# Utilization of Micrornas in Colorectal Cancer: A Review.

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## Abstract

**Colorectal cancer (CRC) is the 3rd most common cancer worldwide causing over half a million deaths annually. Five year survival rate for early stage disease is around 90% which makes early disease detection and management immensely important. Current screening practices include the use of fecal occult blood test (FOBT), radiological scans and endoscopy. However, limitations exist with the use of these screening techniques and there prevails a need to develop noninvasive, reliable and cost-effective screening methods. MicroRNAs are sequences of non-coding RNA that regulate expression of many important cellular functions and are estimated to regulate over 30% of human genes. Alterations in the expression of microRNAs contribute to human disease. Expression of microRNAs in development and progression of CRC has gained widespread attention in the last decade. MicroRNAs have shown the potential to be used as molecular markers in diagnosis, prognosis and chemosensitivity of CRC. However, additional research is needed before they can be adapted in the clinical realm.**

## Introduction

Colorectal cancer (CRC) is the 3rd most common cancer worldwide. Each year, about 1.4 million new cases are diagnosed, causing over half a million deaths [1, 2]. Early disease detection together with improved monitoring has shown to significantly reduce mortality rates [3]. However, there is a lack of noninvasive, reliable and cost-effective screening method, which underscores the need to develop new diagnostic tools that can detect CRC transformations in early stages. MicroRNAs are sequences of non-coding RNA that regulate expression of many important cellular functions such as cell differentiation, multiplication and apoptosis. Expression of microRNAs in development and progression of CRC has gained widespread attention in the last decade [4, 5]. Herein, we review the growing body of literature and summarize the latest developments surrounding microRNAs as makers in diagnosis and prognosis of CRC.

## Current Screening Practices

The development of CRC involves genetic mutations which are most commonly sporadic but may also arise secondary to hereditary syndromes such as familial adenomatous polyposis (FAP) and hereditary non-polyposis colorectal cancer (HNPCC). These mutations lead to transformation of normal epithelial cells of the intestinal mucosa from adenoma to carcinoma in a sequential manner [6].

CRC is known as a "silent disease," as many patients remain symptomless and present at advanced stage when the disease is difficult to cure [7]. The 5-year survival rate for stage I disease is 93.2% as opposed to 8.1% for stage IV cancer, which makes early diagnosis immensely important for treatment and prognosis [8]. There are several screening modalities in current practice including fecal occult blood tests (FOBT), radiologic tests and endoscopic examinations (flexible sigmoidoscopy and colonoscopy). Although FOBT has approximately 95% specificity, its usefulness has been somewhat limited because of its poor sensitivity [9]. In contrast, colonoscopy is far more accurate and is considered the gold standard to identify and remove lesions at early stage. However, this procedure has several practical limitations including the need of bowel preparation and sedation, its invasive nature and cost [10, 11]. Therefore, need exists to develop less invasive screening tests with high sensitivity and specificity.

## Micrornas

### A. Introduction to MicroRNAs

MicroRNAs are sequences of non-coding RNA that regulate expression of many important cellular functions such as cell differentiation, multiplication and apoptosis through post-translational regulation of mRNA, ultimately leading to inhibition of mRNA translation. To date, about 2588 microRNAs have been identified in humans and

they are estimated to regulate over 30% of human genes [12, 13]. Alterations in the expression of microRNAs contribute to human disease and they are implicated in certain cancers. The first cancer to be associated with their dysregulation was chronic lymphocytic leukemia. This was followed by their utility in Hodgkin lymphoma, lung cancer, breast cancer, non-cancerous diseases of heart, kidney and nervous system and in regulatory pathways of obesity and lipid metabolism [14-20]. The evidence for their clinical utility is growing and holds great avenues for breakthrough in medicine.

MicroRNAs may act as tumor suppressors (known as tsmicroRNAs) where their under expression may promote oncogenesis. In contrast, other microRNAs regulate cell migration and invasion and their overexpression may lead to disease progression [6].

### B. Signaling pathways

In the nucleus, RNA polymerase II transcribes primary microRNAs. After processing, this primary transcript is transported to the cytoplasm and worked on by ribonuclease III to produce mature microRNA. The mature stand is ultimately integrated into the RNA-induced silencing complex that negatively regulate the expression of target messenger RNA through various mechanisms [21].

Although it is not entirely clear how the dysregulation of miRNAs occurs in CRC, a number of potential mechanisms have been proposed, including epigenetic modifications and various cellular signaling cascades involving different microRNAs [22]. For example, miR-135 and miR-122 may inactivate and inhibit adenomatous polyposis coli tumor suppressor gene controlled pathways and facilitate cancerous transformation [23, 24]. Other microRNAs such as miR-34, miR-145 and miR-107 mediate the function of p53 and are involved in cell survival, proliferation and angiogenesis, respectively [25].

MicroRNAs have also been implicated in CRC metastasis. Certain microRNAs such as miR-21 miR-31 and miR-200 are dysregulated in epithelial-mesenchymal transition (EMT) that takes places during tumor metastasis. MiR-21 in particular is up-regulated in this pathway; it silences tumor suppressor genes and B-catenin expression, ultimately leading to tumor progression [26, 27].

