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REVIEW ARTICLE

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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Introduction

Currently, colorectal cancer (CRC) is one of the main causes of death in western countries[1]. According to 2012 Globocan data, Mexico was in fourth place in cancer incidence and cancer-related mortality for both genders[2]. 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 participate[1,3,4]. 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 stress[4]. Patients who practice exercise and consume non-steroidal anti-inflammatory drugs have been described as having a decreased risk for the development of CRC[3,4]. Among all CRC cases, approximately 75% are sporadic in origin and the rest are associated with family history and/or inflammatory bowel diseases[5]. Of the familial cases, approximately 5% have a well-defined inheritance pattern[6].

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.

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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 repression[7].

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 expression[8]. In 2000, another miRNA, *miRNA-7*, was found to participate in the control of progression development in nematodes[9]. 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 beings[10,11]. 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 leukemia[12].

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 miRNA[13,14].

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 transcript[15].

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' end[16]. 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 intron[8]. Lagos-Quintana et al. described *let-7* miRNA isomers genomic organization, which were found as gene groups residing in chromosomes 9 and 17[15].

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 DGC8 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 length[17-19]. Then, pre-miRNAs migrate from the nucleus to the cytoplasm through the nuclear membrane transporter named Exportin 5, which is dependent of RanGTP[20,21]. 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 mRNA[22] (Fig. 1).

The mature miRNA associates with the RNA-induced Silencing Complex (RISC), which guides it towards targeted mRNAs, in order for it to act on them by blocking protein synthesis[23]. 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 mRNA degradation, although it has been identified that P-bodies can also store mRNA and later

