

MicroRNAs potential utility in colon cancer: Early detection, prognosis, and chemosensitivity

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Abstract

Over the past decade, research has shown that aberrant expression of microRNA (miRNA) is involved in colorectal cancer development and progression. MicroRNAs are small sequences of non-coding RNA that regulate expression of genes involved in important cellular functions, such as cell differentiation, multiplication, and apoptosis. A specific miRNA may display the effects of a tumor suppressor or oncogene. Altered miRNA expression is found in colorectal cancer (CRC) and patterns of miRNA expression correlate with CRC detection and outcome. Studies also have examined the use of circulating serum miRNA and fecal miRNA expression as non-invasive markers for early detection. Here, we review recent evidence demonstrating the potential role of miRNA in CRC and the implications of its use in the diagnosis, prognosis, and management of CRC.

Key words: Colorectal cancer; MicroRNA; Expression; Serum microRNA; Fecal microRNA; Diagnostic; Prognostic; Therapeutic

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Core tip: Specific microRNA (miRNA) have potential to display the effects of a tumor suppressor or oncogene. Altered miRNA expression is found in colon cancer and patterns of miRNA expression correlate with its detection and outcome.

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INTRODUCTION

Colorectal cancer (CRC) is currently ranked third in the world among the most common cancers in females and second in men^[1]. Each year, approximately more than one million people acquire CRC and over half a million people die from CRC^[2,3]. The incidence varies greatly worldwide, with differences dependent on lifestyle, environment, and genetics. Epidemiological studies have identified many risk factors for the development of CRC which include age, family history, inflammatory bowel disease, and preventable risk factors such as obesity, excess alcohol, excess red meat and processed meat consumption^[4], high-fat diet, cigarette smoke, low socioeconomic status^[5], and sedentary lifestyle^[6].

The etiology of CRC is most commonly sporadic, but may also be hereditary as in familial adenomatous polyposis (FAP) and hereditary non-polyposis colorectal cancer (HNPCC). Regardless, the development of CRC involves genetic mutations leading to the progression of normal epithelial cells of the intestinal mucosa from adenoma to carcinoma. Due to this well-established sequential transformation, there are multiple opportunities to interfere with the natural course of the disease. This may take the form of screening, chemoprevention, chemotherapy, surgical resection, or palliative therapy.

Prognosis depends on the cancer stage at the time of diagnosis. The Tumor Node Metastases (TNM) staging system of the American Joint Committee on Cancer/Union for International Cancer Control is the preferred staging system for CRC. Detection of early stage CRC may confer a 90% 5-year survival rate, compared to 12% if distant metastasis has occurred^[7,8]. Given that symptoms are often not obvious, detection of CRC relies heavily on screening^[9]. Over the past two decades, the introduction of screening programs such as endoscopy, fecal occult blood testing (FOBT), and barium enema have led to improved early detection of CRC, which has shown a reduction in CRC incidence and mortality in many countries^[10]. Unfortunately, less than 40% of CRC patients are identified early enough in the disease when management is most efficacious^[7]. In addition, adherence to such screening programs is insufficient at nearly 50% in high-risk patients^[11]. Endoscopy is invasive and expensive, whereas the less invasive and less expensive FOBT had a sensitivity of only 47%–73% in case control studies^[9,12]. Thus, there is a strong necessity for the development of accurate and non-invasive markers for the diagnosis and prognosis of CRC.

Recent studies have implicated microRNA (miRNA) as serving a key part in the CRC progression and outcome. This article focuses on the utility of miRNA in the diagnosis and prognosis of CRC, as well as its role in predicting sensitivity to chemotherapy.

