Use of micro RNAs in the diagnosis and prognosis of colorectal cancer (CCR)

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Abstract

The aim of this review is to present a general overview about the importance of micro RNAs (miRNAs) in colorectal carcinoma. First, we focused on the mechanisms whereby the miRNAs regulate the expression of target genes, and how an altered regulation of them is associated with several types of cancer, including colorectal carcinoma. Later, examples of some miRNAs that have been associated with cancer development and how the expression patterns of specific miRNAs can be used as potential biomarkers for prognosis, diagnosis and therapeutic outcome in colorectal carcinoma are addressed. Finally, several polymorphisms presents in the miRNAs that have been associated to risk and prognosis in colorectal carcinoma are described. (Gac Med Mex. 2016;152:347-56)

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KEY WORDS: Colorectal cancer. miRNA.

Introduction

Currently, colorectal cancer (CRC) is one of the main causes of death in western countries¹. According to 2012 Globocan data, Mexico was in fourth place in cancer incidence and cancer-related mortality for both genders². CRC is a heterogeneous condition, especially with regard to tumors anatomical location, to genetic and racial differences and, finally, to lifestyle interactions that influence on its development. Hence, it has been established to be a complex condition where genetic and environmental risk factors participate¹,³,⁴. Risk factors include a family history of colorectal neoplasm, development of polyps, inflammatory bowel diseases (ulcerative colitis), obesity, abusive consumption of tobacco and/or alcohol and stress⁴. Patients who practice exercise and consume non-steroidal anti-inflammatory drugs have been described as having a decreased risk for the development of CRC³,⁴. Among all CRC cases, approximately 75% are sporadic in origin and the rest are associated with family history and/or inflammatory bowel diseases⁵. Of the familial cases, approximately 5% have a well-defined inheritance pattern⁶.

Currently, most investigations have focused on analyzing the potential use of microRNAs (miRNAs) as risk, diagnosis and prognosis biomarkers in CRC and, for this reason, the following review will explain some examples of miRNAs involved in these processes.
MiRNAs function

MiRNAs are a class of small non-coding RNAs of 19 to 22 nucleotides that post-transcriptionally regulate gene expression. They bind to target messenger RNAs (mRNA) by base pair complementarity, blocking protein synthesis by any of the mechanisms hitherto known: mRNA destabilization and/or translational repression7.

The first miRNA was discovered in 1993 by the group led by Victor Ambros, who demonstrated that lin-4 was implied in cell-differentiation temporal progression in C. elegans. The only thing they knew at that time was that at larval stage 1, lin-4 negatively regulated the levels of a protein known as LIN-4. This research group found that lin-4 is not a gene that codifies for a protein, but gives origin to 2 RNAs: one of 22 nt and another of approximately 60 nt, which potentially could form a hairpin structure and be the precursor of the shorter RNA. Subsequently, they saw that these RNAs showed anti-sense zones that were complementary to multiple sites of the 3’UTR zone of the lin-4 gene, and they also showed that there was a decrease in the amount of protein without a reduction in mRNA. This way, they discovered that the mechanism whereby the 22-nt lin-4 RNA regulates the LIN-4 protein production is by binding to lin-14 mRNA by base pair complementarity, thereby preventing its translation. These were the first described observations where a small RNA directly bonded to an mRNA to inhibit its expression8. In 2000, another miRNA, miRNA-7, was found to participate in the control of progression development in nematodes9. Soon, these findings were followed by the discovery of other miRNAs that regulated other processes such as apoptosis, proliferation and differentiation in Drosophila, mice and human beings10,11. Calin et al. published the first study associating miRNAs with cancer in 2002. These authors demonstrated that miRNA-15 and miRNA-16 are located at chromosome 13 in a position where there is a deletion of a tumor-suppressing gene, with this deletion being associated with more than half the cases in chronic lymphocytic leukemia12.

Some investigators have proposed that miRNAs can be useful tools for the characterization of specific cancers and that miRNA expression patterns might help to identify human solid tumors, thus suggesting patient prognosis, and even representing a new molecular target for the treatment of cancer.

