRC cells through miRNA microarray, then verified the readout by qRT-PCR. They found that miR-139-3p is downregulated in CRC tissues and that the expression of miR-139-3p is different from the early to advanced stage. Similar data were also reported by Kanaan *et al.*^[84] in that miR-139-3p in plasma may be used to distinguish CRC patients and normal individuals by examining 12 healthy controls and 20 CRC patients. Therefore, miR-139-3p may have a potential role in CRC early diagnosis. In addition, miR-139-3p may be related to poor prognosis of CRC. Liu *et al.*^[82] examined the expression level of miR-139-3p in 63 pairs of CRC and adjacent tissues. Compared with the adjacent normal controls, miR-139-3p expression levels in CRC tissues are notably decreased and decreased miR-139-3p is significantly associated with poor OS, especially in patients with TNM stages I and II. In conclusion, miR-139-3p has potential as an early diagnostic and prognostic biomarker for CRC.

MiR-155

MiR-155 is encoded by the non-protein-coding transcript of the B-cell integration cluster gene (*BIC* gene). Altered expression of miR-155 has been described in multiple

tumors, reflecting staging, progress and treatment outcomes. Zhang *et al.*^[85] found a significant increase in miR-155 in cancer tissues compared to the matched normal samples after analyzing 76 clinical samples of patients with CRC. MiR-155 can suppress E-cadherin and upregulate ZEB-1 through promoting expression of claudin-1, leading to increased cell migration and metastasis. Furthermore, there is a correlation between miR-155 expression and lymph node metastasis, advanced TNM stage and distant metastasis. Together, all of these results indicated that miR-155 plays an important role in CRC development and metastasis^[85]. In another study, Shibuya *et al.*^[11] revealed that patients with increased miR-155 show poorer OS and DFS than those with decreased miR-155, suggesting that miR-155 has independent prognostic values for OS and DFS of CRC patients. The link of miR-155 with the poor prognosis in CRC was also proved by Lv *et al.*^[86] by multivariate analysis. Consistent with the data above, Hongliang *et al.*^[87] assessed the levels of serum carcinoembryonic antigen (CEA) and miR-155 in 84 matched-pairs specimens from patients with CRC before and after surgery. It is well known that the CEA is mainly used for prognosis, observation of curative effect and monitoring recurrence and metastasis in CRC. The authors found that miR-155 expression is significantly increased in CRC tissues and is notably associated with tumor relapse and metastasis. Before surgery, miR-155 expression in patients correlates positively with the serum CEA levels and the high postoperative miR-155 expression level is associated with the short duration before the serum CEA level increases again^[87]. Moreover, Lv *et al.*^[86] discovered that there is no change in serum miR-155 expression level between controls and stage I CRC patients after measuring the serum of 146 CRC patients and 60 healthy controls. However, there is a great elevation of miR-155 expression in stages II-IV patients. Thus, miR-155 in serum cannot be used as a biomarker for early diagnosis^[86]. Taken together, miR-155 in tissues combined with serum CEA could provide concrete clues for the diagnosis of CRC and prediction of recurrence.

MiR-224

MiR-224 is consistently reported to be upregulated in CRC and it can potentially affect many cellular processes associated with cancer, including cell proliferation, growth, differentiation and cell death^[88]. High expression of miR-224 was observed in CRC tissues. The clinicopathological significance of miR-224 in CRC was recently evaluated in 110 CRC patients by Liao *et al.*^[89] who found that increased expression of miR-224 is significantly associated with an aggressive phenotype and poor prognosis of CRC. They also pointed out that miR-224 accelerates the G₁/S-phase transition through activation of Akt/FOXO3a signaling by targeting PHLPP1 and PHLPP2, antagonists of PI3K/Akt. MiR-224 also downregulates p21Cip1 and p27Kip1 and upregulates