MICRO-RNA

In 1993, the first miRNA known as *lin-4* was identified in *C. elegans*^[13,14]. According to a searchable online database, 2588 mature human miRNAs have since been found in humans^[15]. miRNAs are small (18-25 nucleotides) RNA polymers, which are expressed as pre-miRNA and enzymatically cleaved by the protein Dicer into the mature form of miRNA^[16]. They are estimated to regulate the expression of over 30% of human genes by directly engaging with and influencing the transcription of mRNA molecules, ultimately regulating protein translation^[17]. An miRNA can accomplish this through integration with a RNA-induced silencing complex (RISC) and subsequently binding with a target mRNA molecule. The mechanisms by which the miRNA affects the processing of mRNA most commonly involve binding to the mRNA, resulting in either mRNA degradation or inhibition of its translation. mRNA transcripts are degraded if exact base-pairing occurs between miRNA and mRNA and silenced if the base-pairing is imperfect. Other mechanisms include directly binding to DNA open reading frames, epigenetic modifications such as methylation, and targeting mRNA binding proteins. A single miRNA can act on many mRNAs, while a single mRNA can be acted on by multiple miRNAs^[18].

Effect of the miRNA is dependent on the function of the mRNA with which it interacts. Therefore, elevated activities of miRNAs that reduce tumor suppressor expression facilitate cell proliferation and are known as oncomiRs. Depressed activity of miRNAs functioning as tumor suppressors would also promote oncogenesis, and are known as tsmiRs. Other miRNAs regulate cell migration and invasion, and promote metastasis. MicroRNA genes are also often located within regions of the genome that are especially susceptible to loss of heterozygosity and amplification, at fragile sites, or other areas associated with genetic mutations. Since miRNAs are known to regulate cell differentiation, apoptosis, and proliferations^[19], alterations in their expression contribute to human disease, such as colorectal cancer.

MICRO-RNA AND EARLY DETECTION

Successful treatment is best achieved when CRC is detected at its earliest stage. Specifically, detecting CRC and surgically resecting it before it has metastasized is considered the only curative therapy. The most widely used methods for diagnosing early CRC are fecal occult blood tests (FOBT) and colonoscopy. Although these tests have improved the survival rates for CRC, FOBT has a low sensitivity and colonoscopy is both expensive and invasive. In addition, certain foods and medications may lead to false-positive results of FOBT. In recent years, many studies have shown a relationship between miRNA expression and CRC.

Table 1 Summary of miRNA and early detection

miRNA and early detection		Summary
Micro RNA	Ref.	
miR-135b	New article [12,23]	Tumor initiation, progression
miR-106a	[24,25]	Improves sensitivity of FOBT
miR-431	[29]	Diagnosis of colorectal adenocarcinoma
miR-15b	[29]	Diagnosis of colorectal adenocarcinoma
miR-139-3p	[29]	Diagnosis of colorectal adenocarcinoma
miR-532-3p	[29]	Diagnosis of colorectal adenocarcinoma
miR-331	[29]	Diagnosis of colorectal adenocarcinoma
miR-195	[29]	Diagnosis of colorectal adenocarcinoma
miR-17	[29]	Diagnosis of colorectal adenocarcinoma
miR-142-3p	[29]	Diagnosis of colorectal adenocarcinoma
miR-15b	[29]	Diagnosis of colorectal adenocarcinoma
miR-532	[29]	Diagnosis of colorectal adenocarcinoma
miR-652	[29]	Diagnosis of colorectal adenocarcinoma
miR193a-3p	[30]	Diagnosis of colorectal adenocarcinoma, expression levels in tumor
miR-23a	[30]	Diagnosis of colorectal adenocarcinoma, expression levels in tumor
miR-338-5p	[30]	Diagnosis of colorectal adenocarcinoma, expression levels in tumor
miR-18a	[32]	Diagnosis of colorectal adenocarcinoma
miR-20a	[32]	Diagnosis of colorectal adenocarcinoma
miR-21	[32]	Diagnosis of colorectal adenocarcinoma
miR-29a	[32]	Diagnosis of colorectal adenocarcinoma
miR-92a	[32]	Diagnosis of colorectal adenocarcinoma
miR-106b	[32]	Diagnosis of colorectal adenocarcinoma
miR-133a	[32]	Diagnosis of colorectal adenocarcinoma
miR-143	[32]	Diagnosis of colorectal adenocarcinoma
miR-145	[32]	Diagnosis of colorectal adenocarcinoma
miR-1288	[33,34]	Control for miRNA in colorectal cancer

FOBT: Fecal occult blood testing.