MiRNAs processing and mechanism of action

So far, 3 steps have been described to exist in miRNA maturation: pri-miRNA transcription, cleavage in the nucleus to form pre-miRNA, and a final cleavage in the cytoplasm to form the mature miRNA13,14.

MiRNAs are generally transcribed from intergenic regions, although they have also been observed to do it from intronic regions, either individually or in clusters of several miRNAs contained in a single transcript15.

MiRNAs are transcribed by RNA polymerase II to generate precursor molecules or pri-miRNA with a cap (7-methylguanosine) at the 5’ end and a poly(A) tail at the 3’ end16. Pri-miRNAs can be as long as 1 kb and form hairpin structures. They can be found as independent transcripts or inside other gene introns. For example, lin-4 is found inside a host gene, it is flanked by donor and acceptor splicing sites, and it is transcribed as an intron17. Lagos-Quintana et al. described let-7 miRNA isomers genomic organization, which were found as gene groups residing in chromosomes 9 and 1718.

These pri-miRNAs are processed in the nucleus by a microprocessor complex. This complex is composed of the Drosha enzyme (a type III RNase) and the DGCR8 protein (double stranded RNA-binding protein). The DGCR8 protein plays an important role in the recognition of Drosha cleavage sites, which are located at the base of the pri-miRNA structure stem. Cleavage of Drosha gives rise to a smaller precursor known as pre-miRNA, of 60-70 nt in length17-19. Then, pre-miRNAs migrate from the nucleus to the cytoplasm through the nuclear membrane transporter named Exportin 5, which is dependent of RanGTP20,21. In the cytoplasm, pre-miRNA undergoes another processing, where the Dicer enzyme cleaves the terminal loop to form a miRNA-miRNA duplex that is unfolded by helicase to release two miRNAs of approximately 22 nt in length, out of which one or both can be active. Generally, the sense chain is degraded, while the anti-sense chain serves as a guide to recognize the target mRNA22 (Fig. 1).

The mature miRNA associates with the RNA-induced Silencing Complex (RISC), which guides it towards targeted miRNAs, in order for it to act on them by blocking protein synthesis23. The RISC complex is composed of several proteins, especially the Dicer enzyme and the Argonaut 2 (Ago2) proteins. Ago2 proteins are located at specific regions of the cytoplasm known as P-bodies, which are regions with high rates of miRNA degradation, although it has been identified that P-bodies can also store mRNA and later
release it for translation\textsuperscript{24}. The cell machinery responsible for mRNA degradation is mainly concentrated in the P-bodies. These contain an enzyme that cleaves the 5’ cap (hDcp1/2), an exonuclease (hXrn1) and a mRNA-degrading protein (LSm1-7)\textsuperscript{25,26}.

One general feature of miRNAs is their imperfect pairing with target mRNAs in the 3’UTR region (untranslated region)\textsuperscript{27}. Mature miRNAs inhibit protein expression in two forms: by mRNA degradation and by translational repression. In the first, mature miRNAs act through RISC to recognize and cleave mRNA\textsuperscript{28}. MiRNAs can cleave its target mRNA without perfect complementarity; however, the introduction of a synthesized miRNA with perfect complementarity can also mediate the cleavage of its target mRNA\textsuperscript{29}. The second form whereby miRNAs act is through translation inhibition, which occurs when the miRNA is imperfectly paired with its target mRNA, which suggests that miRNAs function largely depends on the complementarity degree of the sequence with their target mRNA\textsuperscript{30}. In other words, if there is perfect complementarity, the miRNA induces target mRNA degradation by the action of RISC. Alternatively, if complementarity is imperfect, RISC acts by silencing or blocking mRNA translation.