In addition, microRNAs may also be involved in angiogenesis of cancer tissue. Prominent markers in this regard are miR-107 (suppresses HIF-1 and VEGF expression) and miR-194 (repress thrombospondin 1, which is a barrier to neovascularization in tumors) [28, 29].

Major regulatory pathways affected by microRNAs are summarized in Table 1.

## Micrornas in Colorectal Cancer

### A. MicroRNAs in detection

The initial work to investigate serum microRNAs as markers of detection in CRC identified 69 microRNAs that were dysregulated in serum of CRC patients, but were not expressed in healthy volunteers [30]. This was followed by a more comprehensive investigation that discovered 95 different microRNAs in samples from CRC patients, compared to healthy controls [31]. This study found that levels of miR-17-3p and miR-92 were elevated in tissue and plasma samples of CRC patients and significantly reduced after surgery.

Further work on the utilization of microRNAs in CRC demonstrated elevated levels of miR-135 in fecal samples from CRC patients. These levels dropped after surgical resection and it was later established that miR-135 overexpression involves APC and PTEN pathways that are involved in CRC pathogenesis [32]. Another study established the role of fecal miR-106a in CRC. It demonstrated that addition of this RNA assay to the FOBT increased the sensitivity of the test from 60.7% to 70.9%, eliminating 1/4th of the false negative patients [33].

Other studies have shown the utility of plasma mircoRNAs in the detection of CRC. Markers have been discovered that can identify patients with CRC as well as differentiate between different stages of CRC [34, 35]. In addition, expression of markers correlating with tumor location has also been worked on. Gopalan et al [36] showed that expression of a specific marker miR-1288 correlated with stage of disease and location of tumor, with higher expressions correlating with more distal location.

In a recent meta-analysis, heterogeneity of several microRNA biomarkers in terms of sensitivity, specificity and other parameters was compared. It was found that out of all diagnostic RNA markers, heterogeneity becomes insignificant for miR-21. Additionally, its diagnostic performance was compared to other markers such as CEA and carbohydrate antigen and was found to be the most accurate [37].

Recent studies have also investigated the combination of various microRNAs in detection of CRC. Panels have been identified that can detect cancer with accuracy more than a single microRNA. Examples include a combination

*Table 1. Major pathways and microRNAs involved in CRC*

| Pathway/ mechanism | Regulators | MicroRNAs involved |
|---|---|---|
| Apoptosis | p-53, Bcl-2 | miR-29 miR-34 miR-195 miR-451 |
| Epithelial-Mesenchymal transition | TGF-B, Zinc finger binding protein (ZEB) | miR-200 miR-21 |
| Angiogenesis | VEGF, HIF-1 | miR-22 miR-619 miR-107 |
| Intracellular signal transduction | KRAS | let-7 miR-143 miR-17-92 |

of miR-409, miR-7 and miR-93 that was successful in discriminating CRC from healthy controls [38]. Another study combined a group of eight plasma microRNAs (miR-532-3, miR-331, miR-195, miR-17, miR-142-3, miR-15, miR-532 and miR-652) that was able to discriminate patients with adenoma from healthy controls [35].

Relationship between various microRNAs and colorectal cancer is summarized in Table 2.

### B. MicroRNAs in prognosis of colorectal cancer

The relapse rate after curative surgery in CRC is variable and is dependent on multiple factors including disease stage and adjuvant chemotherapy. Several studies have shown that adjuvant chemotherapy increases the survival of stage II disease [39]. In contrast, others have observed no relapse in stage III patients, even if adjuvant chemotherapy was not received. This dictates the need to identify patients at high risk of recurrence, in order to appropriately cater beneficial adjuvant treatment [40].

It has been discovered that variation in expression of several mircoRNAs predicts survival. The first study to identify this potential role involved serum miRNA-200c [41]. Later on, more studies demonstrated that the levels of miRNA-200c also correlate with disease stage, lymph node invasion and metastasis. Serum levels were also compared after patients were treated with surgical resection and chemotherapy. Interestingly, it was observed that the levels returned to normal in patients with good prognosis. In contrast, in patients who developed disease recurrence or distant metastasis, levels elevated after an initial drop or remained consistently high [42].

Another marker that received attention in terms of predicting CRC prognosis is miR-21. Studies have shown that elevated miR-21 expression were associated with lymph node and distant metastasis, accurately differentiated both patients with adenoma and CRC from healthy controls and correlated with tumor size [43]. Additional work has also identified miR-21 as a marker of disease recurrence, where it can be combined with traditional patient characteristics to stratify patients as high risk or low risk for recurrence [44]. On the contrary, one particular study found that increased expression of this marker is associated with poorer response to adjuvant chemotherapy, translating to poor clinical outcome [45].

Table 3 summarizes various microRNA markers identified for CRC prognosis.