Much of this work has suggested that miRNA may serve as a reliable, non-invasive biomarker with high sensitivity for early detection of CRC (Table 1).

Colonocytes of the gastrointestinal tract are continuously released into the intestinal lumen and can be evaluated in the feces. The first study to identify miRNA in feces showed that fecal samples from CRC patients had elevated miRNA. This data demonstrated a significant correlation with the histopathology of the patients' tumor tissue samples^[20]. A recent study by Ahmed *et al.*^[20] studied tumor tissue samples from different CRC mouse models and discovered that miR-135 is involved in a complex feedback loop. Mutations of molecular pathways commonly found in CRC involving APC and PTEN/PI3K facilitate the overexpression of miR-135b, which itself promotes tumor initiation and progression. Another study showed that miR-135b was elevated in CRC and adenomatous tissue samples in contrast to adjacent tissue without evidence of lesions. Stool samples demonstrated a trend of increasing miR-135b across the adenoma to carcinoma sequence compared to inflammatory bowel disease patients and healthy controls. Stool miR-135b was also shown to drop significantly after surgical resection of the CRC or

advanced adenoma. The sensitivity of fecal miR-135b was 78% in CRC, 73% in advanced adenoma, and 65% in any adenoma; the specificity was found to be 68%^[21].

Koga *et al.*^[22] found that fecal miR-106a was also of value in improving the sensitivity of FOBT screening. The authors extracted fecal RNA from the residuum of the FOBT to analyze for potential miRNA markers. They showed that the sensitivity and specificity of fecal miR-106a was 34.2% and 97.2% compared to FOBT with 60.7% and 98.1%, respectively. Importantly, the addition of fecal miR-106a analysis to the FOBT results demonstrated a sensitivity and specificity of 70.9% and 96.3%, respectively. One quarter of the CRC patients with a false-negative were found to be a true-positive with the addition of the fecal miR-106a analysis, greatly enhancing the sensitivity of the screening test. The authors' use of the FOBT residuum was validated by their earlier study which found no significant difference in the quality or quantity of the miR-106a extracted from FOBT residuum after 5 d if stored at 4 degrees Celsius^[23].

The most utilized CRC serum marker is currently carcinoembryonic antigen (CEA), but it has also been found to be elevated in other non-cancerous conditions such as inflammation of the intestines, liver, lung, and pancreas^[24]. miRNAs are found circulating in both serum and plasma. They are packaged into microvesicles and exosomes, thus resistant to degradation by RNase^[25]. They are also stable in a variety of other conditions such as low/high pH, freeze-thaw cycles, boiling, and long-term storage^[26].

In many recent studies, specific plasma miRNAs were found to be either up- or down-regulated in patients with CRC versus controls and also discovered their utility for detecting patients with CRC and adenoma. Kanaan *et al.*^[27] identified a group of 8 plasma miRNAs and a group of 3 plasma miRNAs, which could precisely distinguish between patients with colorectal adenoma and patients without colorectal neoplasia. Their panels were also able to distinguish between patients with colorectal adenomas from all stages of CRC. Yong *et al.*^[28] also identified a group of 3 plasma miRNAs whose levels were elevated in patients with CRC and were significantly correlated with their level of expression within their respective CRC tissue samples. They also illustrated an increasing trend of plasma levels from the early to late stages of CRC in comparison to control patients. Furthermore, as a biomarker for CRC detection, this triple miRNA panel performed with a sensitivity of 80% and a specificity of 84.4%. Another 20 miRNAs were either up-regulated or down-regulated, in which changes in their serum levels reliably differentiated between patients with stage IV CRC and controls. A follow-up study led to the development of a partial least squared regression model, which was able to correctly assign patients as stages I or II based on the