**Figure 1. MicroRNA biosynthesis and mechanisms of action** (Taken and modified from \textsuperscript{7}).
In 1999, Olsen and Ambros demonstrated that miRNAs inhibit protein translation by means of isolation of the lin-4 mRNA together with lin-4 miRNA, from the cytoplasmic ribosomal complex. This study also demonstrated that lin-4 mechanism of action was not mediated by miRNA cleavage or degradation, since the lin-4 mRNA level remained constant and the poly-A tails were not shortened. Subsequently, Kim et al. reported similar results in mammal neurons. These authors demonstrated that all temporally-regulated miRNAs are located in polyribosomes. In summary, it appears that miRNAs control the expression of their target mRNAs by regulating the localization of mRNA in the P-bodies, where they are degraded. Additionally, miRNAs interfere with protein translation in polyribosomes through an unknown mechanism.

**MiRNAs in cancer**

Soon after the discovery that deletions in miRNA were associated with chronic myeloid leukemia (CML), other miRNA-related abnormalities (pediatric Burkitt’s lymphoma, lung carcinoma and large cell lymphoma) were reported. For example, miRNA-155, located in the BIC gene, which is overexpressed in many types of B cell lymphoma, including diffuse B cell lymphoma and pediatric Burkitt’s lymphoma. Takamizawa et al. reported a decrease in let-7 miRNA expression in different lung cancers (from non-small cell to large cell carcinomas). These authors also found that let-7 decreased expression was correlated with worse patient prognosis. In 2003, Michael et al. published the first study of miRNAs in colon cancer, which were identified as miRNA-143 and miRNA-145. Subsequent authors identified additional miRNAs by using new research tools and, currently, there are more than 100 miRNAs implicated in CRC. This way, recent studies have correlated miRNA specific expression patterns with certain types of cancer.

**MiRNA candidates for CRC**

Michael et al. identified miRNA-143 and miRNA-145 to be potential factors in colorectal tumorigenesis. They isolated total RNA from a healthy individual and a patient with colon adenocarcinoma and compared the sequences against miRNA published databases. Among the results, they found that miRNA-143 and miRNA-145 are located at chromosome 5, and their expression levels were reduced in colon cancer epithelial cells. Target genes of these miRNAs remain unidentified; however, there are some candidates. The transfection analysis in miRNA-143 precursor-deficient cells reveals a decrease in the ERK5 protein, with normal levels of ERK gene mRNA, suggesting that miRNA-143 post-translationally inhibits ERK5 in a way that doesn’t involve the degradation of its mRNA. These authors found that IRS1 is underexpressed by miRNA-14; in order to verify these results, they created a hybrid reporter of the miRNA-145 3’UTR region luciferase gene and showed that miRNA-145 transfection decreased the reporter’s activity. They also showed that miRNA-145 leads to cell growth inhibition. These studies carried out in miRNA-143 and miRNA-145 suggest that these miRNAs exert a tumor-suppressing effect. Another miRNA example is the let-7 family, which comprises 14 isomers, many of which are altered in CRC. In another study conducted by Akao et al., they reported let-7a-1 underexpression in colon cancer tumors and in colon-derived cell lines (DLD-1). In an independent manner, another study carried out in China corroborated this finding in a small number of patients with CRC, with the same colon-derived cell line showing decreased levels of let-7a-1; on the other hand, when the transfection with the let-7a-1 precursor was performed, it showed reduced cell growth and decreased the expression of the RAS and c-Myc proteins. This inhibitory effect resembles that of miRNA-143 and miRNA-145, where both proteins mRNA levels remain normal. RAS inhibition by let-7a and c-Myc protein expression have been reported in lung cancer and Burkitt’s lymphoma. The specific function and targets of let-7 other isomers remain, to date, unknown. Another example is miRNA-34a, which has been shown to inhibit cell proliferation. Tazawa et al. demonstrated its activity in the cell cycle by using colon-derived cell lines (HTC116 and RKO), where they found cells to be in a senescence-like state. The results showed that miRNA-34a decreases the expression of transcription factor E2F and overexpresses p53.