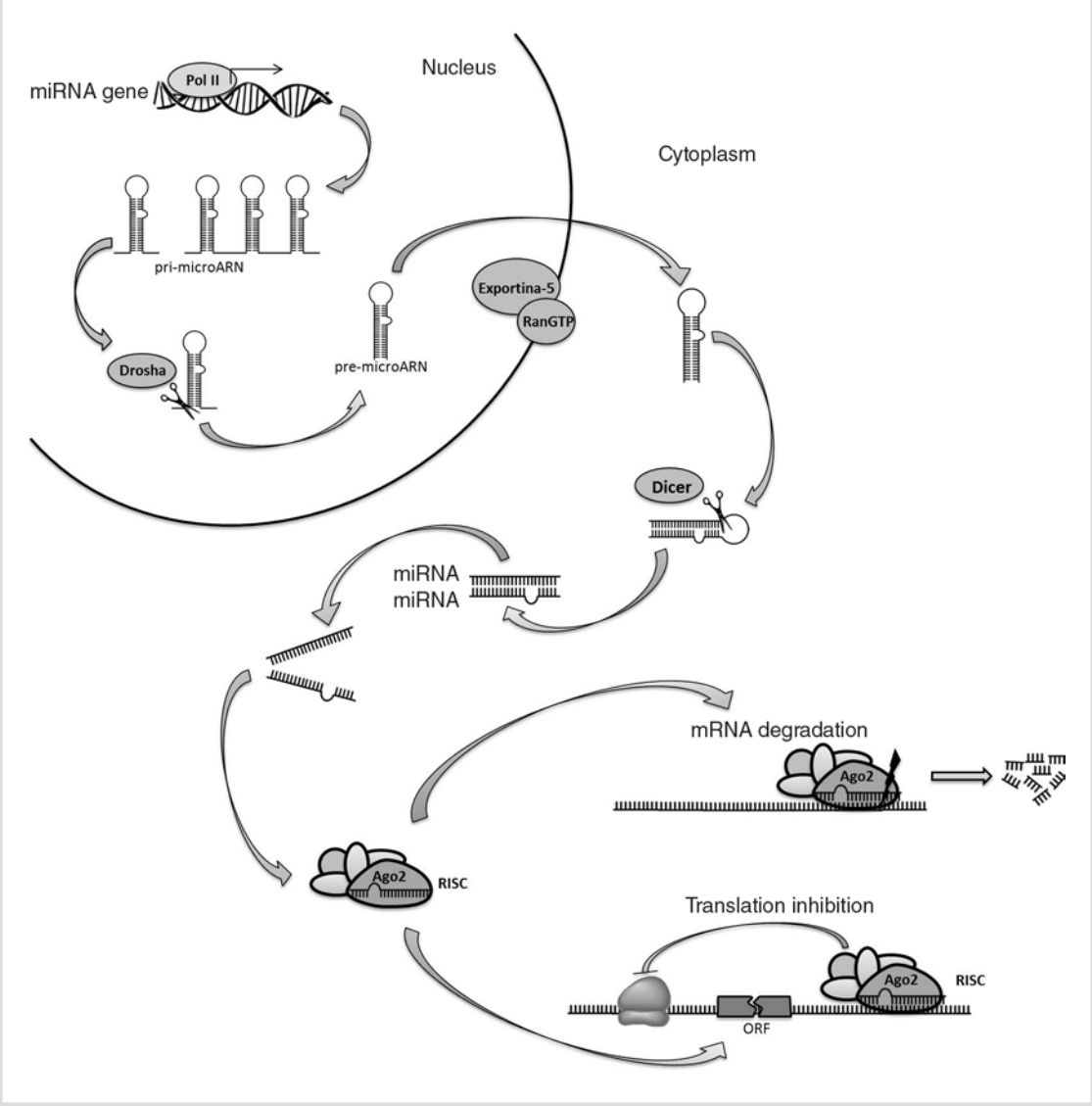

Figure 1. *MicroRNA biosynthesis and mechanisms of action* (Taken and modified from[7]).

release it for translation[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 (hXrnl1) and a mRNA-degrading protein (LSm1-7)[25,26].

One general feature of miRNAs is their imperfect pairing with target mRNAs in the 3'UTR region (untranslated region)[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[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[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[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.

In 1999, Olsen and Ambros[31] 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 mRNA cleavage or degradation, since the *lin-4* mRNA level remained constant and the poly-A tails were not shortened. Subsequently, Kim et al.[32] 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[33]. 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[34,35]. Takamizawa et al.[36] 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.[37] 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[33]. This way, recent studies have correlated miRNA specific expression patterns with certain types of cancer[38].

MiRNA candidates for CRC

Michael et al. identified *miRNA-143* and *miRNA-145* to be potential factors in colorectal tumorigenesis[37]. 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-transcriptionally inhibits ERK5 in a way that doesn't involve the degradation of its mRNA[39]. Shi et al., using 4 miRNA target-prediction methods (miRanda, TargetScan, miRBase, MiRNAMap), identified that *miRNA-145* target RNA was the insulin receptor substrate 1 (*IRS-1*), which is a specific sequence of the binding site in the *IRS-1* mRNA 3'UTR region[40]. 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[33]. 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)[41]. 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-7a1*; on the other hand, when the transfection with the *let-1a1* precursor was performed, it showed reduced cell growth and decreased the expression of the RAS and c- Myc proteins[42]. 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[43,44]. 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[45].

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 end 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[46]. 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[47]; 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%[48]. 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[49].

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[50]. 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 miARNs stemming from samples with CRC could be differentiated from the controls with a sensitivity of 74% and specificity of 79%[51,52]. 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[52]. 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[46].

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 chemo-adjuvant therapy 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[46].

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[53]. 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.[54], one study by Kulda et al.[55] and one study by Nielsen et al.[56]). 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 lung[57,58], breast[59], pancreas[60], tongue[61], gastric[62] and head and neck[63] cancers, as well as chronic lymphocytic leukemia[64], melanoma[65] and astrocytoma[66]. These findings are consistent with the hypothesis that overexpression of this miRNA is a prognostic marker for different types of malignancies[46].

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*[67-73]. On the other hand, elevated expression of the gene that codifies for the Dicer enzyme has been associated with poor prognosis in CRC[74]. 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 risk[74]. 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 factors[120]. These factors can be due to single nucleotide polymorphisms (SNPs) and other genetic abnormalities in both coding and non-coding genes[46]. 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 CRC[121]. 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 China[122]. 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 cancer[123]. 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 CRC[124].

Similar studies have assessed the relationship of SNPs present in miRNAs and their likely association with prognosis and treatment response[46]. 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 CRC[125]. 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 survival[126]. 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 therapy[127]. 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 stage[128]. 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

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

Continue

Table 1. Examples of microRNAs associated with prognosis and therapeutic response in CRC (*Continued*)