Table 2 Summary of miRNA and prognosis

miRNA and prognosis		Summary
Micro RNA	Ref.	
miR-200c	[35-38]	Increased expression level predicts worse prognosis
miR-378	[46]	Potential prognostic biomarker
miR-126	[47]	Potential prognostic biomarker
miR-224	[48,49]	Potential prognostic biomarker
miR-429	[50]	Potential prognostic biomarker
miR-182	[51]	Potential prognostic biomarker
mir-32	[52]	Potential prognostic biomarker
miR-214	[53]	Potential prognostic biomarker
miR-182	[54]	Potential prognostic biomarker
miR-92a	[55]	Potential prognostic biomarker
miR-124	[56]	Potential prognostic biomarker
miR-30b	[57]	Potential prognostic biomarker
miR-625	[58]	Potential prognostic biomarker
miR-155	[37]	Potential prognostic biomarker
miR-210	[37]	Potential prognostic biomarker
miR-215	[59]	Potential prognostic biomarker
miR-130b	[60]	Potential prognostic biomarker
miR-148b	[61]	Potential prognostic biomarker
miR-148	[61]	Potential prognostic biomarker
miR-16	[62]	Potential prognostic biomarker
miR-21	[10,39-45,47,65-68]	Upregulated in CRC, associated with tumor size, distant metastasis, poor survival and independent biomarker

CRC: Colorectal cancer.

serum miRNA profile of stage IV CRC patients^[29]. Luo *et al.*^[30] demonstrated the ability of 9 plasma miRNAs to differentiate between patients with CRC and controls. Gopalan *et al.*^[31] discovered that expression of miR-1288 was correlated with not only stage, but also location within the gastrointestinal tract; higher miR-1288 expression was found in tumors located more distally within the colon.

In the study of serum miRNAs in CRC, a stable control is needed for the accurate measurement of circulating miRNAs. Hu *et al.*^[32] found that miR-1228 was steadily expressed among patients with different cancer types, including CRC, and among patients with CRC at different stages. Therefore, they suggest that miR-1228 is the most stable endogenous control for studying circulating miRNAs in CRC.

MICRO RNA AND PROGNOSIS

Although early detection of CRC promotes a reduction in mortality due to the disease, it is frequently diagnosed at a later stage when the prognosis is unfavorable. Current management of CRC relies on clinical and histopathologic factors including, but not limited to, extent of the tumor (T), the extent of spread to the lymph nodes (N), and the presence of metastasis (M) or TNM stage, tumor margin involvement, differentiation, and lymphovascular invasion. Increasing evidence supports the use of molecular markers in estimating prognosis and refining clinical management. Many studies demonstrate the utility of miRNAs as prognostic biomarkers (Table 2).

The first study to establish a relationship between

miRNAs and CRC prognosis found a connection between the levels of miRNA-200c and survival^[33]. Since then, multiple studies have shown that both decreased and increased levels of various miRNAs are associated with poor outcome. A study by Toiyama *et al.*^[34] demonstrated elevated serum miR-200c in stage IV CRC compared to stages I-III, and showed that it served as a predictor for lymph node metastasis and recurrence. miR-200c was also found to serve as an independent indicator for CRC prognosis. Another study also found elevated miR-200c in the serum and tumor tissue of CRC patients compared to healthy controls^[35]. Serum miR-200c was also compared among CRC patients treated with surgical resection and chemotherapy. The serum miR-200c levels returned to normal levels in those with good prognosis, whereas in those with recurrence or distant metastasis miR-200c either remained elevated or elevated again after a transient decline. Hur *et al.*^[36] identified elevated expression of miR-200c in liver metastasis tissue compared to the primary CRC tissue. The miR-200c was found to be epigenetically regulated.