**MiRNAs as diagnostic biomarkers for CRC**

Undoubtedly, CRC early detection provides with better opportunity of success in the treatments used. In addition, current chemotherapeutic treatments have
significantly improved survival rates in patients with CRC; therefore, it is important for efficacy of the methods used in the detection of CRC to be increased. Methods currently used include colonoscopy and fecal occult blood test (FOBT), which have improved CRC survival rates through the detection of patients at cancer early stages. For example, colonoscopy is considered the best diagnostic test, since it can remove pre-malignant polyps during the procedure; however, it is an invasive and expensive test, which results in low conformity rates. On the other hand, FOBT is a less invasive test, but, in turn, it is less sensitive and specific; unfortunately, none of these methods complement the diagnosis due to lack of specificity. Therefore, new non-invasive tests and more accurate biomarkers are required in order to be able to improve CRC both accuracy and diagnosis rates. In this sense, the use of miRNAs is being assessed owing to the potential they show in this area, as a complement to diagnostic tests. The presence of circulating miRNAs can be detected in serum or plasma. Ng et al. were the first to report that miRNA circulating levels were different in the blood plasma of patients with CRC, in a case-control study, they found miRNA-92 to be highly expressed in the plasma of patients with CRC, and could be easily differentiated from clinically healthy controls with 70% specificity and 89% specificity. MiRNA-92 expression was reduced after surgical removal of the tumor, suggesting that miRNA plasma levels could be a useful marker of disease recurrence. In another study, Huang et al. validated these discoveries showing that miRNA-92 plasma levels could discriminate CRC cases from controls with a sensitivity of 65% and specificity of 82%. Although miRNA-92 levels are not accurate enough by themselves to be considered as a diagnostic marker, they can be developed together with additional markers to improve diagnostic accuracy. A similar study carried out by Cheng et al. reported miRNA-144 circulating levels to be elevated in patients with metastatic CRC and their expression to be associated with poor prognosis, suggesting that this miRNA can be used in combination with carcinoembryonic antigen (CEA) to detect metastasis in patients with CRC.

Fecal miRNA measurement offers another non-invasive alternative test to detect CRC. Link et al., in a case-control trial, reported that feces from patients with CRC expressed miRNA-21 and miRNA-106a increased levels. In another study with patients with CRC and control subjects conducted by Koga et al., the expression patterns of some miRNAs stemming from feces-isolated colonocytes were investigated, and demonstrated that the expression pattern of miRNAs stemming from samples with CRC could be differentiated from the controls with a sensitivity of 74% and specificity of 79%. Kalimutho et al. reported that the methylation patterns in feces-isolated DNA that codifies for miRNA might have a promising application as CRC diagnostic test. The hypermethylation pattern of miRNA-34b/c stemming from CRC-patients' fecal samples could be differentiated from controls with 75% sensitivity and 84% specificity. Future analysis are required to ensure that the expression or methylation patterns of miRNAs stemming from fecal samples can be used either individually or in combination with tests such as FOBT as an effective diagnostic strategy to detect CRC.

MiRNA expression as a predictive and prognostic marker

MiRNAs as molecular biomarkers can be used as predictive or prognostic tools to help to stratify cancer patients within appropriate risk groups in order to aid doctors in therapeutic decision-making. These decisions may include the decision to provide or not chemotherapy or any kind of therapy that may be the most appropriate. MicroRNA expression patterns have been associated both with prognostic and predictive results in CRC. MiRNA-21 increased expression has a wide and reproducible association with colon cancer prognosis. Schetter et al. were the first to report such association based on miRNA expression patterns obtained from microarray analyses conducted in patients with colon cancer and from an additional study carried out in a cohort of Chinese individuals. In both cohorts, the increased expression levels of miRNA-21 found in tumors were associated with worse prognosis and poor therapeutic response. This association was significant for patients classified as stage II according to the TNM classification, thus demonstrating that miRNA-21 expression might be useful as an early-stage biomarker to identify subjects at high risk of cancer progression who have no evidence of metastasis or advanced disease.