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

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

1. Manne U, Shanmugam C, Katkouri VR, Bumpers HL, Grizzie WE. Development and progression of colorectal neoplasia. Cancer Biomark. 2010;9(1-6):235-65.
2. Globocan, 2012. Disponible en: http://globocan.iarc.fr.
3. Huxley RR, Ansary-Moghaddam A, Clifton P, Czernichow S, Parr CL, Woodward M. The impact of dietary and lifestyle risk factors on risk of colorectal cancer: a quantitative overview of the epidemiological evidence. Int J Cancer. 2009;125:171-80.
4. Juárez Vázquez CI, Rosales Reynoso MA. Cáncer Colorrectal (CCR): alteraciones genéticas y moleculares. Gaceta Médica de México. 2014;150:154-64.
5. Hisamudding IM, Yang VW. Genetics of colorectal cancer. Med Gen Med. 2004;6:13-19.
6. Worthley DL, Leggett BA. Colorectal cancer: molecular features and clinical opportunities. Clin Biochem Rev. 2010;31(2):31-8.
7. Yang L, Belaguli N, Berger DH. MicroRNA and colorectal cancer. World J Surg. 2009;33(4):638-46.
8. Lee RC, Feinbaum RL, Ambros V. The *C. elegans* heterochronic gene lin-4 encodes small RNAs with antisense complementarity to lin-14. Cell. 1993;75:843-54.
9. Reinhart BJ, Slack FJ, Basson M, et al. The 21 nucleotide let-7 RNA regulates developmental timing in *Caenorhabditis elegans.* Nature. 2000;403:901-6.
10. Brennecke J, Hipfner DR, Stark A, Russell RB, Cohen SM. Bantam encodes a developmentally regulated microRNA that controls cell proliferation and regulates the proapoptotic gene hid in *Drosophila*. Cell. 2003;113:25-36.
11. Lagos-Quintana M, Rauhut R, Yalcin A, Meyer J, Lendeckel W, Tuschl T. Identification of tissue-specific microRNAs from mouse. Curr Biol. 2002;12:735-9.
12. Calin GA, Dumitru CD, Shimizu M, et al. Frequent deletions and down-regulation of micro-RNA genes miR15 and miR16 at 13q14 in chronic lymphocytic leukemia. Proc Natl Acad Sci USA. 2002;99:15524-9.
13. Ambros V. The functions of animal microRNAs. Nature. 2004;431:350-5.
14. Bartel DP. MicroRNA: genomics, biogenesis, mechanisms, and functions. Cell. 2004;116:281-97.
15. Lagos-Quintana M, Rauhut R, Lendeckel W, Tuschl T. Identification of novel genes coding for small expressed RNAs. Science. 2001;294: 853-8.
16. Lee Y, Kim M, Han J, et al. MicroRNA genes are transcribed by RNA polymerase II. Embo J. 2004;23:4051-60.
17. Lee Y, Jeon K, Lee JT, Kim S, Kim VN. MicroRNA maturation: stepwise processing and subcellular localization. Embo J. 2002;21:4663-70.
18. Lee Y, Ahn C, Han J, et al. The nuclear RNase III Drosha initiates microRNA processing. Nature. 2003;425:415-9.
19. Denli AM, Tops BB, Plasterk RH, Ketting RF, Hannon GJ. Processing of primary microRNAs by the Microprocessor complex. Nature. 2004; 432:231-5.
20. Yi R, Qin Y, Mascara IG, Cullen BR. Exportin-5 mediates the nuclear export of pre-microRNA and short hairpin RNAs. Genes Dev. 2003;17:3011-6.
21. Bohnsack MT, Czaplinski K, Görlich D. Exportin 5 is a RanGTP-dependent dsRNA-binding protein that mediates nuclear export of pre-miRNA. RNA. 2001;10:185-91.
22. Hutvágner G, McLachlan J, Pasquinelli AE, Bálint E, Tuschl T, Zamore PD. A cellular function for the RNA-interference enzyme Dicer in the maturation of the let-7 small temporal RNA. Science. 2001;293:834-8.
23. Ma C, Liu Y, He L. MicroRNAs- powerful repression comes from small RNAs. Sci China C Life Sci. 2009;52:323-30.