Another miRNA with significant potential as a prognostic marker is miR-21. miR-21 is upregulated in six different forms of cancer, including CRC^[37]. Previous studies have shown that tissue samples with elevated miR-21 expression were associated with lymph node and distant metastases; it was also correlated with clinical stage of CRC^[38]. Another study found that serum miR-21 was significantly elevated in CRC patients^[39]. Moreover, serum miR-21 accurately differentiated both adenoma and CRC patients from healthy controls. Elevated serum miR-21 was also

Table 3 Summary of miRNA and chemosensitivity

miRNA and chemosensitivity		Summary
Micro RNA	Ref.	
miR-21	[65-68]	Increased expression causes decreased chemosensitivity
miR-153	[69]	Up regulation, increased resistance to oxaliplatin and cisplatin
miR-19a	[70]	Up regulation leads to resistance of FOLFOX therapy
miR-106a	[71]	Up regulation leads to resistance of 5-FU and oxalilatin
miR-130b	[71]	Up regulation leads to resistance of 5-FU and oxalilatin
miR-484	[71]	Up regulation leads to resistance of 5-FU and oxalilatin
miR-129	[72]	Down regulation increases resistance to 5-FU, transfection of miRNA into existing cells increase cytotoxic effect 5-FU
miR-15b	[73]	Down regulation increases resistance to 5-FU
miR-1915	[74]	Down regulation decreases chemotherapy by modulating apoptotic pathway
miR-122	[75]	Down regulation increases resistant to 5-FU

5-FU: 5-fluorouracil.

associated with tumor size, distant metastasis, and poor survival, and served as an independent biomarker for CRC prognosis. Schetter *et al*^[40] reported a strong association between elevated miR-21 expression and CRC prognosis based on two patient cohorts, one comprised of 84 American CRC patients and the other of 113 Chinese CRC patients. Elevated expression conferred upon each cohort a worse prognosis and was independent of staging and other clinical characteristics. Subsequent studies performed on cohorts of patients from other ethnic populations has validated their findings and suggest that elevated miR-21 serves as a strong prognostic biomarker regardless of ethnicity^[41-43].

Kjaer-Frifeldt *et al*^[44] performed another cohort study demonstrating the use of miR-21 as a prognostic indicator in patients with stage II CRC. The authors showed that miR-21 expression may be combined with traditional characteristics used to stratify patients as either high- or low-risk of disease recurrence. Their thinking was that patients that had high miR-21 expression, and therefore a high-risk of recurrence, would be more likely to benefit from adjuvant chemotherapy. However, Oue *et al*^[45] found that in a cohort of Japanese patients with stage II CRC, high expression of miR-21 was correlated with a poorer response to adjuvant chemotherapy. The authors showed instead that low miR-21 expressing patients had a positive response to adjuvant chemotherapy.

Many other miRNAs expression patterns have been discovered as potential prognostic biomarkers. The expression levels of the following miRNAs have each been reportedly correlated with prognosis in at least one study: miR-378^[46], miR-126^[47], miR-224^[48,49],

miR-429^[50], miR-182^[51], miR-32^[52], miR-214^[53], miR-182^[54], miR-92a^[55], miR-124^[56], miR-30b^[57], miR-625^[58], miR-155 and miR-210^[35], miR-215^[59], miR-130b^[60], miR-148^[61], and miR-16^[62]. The RNA III endonuclease known as Dicer is involved in the processing of miRNA and its expression is associated with poor prognosis^[63]. Iliou *et al*^[64] showed that impairment of Dicer function lead to the downregulation of miRNAs associated with the regulation of the stem cell marker, CD44, and epithelial-to-mesenchymal transition-inducing transcription factors. The authors also identified that such changes enhanced tumor initiation and liver metastasis.

MICRO-RNA AND CHEMOSENSITIVITY

In addition to serving as biomarkers for diagnosis and prognosis, several studies have identified the ability of miRNAs to predict the sensitivity of CRC to chemotherapy. The response to chemotherapy varies between patients, the mechanisms for which are complex and poorly established. The use of miRNAs to predict chemotherapy efficacy allows for a more personalized approach to the treatment of CRC (Table 3).