The association of miRNA-21 increased expression levels with poor or reduced survival in CRC has been validated in at least 3 additional studies with different populations (one study by Shibuya et al., one study by Kulda et al., and one study by Nielsen et al.). The fact that such association is observed in different populations using different methods to measure miRNA-21, determines that miRNA-21 expression is a prognostic marker to detect CRC. In fact, the association of
increased levels of this miRNA-21 with poor prognosis has already been reported in at least 9 different types of cancer, including lung57,58, breast69, pancreas60, tongue61, gastric62 and head and neck63 cancers, as well as chronic lymphocytic leukemia64, melanoma65 and astrocytoma66. These findings are consistent with the hypothesis that overexpression of this miRNA is a prognostic marker for different types of malignancies46.

Additional studies have identified miRNA expression patterns that have been associated either with prognosis or therapeutic response. Some examples include the expression levels of miRNA-106b, miRNA-320, miRNA-489, miRNA-125b, miRNA-145, miRNA-185, miRNA-133b, miRNA-215 and miRNA-17-5p73. On the other hand, elevated expression of the gene that codifies for the Dicer enzyme has been associated with poor prognosis in CRC74. The combination of multiple independent validated biomarkers may provide better patient-risk stratification. As an example of this, the combination of data on miRNA-21 expression accompanied by some inflammatory gene used as a classifier has been reported to have demonstrated to significantly improve stratification by cancer-specific mortality risk74.

This combination was significant for patients with colon cancer at stage II (TNM), indicating its possible usefulness to identify patients with higher probability to develop non-detectable micro-metastasis. Table 1 shows some examples of miRNAs potentially associated with prognosis and therapeutic response in patients with CRC.

### Polymorphisms in miRNAs and risk for CRC

Recent studies have suggested that 35% of CRC cases can be attributed to genetic-hereditary factors129. These factors can be due to single nucleotide polymorphisms (SNPs) and other genetic abnormalities in both coding and non-coding genes46. Since miRNAs play an important role in CRC initiation and development, it is possible that the presence of SNPs that disrupt miRNAs expression, sequence, binding site or processing can alter an individual’s susceptibility to develop CRC121. Zhan et al. reported that one polymorphism in miRNA-196a led to altered expression of the miRNA and to an increase in CRC incidence in China122. Landi et al. conducted a global analysis of the 3’UTR region in candidate genes that led to the identification of 2 SNPs; one of them altered the binding site of miRNA-337, miRNA-582, miRNA-200a, miRNA-184 and miRNA-212 with the CD86 mRNA, whereas the second SNP altered miRNA-612 binding site with the INSR mRNA. Each one of these SNPs was associated with higher risk for cancer123. Recently, Zanetti et al. reported that the presence of a SNP in miRNA-257a altered its binding to the MBL2 mRNA 3’UTR region and that this SNP was associated with the risk for developing CRC124.

Similar studies have assessed the relationship of SNPs present in miRNAs and their likely association with prognosis and treatment response46. For example, Lee et al. conducted a study in patients with CRC and found a SNP in miRNA-492 that was associated with better survival prognosis in CRC125. KRAS-LCS6 is a SNP of particular interest because its presence alters let-7 binding site to the KRAS 3’UTR region. CRC patients who bear mutations in KRAS have been shown to be irresponsive to therapies with antibodies targeted against the epidermal growth factor receptor (anti-EGFR). Since the (KRAS-LCS6) variant can alter KRAS protein levels, the hypothesis that the variant may be involved in treatment response has been proposed. In a study carried out by Graziano et al. in patients with metastatic CRC with no mutations in BRAF who received anti-EGFR therapy, patients with the KRAS-LCS6 SNP were reported to show very poor survival126.

In contrast, in another study performed by Zhang et al. in metastatic CRC patients with wild-type KRAS, the KRAS-LCS6 SNP was found to be associated with better response to anti-EGFR therapy127. In a third study conducted by Smits et al. in patients with CRC, the KRAS-LCS6 SNP was associated with improved survival only in cases at early stage; however no survival benefit was observed in patients at late stage128. These apparently contradicting results highlight the need of independent validation in multiple cohorts, with special attention to KRAS and BRAF mutation status and its interaction with specific chemotherapeutical regimens.