24. Sen GL, Blau HM. Argonaute 2/RISC resides in sites of mammalian mRNA decay known as cytoplasmic bodies. Nat Cell Biol. 2005;7:633-6.
25. Ingelfinger D, Arndt-Jovin DJ, Luhrmann R, Achsel T. The human LSm1-7 proteins colocalize with the mRNA-degrading enzymes Dcp1/2 and Xrnl in distinct cytoplasmic foci. RNA. 2002;8:1489-501.
26. Van Dijk E, Cougot N, Meyer S, Babajko S, Wahle E, Séraphin B. Human Dcp 2: a catalytically active mRNA decapping enzyme located in specific cytoplasmic structures. Embo J. 2002;21:6915-24.
27. Chu CY, Rana TM. Small RNAs: Regulators and guardians of the genome. J Cell Physiol. 2007;213:412-9.
28. Hammond SM, Bernstein E, Beach D, Hannon GJ. An RNA-directed nuclease mediates post-transcriptional gene silencing in *Drosophila* cells. Nature. 2000;404:293-6.
29. Hutvágner G, Zamore PD. A microRNA in a multiple turnover RNAi enzyme complex. Science. 2002;297:2056-60.
30. Zeng Y, Yi R, Cullen BR. MicroRNAs and small interfering RNAs can inhibit mRNA expression by similar mechanisms. Proc Natl Acad Sci USA. 2003;100:9779-84.
31. Olsen PH, Ambros V. The lin-4 regulatory RNA controls developmental timing in *Caenorhabditis elegans* by blocking LIN-14 protein synthesis after the initiation of translation. Dev Biol. 1999;216:671-80.
32. Kim J, Krichevsky A, Grad Y, et al. Identification of many microRNAs that copurify with polyribosomes in mammalian neurons. Proc Natl Acad Sci USA. 2004;101:360-5.
33. Croce CM, Calin GA. miRNA, Cancer and stem cell division. Cell. 2005;122(1):6-7.
34. Metzler M, Wilda M, Busch K, Viehmann S, Borkhardt A. High expression of precursor microRNA 155/BIC RNA in children with Burkitt lymphoma. Genes Chrom Cancer. 2004;39:167-9.
35. Eis PS, Tam W, Sun L, et al. Accumulation of miR-155 and BIC RNA in human B cell lymphomas. Proc Natl Acad Sci USA. 2005;103:3627-32.
36. Takamizawa J, Konishi H, Yanagisawa K, et al. Reduced expression of the let-7 microRNA in human lung cancers in association with shortened postoperative survival. Cancer Res. 2005;64:3753-6.
37. Michael MZ, O' Connor SM, van Holst Pellekaan NG, Young GP, James RJ. Reduced accumulation of specific microRNAs in colorectal neoplasia. Mol Cancer Res. 2003;1:882-91.
38. Volinia S, Calin GA, Liu CG, et al. miRNA expression signature of human solid tumors defines cancer gene targets. Proc Natl Acad Sci USA. 2006;103:2257-61.
39. Akao Y, Nakagawa Y, Naoe T. MicroRNAs 143 and 145 are possible common onco-microRNAs in human cancers. Oncol Rep. 2006;16:845-50.
40. Shi B, Sepp-Lorenzino L, Prisco M, Linsley P, deAngelis T, Baserga R. Micro RNA 145 targets the insulin receptor substrate-1 and inhibits the growth of colon cancer cells. J Biol Chem. 2007;282:32582-90.
41. Akao Y, Nakagawa Y, Naoe T. Let-7 microRNA functions as a potential growth suppressor in human colon cancer cells. Biol Pharm Bull. 2007;29:903-6.
42. Fang WJ, Lin CZ, Zhang HH, Qian J, Zhong L, Xu N. Detection of let-7a microRNA by real-time PCR in colorectal cancer: a single-centre experience from China. J Int Med Res. 2007;3:716-23.
43. Brueckner B, Stresemann C, Kuner R, et al. The human let-7a–3 locus contains an epigenetically regulated microRNA gene with oncogenic function. Cancer Res. 2007;67:1419-23.
44. Sampson VB, Rong NH, Han J, et al. MicroRNA let-7a down-regulates MYC and reverts MYC-induced growth in Burkitt lymphoma cells. Cancer Res. 2007;67:9762-70.