A previous study has demonstrated that miR-21 expression correlates with poor prognosis and treatment response after 5-fluorouracil (5-FU) treatment^[40]. This suggests that elevated miR-21 plays a role in the resistance to 5-FU. CRC tumor cell exposure to 5-FU facilitates an elevated expression of miR-21, perhaps as a means to overcoming the drug's cytotoxic effects^[65]. Recently, Deng *et al*^[66] demonstrated that forced overexpression of miR-21 in CRC cell lines increased resistance to 5-FU, which was reversed with genetic knockdown of miR-21 expression. This was also demonstrated by the effects of the dietary curcumin analog, difluorinated curcumin (CDF), on CRC cell lines resistant to treatment with 5-FU and oxaliplatin^[67,68]. CDF was shown to inhibit growth of these cells when treated with 5-FU and oxaliplatin, while demonstrating a reduced expression of miR-21. The authors suggest that CDF leads to a decline in miR-21 expression, therefore sensitizing the cells to 5-FU and oxaliplatin treatment.

Additional research has recognized several miRNAs whose expression patterns are associated with sensitivity to chemotherapeutic agents. For example, up-regulation of miR-153 was associated with increased resistance to oxaliplatin and cisplatin both *in vivo* and *in vitro*^[69]. Additionally, miR-19a was found to be up-regulated in the serum of resistance-phase advanced CRC and was able to distinguish between patients who respond to FOLFOX therapy and those who are resistant^[70]. Kjersem *et al*^[71] identified 3 miRNAs (miR-106a, miR-130b, and miR-484) whose up-regulation correlated with a lack of response to 5-FU and oxalilatin. Interestingly, this lack of response was

not associated with a reduction in progression-free or overall survival.

Down-regulation of other miRNAs has also been associated with chemoresistance. Reduced expression of miR-129^[72] and miR-15b^[73] was found in CRC tissues resistant to 5-FU when compared to normal specimens. Transfection of miR-129 into resistant cells enhanced the cytotoxic effects of 5-FU^[72]. miR-1915 was also found to play a role in multi-drug resistant CRC. Overexpression of Bcl-2 has been generally accepted as conferring drug resistance in multiple cancers, including CRC. A study by Xu *et al.*^[74] found reduced levels of miR-1915 and up-regulation of Bcl-2 in a multi-drug resistant CRC cell line. Through transfection of miR-1915, they discovered that increased expression of miR-1915 lead to a reduction in Bcl-2 protein levels and sensitized the cells to multiple chemotherapeutic drugs through modulation of apoptotic pathways.

A recent study by He *et al.*^[75] illustrated the role of miRNAs on the "Warburg effect" and chemoresistance. The "Warburg effect" is the observation that most cancer cells utilize high rates of glycolysis relative to oxidative phosphorylation when compared to normal cells. The study demonstrated that miR-122 directly targets the glycolytic enzyme pyruvate kinase type M2 (PKM2) and consequently, miR-122 is downregulated in 5-FU-resistant CRC cells. The resistance to 5-FU was found to be correlated with the increase in glycolytic glucose metabolism, evidenced by increased glucose consumption and lactate release and increased expression of PKM2, lactate dehydrogenase, and the GLUT-1 glucose transporter. Interestingly, over-expression of miR-122 was shown to suppress PKM2 and significantly improve the cytotoxic effects of 5-FU on these resistant cells.

CONCLUSION

The discovery of microRNAs has since bolstered immense popularity in the scientific community and knowledge of their mechanisms continues to expand in the area of colorectal cancer. Certainly, miRNA plays an important part in initiating and fostering the progression of colorectal cancer. Many studies report associations between miRNA expression patterns and the diagnosis, prognosis, and sensitivity to chemotherapy. These studies indicate the utility of miRNA as markers for early CRC detection and their use in directing the management of CRC at all stages. Further research must be conducted to validate these findings and, most importantly, determine if the results provide information that can be adapted in the clinical realm. Additionally, studies illustrate the potential therapeutic utility of miRNAs. More research must be conducted to investigate strategies for the use of miRNAs in CRC treatment such as mechanisms for the delivery of miRNA into cells, enhanced miRNA and mRNA binding, and inhibition of endogenous

miRNAs. Research must also continue to develop a more detailed understanding of miRNA biochemical mechanisms and improve precision in the detection, prognosis, and chemosensitivity of colorectal cancer.

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