### Conclusions

miRNA identification has tried to explain the complexity of control in expression. Recent investigations have suggested that miRNAs alteration is an important step in the development of many cancers, including CRC. Currently, miRNAs are being studied owing to the potential they display as tools for the characterization of different types of cancer, since different studies have reported different miRNA expression patterns to be characteristic in certain types of cancer. It is widely known that CRC opportune detection provides better opportunities for successful treatment; therefore, miRNAs have great potential as predictive, diagnostic and treatment response biomarkers, as well as for disease
Table 1. Examples of microRNAs associated with prognosis and therapeutic response in CRC

<table>
<thead>
<tr>
<th>miRNA</th>
<th>Expression</th>
<th>Association with prognosis</th>
<th>Association with response to therapy</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>miRNA-133b</td>
<td>↓</td>
<td>Metastasis and poor survival</td>
<td></td>
<td>76, 77</td>
</tr>
<tr>
<td>Let-7g</td>
<td>↑</td>
<td></td>
<td>Clinical response to S-1</td>
<td>78, 79</td>
</tr>
<tr>
<td>miRNA-106a</td>
<td>↑</td>
<td>Progression and metastasis, poor survival</td>
<td></td>
<td>38, 80, 81, 82, 83</td>
</tr>
<tr>
<td>miRNA-200c</td>
<td>↑</td>
<td>Poor survival</td>
<td></td>
<td>84</td>
</tr>
<tr>
<td>miRNA-21</td>
<td>↑</td>
<td>CRC progression, survival regardless of progression with worse prognosis</td>
<td>Poor therapeutic response (especially FU) with or without generics</td>
<td>43, 85, 80, 86, 54, 87, 56</td>
</tr>
<tr>
<td>miRNA-145</td>
<td>↓</td>
<td>Inhibits tumor growth and angiogenesis</td>
<td></td>
<td>40, 88, 89, 90, 91, 92</td>
</tr>
<tr>
<td>miRNA-143</td>
<td>↓</td>
<td>Size of primary tumor, more aggressive phenotype, survival regardless of shorter disease</td>
<td>Increased sensitivity to 5-FU</td>
<td>85, 93, 88, 89, 47, 55, 91</td>
</tr>
<tr>
<td>miRNA-34a</td>
<td>↓</td>
<td>Tumor suppressing capacity</td>
<td>Chemoresistance to 5-FU</td>
<td>45, 94</td>
</tr>
<tr>
<td>miRNA-215</td>
<td>↓</td>
<td>Poor survival</td>
<td>Chemoresistance to methotrexate and tomudex</td>
<td>95, 96, 97</td>
</tr>
<tr>
<td>miRNA-17-5p</td>
<td>↑</td>
<td>Survival regardless of disease addressed at CRC early stage (I and II)</td>
<td></td>
<td>67</td>
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<tr>
<td>miRNA-498</td>
<td>↓</td>
<td>Worse survival regardless of progression at CRC stage II with microsatellite stability (MSS)</td>
<td></td>
<td>68</td>
</tr>
<tr>
<td>miRNA-181</td>
<td>↑</td>
<td>Poor survival</td>
<td></td>
<td>80</td>
</tr>
<tr>
<td>miRNA-20a</td>
<td>↑</td>
<td>Very poor prognosis</td>
<td>Chemoresistance to 5-FU, oxaliplatin and teniposide</td>
<td>80, 98, 99, 100</td>
</tr>
<tr>
<td>miRNA-203</td>
<td>↑</td>
<td>Poor survival</td>
<td>Increases sensitivity to paclitaxel in CRC with mutated p53</td>
<td>80, 101, 102</td>
</tr>
<tr>
<td>miRNA-224</td>
<td>↑</td>
<td>Tumor progression</td>
<td>Low expression has been associated with resistance to methotrexate</td>
<td>81, 103</td>
</tr>
<tr>
<td>miRNA-451</td>
<td>↓</td>
<td>Poor prognosis</td>
<td>Reduces sensitivity to radiotherapy, produces chemoresistance to irinotecan</td>
<td>104, 105</td>
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<tr>
<td>miRNA-181b-2</td>
<td>↑</td>
<td></td>
<td>Clinical response to S-1</td>
<td>93, 79</td>
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<tr>
<td>miRNA-92a-1</td>
<td>↑</td>
<td>Poor prognosis</td>
<td></td>
<td>89</td>
</tr>
<tr>
<td>miRNA-183</td>
<td>↑</td>
<td>Very poor prognosis</td>
<td></td>
<td>89, 106</td>
</tr>
<tr>
<td>miRNA-31</td>
<td>↑</td>
<td>Advanced TNM stage and tumor deep invasion, poor prognosis</td>
<td>Chemoresistance to 5-FU</td>
<td>89, 107</td>
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<tr>
<td>miRNA-18a</td>
<td>↑</td>
<td>Poor prognosis</td>
<td>Chemoresistance to 5-FU</td>
<td>89, 108</td>
</tr>
<tr>
<td>miRNA-195</td>
<td>↓</td>
<td>Lymph node metastasis, advanced tumor stage, poor survival</td>
<td></td>
<td>109, 110</td>
</tr>
<tr>
<td>let-7b</td>
<td>↓</td>
<td></td>
<td>Chemoresistance to cetuximab</td>
<td>111</td>
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</table>
Table 1. Examples of microRNAs associated with prognosis and therapeutic response in CRC (Continued)