cyclin-D1. Therefore, miR-224 promotes CRC tumor growth^[89]. The study by Nicoloso's group^[90] supported that miR-224 is an activator for CRC metastasis *via* targeting SMAD4 and miR-224, alone or combination with SMAD4, may be an independent prognostic marker for survival of patients with CRC. Clinical outcomes correlated with miR-224 status were analyzed in 6 sets of 449 CRC cases in order to assess the difference in survival between patients with low or high levels of miR-224 expression. Their data indicated that miR-224 expression increases consistently with tumor burden and microsatellite stability status and enhances CRC metastasis through targeting SMAD4. Patients with high miR-224 levels display shorter OS in multiple CRC cohorts and shorter metastasis-free survival^[90,91]. Consistent with the data from Nicoloso's lab, Zhang *et al.*^[92] also pointed out that SMAD4 is regulated by miR-224, suggesting miR-224 as a new biomarker for recurrence of CRC. They collected a total of 108 stage I - II colorectal patients who received radical resection and evaluated clinicopathological information of 40 patients with tumor relapse and 68 without relapse within 3 years after surgery. Their data suggested that miR-224 is notably increased in CRC tissues and this upregulation is associated with recurrence and poor DFS. By analyzing precancerous polyps, a similar conclusion was also achieved by Adamopoulos *et al.*^[93]. In addition, miR-224 also has some links with the treatment of CRC. Preoperative chemoradiotherapy (CRT) is the standard treatment for locally advanced rectal cancer and miR-224 was found to result in an increased resistance to CRT in CRC cell lines^[94]. In another study, when the expression of miR-224 was investigated in 79 specimens from CRC patients and 18 healthy controls, miR-224 in CRC tissues was greatly downregulated. Moreover, miR-224 suppresses the migratory ability of the CRC cell line through targeting Cdc42. In a word, this research indicated the vital role of miR-224 in suppressing cell migration of CRC. They concluded that miR-224 might be used as a promising biomarker to predict CRC development. The high expression of miR-224 predicts the short-time relapse and shorter metastasis-free survival and besides, miR-224 can increase the resistance to CRT^[95]. Collectively, MiR-224 may be a prognostic biomarker predicting the patients' survival outlook.

MiR-378

MiR-378 is expected to participate in the process of multiple tumorigenesis and play an important role in CRC. Previous studies demonstrated that miR-378 is upregulated in CRC samples^[96,97], targets the tumor suppressor genes Sufu and Fus-1 and regulates cancer progression by promoting cell survival, invasion and angiogenesis^[98,99]. The difference of miR-378 expression level between cancer individuals and healthy individuals in blood and tumor tissues was reported. For example, Hauser *et al.*^[100] reported that miR-378 in serum is significantly increased in 25 cCRC patients compared with 25 healthy individuals. Liu *et al.*^[101] showed that

serum miR-378 could serve as a novel noninvasive biomarker in gastric cancer detection. All of the above suggested that miR-378 might be a possible tumor biomarker. Moreover, miR-378 in plasma may have the highest predictive capability in CRC^[102]. The authors further investigated miRNA expression in the plasma of 65 CRC patients and 70 healthy individuals and found that miR-378 significantly increases in plasma from CRC patients once the level of miR-378 goes down notably after surgery. In addition, they also found that miR-378 expression decreases in patients who have no relapse within 4-6 mo after surgery, which further explained that plasma levels of miR-378 may be used to discriminate CRC patients from normal individuals^[102].

However, in another study, Zhang *et al.*^[103] pointed out the downregulation of miR-378 in 84 matched pairs CRC samples and cell lines. MiR-378 was considered a tumor inhibitor since it can suppress tumor cell growth in a nude mice model^[103,104]. In addition, there is a strong association between the reduction of miR-378 and increased tumor volume, metastasis and short OS of CRC patients. Consistently, miR-378 as a tumor suppressor was also observed by Wang *et al.*^[105] after analyzing the expression of miR-378 in 47 pairs of CRC samples. All of the above suggested that miR-378 plays a vital role in carcinogenesis and could serve as a biomarker to predict the outcome of CRC.

In a word, miR-378 may predict the presence of CRC and serve as a potential and reasonable biomarker for the early diagnosis of CRC.

CONCLUSION

MiRNA might be a powerful tool in diagnosis and treatment of CRC through modulating various crosstalks of oncogenic signaling pathways. MiRNAs we discussed here are, to date, the most extensively investigated tumor suppressor/enhancer miRNAs in CRC. Through *in vivo* and *in vitro* experiments, related miRNAs have been proved to be dysregulated in CRC and to be possible ideal diagnostic, prognostic and therapeutic tools (Table 1). However, some obstacles in miRNA-based therapies need to be overcome, such as degradation by nucleases, inefficient delivery to cells, fast blood clearance, renal toxicity and hemodynamic toxicity. Currently, much more efficient intracellular delivery systems are being developed to benefit miRNA-based clinical treatments, such as nanoparticle and the combination of miRNA in combination with other anticancer agents. In our review, contradictory findings regarding some miRNAs are introduced since we consider that the phenomenon could be explained by less informative clinical data, especially the lack of the definition of "healthy" control subjects, which will very likely affect the miRNA quality. Secondly, population ethnicity may be a potential confounding variable. Lastly, we hope that further studies concerning diagnosis and therapy will be done by more groups in the future in order to finally optimize the uses of miRNAs for

subsequent translation in the clinical setting.

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