### C. MicroRNAs in Chemosensitivity

MicroRNAs have been studied in predicting the response and resistance to different chemotherapeutic drugs. Studies have shown that elevated levels of miR-21 correlate with poor treatment response to 5-flurouracil [46]. Interestingly, this response was shown to be reversed after genetic knock down of miR-21. Similarly, elevated levels of miR-153 are associated with resistance to oxaliplatin and cisplatin and miR-19a upregulation is linked with decrease response to FOLFOX [47].

Reduced expression of microRNAs has also been correlated with chemosensitivity. Prominent markers of interest include miR-129, miR-15b and miR-1915. Lower expressions of miR-129 and miR-15b have been demonstrated to correlate with increase resistance to 5-flurouracil [48, 49]. MiR-1915 has been indicted to play a role in multi-drug resistant CRC by interacting with the Bcl-2 pathway [50].

### Limitations and Future Perspectives

The development of suitable noninvasive biomarkers for the diagnosis and prognosis of CRC is vital given the high burden of disease. MicroRNAs certainly play an important role in the CRC pathways and this has been capitalized to correlate their levels with disease parameters. Many studies have reported associations between expression of microRNAs and the diagnosis, prognosis and chemoreactivity of CRC patients. However, despite promising initial outcomes, there are contradictions, inconsistencies and technical obstacles when it comes to their role in CRC.

**Table 2.** *List of selected microRNAs and their significance in diagnosis of colorectal cancer* [6, 21]

| MicroRNA profile | Specimen | Dysregulation | Sensitivity (%) | Specificity (%) | Ref. |
|---|---|---|---|---|---|
| miR-135b | Stool | Increased | 78 | 68 | [32] |
| miR-17-3p | Plasma | Increased | 64 | 70 | [54] |
| miR-92a | Plasma | Increased | 89 | 70 | [54] |
| miR-29a | Plasma | Increased | 69 | 89.1 | [55] |
| miR-92a | Plasma | Increased | 84 | 71.2 | [55] |
| miR-221 | Plasma | Increased | 86 | 41 | [56] |
| miR-21 | Plasma | Increased | 90 | 90 | [57] |
| miR-601 | Plasma | Decreased | 69.2 | 72.4 | [31] |
| miR-760 | Plasma | Decreased | 80 | 72.4 | [31] |
| miR-21 | Serum | Increased | 91.9 | 82.1 | [58] |
| miR-21 | Serum | Increased | --- | --- | [59] |
| miR-92a | Serum | Increased | --- | --- | [59] |
| miR-106a | Improves sensitivity of FOBT to 70.9% | | | | [33] |
| miR-135b | Tumor initiation, progression | | | | [60] |

*Table 3. List of selected microRNAs identified for CRC prognosis (21)*

| MicroRNA | Specimen | Dysregulation | Significance |
|----------|----------|---------------|--------------|
| miR-200c | Serum | Increased | Prognostic marker |
| miR-221 | Plasma | Increased | Prognostic marker |
| miR-141 | Plasma | Increased | Prognostic marker |
| miR-29 | Serum | Increased | Liver metastasis |
| miR-21 | Serum | Increased | Prognostic marker |

A recent meta-analysis showed that the sensitivity and specificity of microRNA in a pooled data analysis was 78% and 79% respectively but with significant heterogeneity and indicated that the circulating microRNAs may not have sufficient power either to confirm or exclude cancer [37]. Moreover, the clinical value of microRNAs has only been explored in small sample sized studies, necessitating the need of large scale prospective trials in the future.

The technical issues with use of microRNAs start with their source, extraction and processing. MicroRNAs can be isolated from stool or blood (plasma or serum), with more interest seen in blood specimens. Recent studies have recommended plasma as a more suitable source of extraction since coagulation process in the serum cause hemolysis resulting in artificially higher levels of microRNAs [51]. Secondly, differences in preparation i-e filtration, centrifugation, controlling contamination and use of different extraction kits also affect levels of microRNAs. So, it is imperative to standardize extraction and processing mechanisms to control for difference in microRNA yield and potentially eliminate confounding [52]. Once microRNAs are isolated from samples they must be quantified for further analysis. Currently, there is no consensus regarding the use of suitable reference RNA controls and development of an absolute quantification method, both of which are important to make use of microRNAs accurate [53-55].

Another problem with use of microRNAs is disease specificity. As mentioned already, the spectrum of microRNA expression in human disease is enormous with correlations identified in various cancers. It is vital to clarify the interaction between specific microRNAs and CRC and to establish and identify overlap with other diseases. Moreover, there are several important factors to consider while designing RNA based markers for human disease. Ribonuclease, that is present in body fluids can easily degrade RNA molecules and has so far presented the biggest challenge in their development. However, properties of microRNAs make them suitable and promising markers for detection. Packaged into microvesicles and exosomes, they are resistant to degradation by RNase and are relatively stable to degradation by changes in temperature and PH [56-58].

Despite all these limitations, microRNAs have shown the potential to be used as molecular markers in diagnosis, prognosis and chemosensitivity of CRC. To massively screen and identify all possible microRNA markers at full gene level and to understand their function and regulatory pathways completely, we need additional research before they can be adapted in the clinical realm [59-60].

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