<table>
<thead>
<tr>
<th>miRNA</th>
<th>Expression</th>
<th>Association with prognosis</th>
<th>Association with response to therapy</th>
<th>References</th>
</tr>
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<tbody>
<tr>
<td>miRNA-155</td>
<td>↑</td>
<td>Lymph node metastasis, worse survival regardless of disease</td>
<td></td>
<td>54</td>
</tr>
<tr>
<td>miRNA-22</td>
<td>↓</td>
<td>Liver metastasis and poor survival</td>
<td>Produces mutated p53 overexpression in CRC leading to increased chemosensitivity to paclitaxel</td>
<td>112, 113</td>
</tr>
<tr>
<td>miRNA-150</td>
<td>↓</td>
<td>Poor survival</td>
<td>Unfavorable response to adjuvant chemotherapy with 5-FU in patients with stage II and III</td>
<td>114</td>
</tr>
<tr>
<td>miRNA-125</td>
<td>↑</td>
<td>Advance in tumor size and invasion, very poor prognosis</td>
<td></td>
<td>69</td>
</tr>
<tr>
<td>miRNA-185</td>
<td>↑</td>
<td>Metastasis and poor prognosis</td>
<td></td>
<td>115</td>
</tr>
<tr>
<td>miRNA-19b</td>
<td>↑</td>
<td>Metastasis and poor prognosis</td>
<td></td>
<td>108</td>
</tr>
<tr>
<td>miRNA-365</td>
<td>↓</td>
<td>Cancer progression and poor survival</td>
<td>Increases responsiveness to 5-FU</td>
<td>116</td>
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<tr>
<td>miRNA-10b</td>
<td>↑</td>
<td>Lymphatic invasion and reduced survival</td>
<td>Chemoresistance to 5-FU</td>
<td>117</td>
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<tr>
<td>let-7a</td>
<td>↑</td>
<td>Metastasis</td>
<td></td>
<td>118</td>
</tr>
<tr>
<td>miRNA-29a/c</td>
<td>↑</td>
<td>Prolonged survival regardless of disease at stage II</td>
<td></td>
<td>119</td>
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</tbody>
</table>

Recurrence. Since they are easily detected, they can be used to complement diagnostic tests, thereby helping to increase their specificity. However, further studies are required to endorse and validate the use of miRNAs for the detection of CRC.

References