45. Tazawa H, Tsuchiya N, Izumiya M, Nakagama H. Tumor-suppressive miR-34a induces senescence-like growth arrest through modulation of the E2F pathway in human colon cancer cells. Proc Natl Acad Sci USA. 2007;104:15472-7.
46. Schetter AJ, Okayama H, Harris CC. The role of microRNAs in Colorectal Cancer. Cancer J. 2012;18(3):244-52.
47. Ng EK, Chong WW, Jin H, et al. Differential expression of microRNAs in plasma of patients with colorectal cancer: a potential marker for colorectal cancer screening. Gut. 2009;58(10):1375-81.
48. Huang Z, Huang D, Ni S, Peng Z, Sheng W, Du X. Plasma microRNAs are promising novel biomarkers for early detection of colorectal cancer. Int J Cancer. 2010;127(1):118-26.
49. Cheng H, Zhang L, Cogdell DE, et al. Circulating plasma MiR-141 is a novel biomarker for metastatic colon cancer and predicts poor prognosis. PLoS One. 2011;6(3):e17745.
50. Link A, Balaguer F, Shen Y, et al. Fecal MicroRNAs as novel biomarkers for colon cancer screening. Cancer Epidemiol Biomarkers Prev. 2010;19(7):1766-74.
51. Koga Y, Yasunaga M, Takahashi A, et al. MicroRNA expression profiling of exfoliated colonocytes isolated from feces for colorectal cancer screening. Cancer Prev Res (Phila). 2010;3(11):1435-42.
52. Kalimutho M, Di Cecilia S, Del Vecchio Blanco G, et al. Epigenetically silenced miR-34b/c as a novel faecal-based screening marker for colorectal cancer. Br J Cancer. 2011;104(11):1770-8.
53. Schetter AJ, Leung SY, Sohn JJ, et al. MicroRNA expression profiles associated with prognosis and therapeutic outcome in colon adenocarcinoma. Jama. 2008;299(4):425-36.
54. Shibuya H, Iinuma H, Shimada R, Horiuchi A, Watanabe T. Clinicopathological and prognostic value of microRNA-21 and microRNA-155 in colorectal cancer. Oncology. 2010;79:313-20.
55. Kulda V, Pesta M, Topolcan O, et al. Relevance of miR-21 and miR-143 expression in tissue samples of colorectal carcinoma and its liver metastases. Cancer Genet Cytogenet. 2010;200:154-60.
56. Nielsen BS, Jørgensen S, Fog JU, et al. High levels of microRNA-21 in the stroma of colorectal cancers predict short disease-free survival in stage II colon cancer patients. Clin Exp Metastasis. 2011;28(1):27-38.
57. Markou A, Tsaroucha EG, Kaklamanis L, Fotinou M, Georgoulias V, Lianidou ES. Prognostic value of mature microRNA-21 and microRNA-205 overexpression in non-small cell lung cancer by quantitative real-time RT-PCR. Clin Chem. 2008;54(10):1696-704.
58. Yanaihara N, Caplen N, Bowman E, et al. Unique microRNA molecular profiles in lung cancer diagnosis and prognosis. Cancer Cell. 2006;9(3):189-98.
59. Yan LX, Huang XF, Shao Q, et al. MicroRNA miR-21 overexpression in human breast cancer is associated with advanced clinical stage, lymph node metastasis and patient poor prognosis. RNA. 2008;14(11):2348-60.
60. Dillhoff M, Liu J, Frankel W, Croce C, Bloomston M. MicroRNA-21 is overexpressed in pancreatic cancer and a potential predictor of survival. J Gastrointest Surg. 2008;12(12):2171-6.
61. Li J, Huang H, Sun L, et al. MiR-21 indicates poor prognosis in tongue squamous cell carcinomas as an apoptosis inhibitor. Clin Cancer Res. 2009;15(12):3998-4008.
62. Jiang J, Zheng X, Xu X, et al. Prognostic significance of miR-181b and miR-21 in gastric cancer patients treated with S-1/Oxaliplatin or Doxifluridine/Oxaliplatin. PLoS One. 2011;6(8):e23271.
63. Avissar M, McClean MD, Kelsey KT, Marsit CJ. MicroRNA expression in head and neck cancer associates with alcohol consumption and survival. Carcinogenesis. 2009;30(12):2059-63.
64. Rossi S, Shimizu M, Barbarotto E, et al. MicroRNA fingerprinting of CLL patients with chromosome 17p deletion identify a miR-21 score that stratifies early survival. Blood. 2010;116(6):945-52.
65. Jiang L, Lv X, Li J, et al. The status of microRNA-21 expression and its clinical significance in human cutaneous malignant melanoma. Acta Histochem. 2011;114(6):582-8.
66. Zhi F, Chen X, Wang S, et al. The use of hsa-miR-21, hsa-miR-181b and hsa-miR-106a as prognostic indicators of astrocytoma. Eur J Cancer. 2010;46(9):1640-9.
67. Diaz R, Silva J, García JM, et al. Deregulated expression of miR-106a predicts survival in human colon cancer patients. Genes Chromosomes Cancer. 2008;47(9):794-802.
68. Schepeler T, Reinert JT, Ostenfeld MS, et al. Diagnostic and prognostic microRNAs in stage II colon cancer. Cancer Res. 2008;68(15):6416-24.
69. Nishida N, Yokobori T, Mimori K, et al. MicroRNA miR-125b is a prognostic marker in human colorectal cancer. Int J Oncol. 2011;38(5):1437-43.
70. Drebber U, Lay M, Wedemeyer I, et al. Altered levels of the onco-microRNA 21 and the tumor-supressor microRNAs 143 and 145 in advanced rectal cancer indicate successful neoadjuvant chemoradiotherapy. Int J Oncol. 2011;39(2):409-15.
71. Akcakaya P, Ekelund S, Kolosenko I, et al. miR-185 and miR-133b deregulation is associated with overall survival and metastasis in colorectal cancer. Int J Oncol. 2011;39(2):311-8.
72. Karaayvaz M, Pal T, Song B, et al. Prognostic significance of miR-215 in colon cancer. Clin Colorectal Cancer. 2011;10(4):340-7.
73. Yu G, Tang JQ, Tian ML, et al. Prognostic values of the miR-17-92 cluster and its paralogs in colon cancer. J Surg Oncol. 2011;106(3):232-7.
74. Faber C, Horst D, Hlubek F, Kirchner T. Overexpression of Dicer predicts poor survival in colorectal cancer. Eur J Cancer. 2011;47(9):1414-9.
75. Schetter AJ, Nguyen GH, Bowman ED, et al. Association of Inflammation-Related and microRNA Gene Expression with Cancer-Specific Mortality of Colon Adenocarcinoma. Clin Cancer Res. 2009;15(18):5878-87.
76. Bandrés E, Cubedo E, Agirre X, Malumbres R, Zárate R, Ramirez N, et al. Identification by Real-time PCR of 13 mature microRNAs differentially expressed in colorectal cancer and non-tumoral tissues. Mol Cancer. 2006;5:29.
77. Tang JT, Wang JL, Du W, et al. MicroRNA 345, a methylation-sensitive microRNA is involved in cell proliferation and invasion in human colorectal cancer. Carcinogenesis. 2011;32:1207-15.
78. Nakajima G, Hayashi K, Xi Y, et al. Non-coding MicroRNAs hsa-let-7g and hsa-miR-181b are Associated with Chemoresponse to S-1 in Colon Cancer. Cancer Genomics Proteomics. 2006;5:317-24.
79. Hummel R, Hussey DJ, Haier J. MicroRNAs: predictors and modifiers of chemo- and radiotherapy in different tumour types. Eur J Cancer. 2010;46:298-311.
80. Schetter AJ, Leung SY, Sohn JJ, et al. MicroRNA expression profiles associated with prognosis and therapeutic outcome in colon adenocarcinoma. JAMA. 2008;299:425-36.
81. Arndt GM, Dossey L, Cullen LM, et al. Characterization of global microRNA expression reveals oncogenic potential of miR-145 in metastatic colorectal cancer. BMC Cancer. 2009;9:374.

82. Baffa R, Fassan M, Volinia S, et al. MicroRNA expression profiling of human metastatic cancers identifies cancer gene targets. J Pathol. 2009;219:214-21.
83. Xiao B, Guo J, Miao Y, et al. Detection of miR-106a in gastric carcinoma and its clinical significance. Clin Chim Acta. 2009;400:97-102.
84. Xi Y, Formentini A, Chien M, et al. Prognostic Values of microRNAs in Colorectal Cancer. Biomark Insights. 2006;2:113-21.
85. Slaby O, Svoboda M, Fabian P, et al. Altered expression of miR-21, miR-31, miR-143 and miR-145 is related to clinicopathologic features of colorectal cancer. Oncology. 2007;72:397-402.
86. Liu L, Chen L, Xu Y, Li R, Du X. MicroRNA-195 promotes apoptosis and suppresses tumorigenicity of human colorectal cancer cells. Biochem Biophys Res Commun. 2010;400:236-40.
87. Valeri N, Gasparini P, Braconi C, et al. MicroRNA-21 induces resistance to 5-fluorouracil by down-regulating human DNA MutS homolog 2 (hMSH2). Proc Natl Acad Sci USA. 2010;107:21098-103.
88. Chen X, Guo X, Zhang H, et al. Role of miR-143 targeting KRAS in colorectal tumorigenesis. Oncogene. 2009;28:1385-92.
89. Motoyama K, Inoue H, Takatsuno Y, et al. Over- and under-expressed microRNAs in human colorectal cancer. Int J Oncol. 2009;34:1069-75.
90. Kanwal R, Gupta S. Epigenetics and cancer. J Appl Physiol. 2010;109: 598-605.
91. Chang KH, Miller N, Kheirelseid EA, et al. MicroRNA signature analysis in colorectal cancer: identification of expression profiles in stage II tumors associated with aggressive disease. Int J Colorectal Dis. 2011;26:1415-22.
92. Liu M, Lang N, Qiu M, et al. miR-137 targets Cdc42 expression, induces cell cycle G1 arrest and inhibits invasion in colorectal cancer cells. Int J Cancer. 2011;128:1269-79.
93. Borralho PM, Kren BT, Castro RE, da Silva IB, Steer CJ, Rodrigues CM. MicroRNA-143 reduces viability and increases sensitivity to 5-fluorouracil in HCT116 human colorectal cancer cells. FEBS J. 2009;276:6689-700.
94. Akao Y, Noguchi S, Iio A, Kojima K, Takagi T, Naoe T. Dysregulation of microRNA-34a expression causes drug-resistance to 5-FU in human colon cancer DLD-1 cells. Cancer Lett. 2011;300:197-204.
95. Braun CJ, Zhang X, Savelyeva I, et al. p53-Responsive micrornas 192 and 215 are capable of inducing cell cycle arrest. Cancer Res. 2008;68:10094-104.
96. Boni V, Bitarte N, Cristobal I, et al. miR-192/miR-215 influence 5-fluorouracil resistance through cell cycle-mediated mechanisms complementary to its post-transcriptional thymidilate synthase regulation. Mol Cancer Ther. 2010;9:2265-75.
97. Song B, Wang Y, Titmus MA, et al. Molecular mechanism of chemoresistance by miR-215 in osteosarcoma and colon cancer cells. Mol Cancer. 2010;9:96.
98. Yantiss RK, Goodarzi M, Zhou XK, et al. Clinical, pathologic, and molecular features of early-onset colorectal carcinoma. Am J Surg Pathol. 2009;33:572-82.
99. Chai H, Liu M, Tian R, Li X, Tang H. miR-20a targets BNIP2 and contributes chemotherapeutic resistance in colorectal adenocarcinoma SW480 and SW620 cell lines. Acta Biochim Biophys Sin (Shanghai). 2011;43:217-25.
100. Wang YX, Zhang XY, Zhang BF, Yang CQ, Chen XM, Gao HJ. Initial study of microRNA expression profiles of colonic cancer without lymph node metastasis. J Dig Dis. 2010;11:50-4.
101. Chiang Y, Song Y, Wang Z, et al. Aberrant expression of miR-203 and its clinical significance in gastric and colorectal cancers. J Gastrointest Surg. 2011;15(1):63-70.
102. Li J, Chen Y, Zhao J, Kong F, Zhang Y. miR-203 reverses chemoresistance in p53-mutated colon cancer cells through downregulation of Akt2 expression. Cancer Lett. 2011;304(1):52-9.
103. Mencia N, Selga E, Noe V, Cuidad CJ. Underexpression of miR-224 in methotrexate resistant human colon cancer cells. Biochem Pharmacol. 2011;82:1572-82.
104. Bandres E, Bitarte N, Arias F, et al. microRNA-451 regulates macrophage migration inhibitory factor production and proliferation of gastrointestinal cancer cells. Clin Cancer Res. 2009;15:2281-90.
105. Bitarte N, Bandres E, Boni V, et al. MicroRNA-451 is involved in the self-renewal, tumorigenicity, and chemoresistance of colorectal cancer stem cells. Stem Cells. 2011;29:1661-71.
106. Sarver AL, French AJ, Borralho PM, et al. Human colon cancer profiles show differential microRNA expression depending on mismatch repair status and are characteristic of undifferentiated proliferative states. BMC Cancer. 2009;9:1-15.
107. Wang CJ, Stratmann J, Zhou ZG, Sun XF. Suppression of microRNA-31 increases sensitivity to 5-FU at an early stage, and affects cell migration and invasion in HCT-116 colon cancer cells. BMC Cancer. 2010;10:1-11.
108. Kurokawa K, Tanahashi T, Iima T, et al. Role of miR-19b and its target mRNAs in 5-fluorouracil resistance in colon cancer cells. J Gastroenterol. 2012;47(8):883-95.
109. Liu L, Chen L, Xu Y, Li R, Du X. MicroRNA-195 promotes apoptosis and suppresses tumorigenicity of human colorectal cancer cells. Biochem Biophys Res Commun. 2010;400:236-40.
110. Wang X, Wang J, Ma H, Zhang J, Zhou X. Downregulation of miR-195 correlates with lymph node metastasis and poor prognosis in colorectal cancer. Med Oncol. 2012;29:919-27.
111. Ragusa M, Majorana A, Statello L, et al. Specific alterations of microRNA transcriptome and global network structure in colorectal carcinoma after cetuximab treatment. Mol Cancer Ther. 2010;9:3396-409.
112. Li J, Zhang Y, Zhao J, Kong F, Chen Y. Overexpression of miR-22 reverses paclitaxel-induced chemoresistance through activation of PTEN signaling in p53-mutated colon cancer cells. Mol Cell Biochem. 2011;357:31-8.
113. Zhang G, Xia S, Tian H, Liu Z, Zhou T. Clinical significance of miR-22 expression in patients with colorectal cancer. Med Oncol. 2012;29: 3108-12.
114. Ma Y, Zhang P, Wang F, et al. miR-150 as a potential biomarker associated with prognosis and therapeutic outcome in colorectal cancer. Gut. 2012;61:1447-53.
115. Tang JT, Wang JL, Du W, et al. MicroRNA 345, a methylation-sensitive microRNA is involved in cell proliferation and invasion in human colorectal cancer. Carcinogenesis. 2011;32(8):1207-15.
116. Nie J, Liu L, Zheng W, et al. MicroRNA-365, down-regulated in colon cancer, inhibits cell cycle progression and promotes apoptosis of colon cancer cells by probably targeting Cyclin D1 and Bcl-2. Carcinogenesis. 2012;33:220-5.
117. Nishida N, Yamashita S, Mimori K, et al. MicroRNA-10b is a prognostic indicator in colorectal cancer and confers resistance to the chemotherapeutic agent 5-fluorouracil in colorectal cancer cells. Ann Surg Oncol. 2012;9:3065-71.
118. Vickers MM, Bar J, Gorn-Hondermann I, Yarom N, Daneshmand M, Hanson JE. Stage-dependent differential expression of microRNAs in colorectal cancer: potential role as markers of metastatic disease. Clin Exp Metastasis. 2012;2:123-32.
119. Weissmann-Brenner A, Kushnir M, Lithwick Yanai G, Aharonov R, Gibori H, et al. Tumor microRNA-29a expression and the risk of recurrence in stage II colon cancer. Int J Oncol. 2012;40(6):2097-103.
120. Lichtenstein P, Holm NV, Verkasalo PK, et al. Environmental and heritable factors in the causation of cancer-analyses of cohorts of twins from Sweden, Denmark, and Finland. N Engl J Med. 2000;343(2):78-85.
121. Ryan BM, Robles AI, Harris CC. Genetic variation in microRNA networks: the implications for cancer research. Nat Rev Cancer. 2010;10(6): 389-402.
122. Zhan JF, Chen LH, Chen ZX, et al. A functional variant in microRNA-196a2 is associated with susceptibility of colorectal cancer in a Chinese population. Arch Med Res. 2011;42(2):144-8.
123. Landi D, Gemignani F, Naccarati A, et al. Polymorphisms within micro-RNA-binding sites and risk of sporadic colorectal cancer. Carcinogenesis. 2008;29(3):579-84.
124. Zanetti KA, Haznadar M, Welsh JA, et al. 3'-UTR and Functional Secretor Haplotypes in Mannose-Binding Lectin 2 Are Associated with Increased Colon Cancer Risk in African Americans. Cancer Res. 2012; 72(6):1467-77.
125. Lee HC, Kim JG, Chae YS, et al. Prognostic impact of microRNA-related gene polymorphisms on survival of patients with colorectal cancer. J Cancer Res Clin Oncol. 2010;136(7):1073-8.
126. Graziano F, Canestrari E, Loupakis F, et al. Genetic modulation of the Let-7 microRNA binding to KRAS 3'-untranslated region and survival of metastatic colorectal cancer patients treated with salvage cetuximab-irinotecan. Pharmacogenomics J. 2010;10(5):458-64.
127. Zhang W, Winder T, Ning Y, et al. A let-7 microRNA-binding site polymorphism in 3'-untranslated region of KRAS gene predicts response in wild-type KRAS patients with metastatic colorectal cancer treated with cetuximab monotherapy. Ann Oncol. 2011;22(1):104-9.
128. Smits KM, Paranjape T, Nallur S, et al. A let-7 microRNA SNP in the KRAS 3'UTR is prognostic in early-stage colorectal cancer. Clin Cancer Res. 2011;17(24):7723-31.