

MicroRNAs in colorectal cancer: Role in metastasis and clinical perspectives

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Abstract

Colorectal cancer (CRC) is the third most common malignancy and the third leading cause of cancer related deaths in the United States. Almost 90% of the patients diagnosed with CRC die due to metastases. MicroRNAs (miRNAs) are evolutionarily conserved molecules that modulate the expression of their target genes post-transcriptionally, and they may participate in various physiological and pathological processes including CRC metastasis by influencing various factors in the human body. Recently, the role miRNAs play throughout the CRC metastatic cascade has gain attention. Many studies have been published to link them with CRC metastasis. In this review, we will briefly discuss metastatic steps in the light of miRNAs, along with their target genes. We will discuss how the aberration in the expression of miRNAs leads to the formation of CRC by effecting the regulation of their target genes.

As miRNAs are being exploited for diagnosis, prognosis, and monitoring of cancer and other diseases, their high tissue specificity and critical role in oncogenesis make them new biomarkers for the diagnosis and classification of cancer as well as for predicting patients' outcome. MiRNA signatures have been identified for many human tumors including CRC, and miRNA-based therapies to treat cancer have been emphasized lately. These will also be discussed in this review.

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Key words: MicroRNAs; Colorectal Cancer; Metastasis; Biomarkers; Therapeutics

Core tip: MicroRNAs (miRNAs) are evolutionarily conserved molecules that modulate expression of their target genes post-transcriptionally, and they may participate in various physiological and pathological processes including colorectal cancer (CRC) metastasis by influencing various factors in the human body. They have been associated with every step of the CRC metastatic cascade. More recently, miRNAs have been used as biomarkers for CRC early detection. MiRNA-based therapies are have been emphasized recently to treat various pathological conditions.

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INTRODUCTION

Colorectal cancer (CRC) is the third most common ma-

lignancy in the United States, with > 148000 cases projected to have occurred in 2008^[1]. Despite improvements in diagnosis and treatment, more than 52000 patients are estimated to have died of CRC at the end of 2007, and approximately 50% of all patients diagnosed with CRC will eventually die of metastatic disease^[2]. Approximately 90% of CRC related mortalities are due to metastases, yet the mechanism underlying this process remains unclear^[3]. The complex multistep process of metastasis can be divided into multiple stages, including invasion of the surrounding tissues, vasculature intravasation, translocation through the systemic circulation, extravasation into the parenchyma of distant secondary sites (liver and lungs), establishment of micrometastases, and finally the formation of macroscopic secondary tumors^[4]. Multiple studies have been conducted recently to investigate the genes and their products that are involved in metastasis^[5]. In recent years, studies have evidenced the role of microRNAs (miRNAs) in the establishment and progression of CRC. The fragile chromosomal regions, where more than 50% of miRNA genes are situated, alter during tumor progression^[6]. MiRNAs are small, endogenous, regulatory RNA molecules that modulate the expression of their target genes post-transcriptionally. MiRNAs are located in the spacer regions between protein-coding genes or in the introns of protein-coding genes, and they have either their own promoters or use the same promoters as protein-coding genes, and are transcribed as primary miRNAs (pri-miRNAs) in the same manner as the mRNAs of the protein-coding genes. After being processed within the nucleus, pri-miRNAs become miRNA precursors (pre-miRNAs), which are then transported to the cytoplasm, where they are further processed into mature miRNAs, and function through post-transcriptional regulation of gene expression *via* base-pairing with complementary sequences in target mRNAs, resulting in translational suppression of imperfectly matched mRNAs or degradation of perfectly matched mRNAs^[7]. The two strands of a pre-miRNA can be processed into two mature miRNAs either having similar efficiencies that are discriminated by -5p and -3p or can develop into one dominantly processed and the other being the recessive one star-labeled(*), and they function differently against target genes^[8]. MiRNAs are evolutionarily conserved molecules and may participate in various physiological and pathological processes including CRC metastasis by influencing cancer stem-cell biology, angiogenesis, epithelial-mesenchymal and mesenchymal-epithelial transition or drug resistance^[9]. An aberration in the expression of miRNAs leads to the progression of CRC^[10]. This effect may be underlined by deletions, amplifications or point mutations of miRNA loci, epigenetic silencing, deregulation of transcription factors (modifiers of miRNA expression) or inhibition of processing of primary miRNA to its mature form^[11]. Certain specific miRNAs, when upregulated, can suppress genes responsible for growth/proliferation inhibition, and downregulation of other specific miRNAs can enhance the expression of genes responsible for

growth/proliferation promotion, resulting in either development or progression of cancer. However, the processes of dysregulated expression of miRNAs in human cancers are still not fully understood. Aberrant methylation of the miRNA gene promoters located in or near CpG islands is a mechanism which has gained attention recently. Recent studies have demonstrated that aberrant hypermethylation of certain miRNAs (miR-34b, miR-34c, miR-9-1, miR-129-2, and miR-137), which are all located in CpG islands, is associated with their reduced expression in CRC cell lines and cancerous tissues^[12-14]. By comparing miRNA expression and histone modifications (H3K4me3, H3K27me3, and H3K79me2) before and after the DNA demethylation, it was found that 47 miRNAs, including miR-1-1, were potential targets of epigenetic silencing in early and advanced CRCs^[15]. The DNA demethylation of these miRNA promoters resulted in upregulation of H3K4me3 and H3K27me3, which has provided a new insight into the association between hypermethylation, chromatin modifications, and miRNA dysregulation in cancer. In addition, expression profiling analysis has revealed characteristic miRNA signatures that can predict the clinical outcomes of CRC^[16]. The recent discovery of miRNAs secreted in membrane vesicles (exosomes)^[17,18] as well as in the blood serum^[19,20] and other body fluids^[21], suggests that miRNAs play a role in intracellular communication in both paracrine and endocrine manner, and some miRNAs have been identified as oncogenes or tumor suppressor genes in CRC^[22]. These findings have also opened a new exciting direction for the study of miRNAs as biomarkers for diseases, and cancer diagnostics by miRNA profile in blood serum has quickly become a growing field^[23]. In this article, we will review the role of miRNAs in the metastatic process of CRC as well as in the diagnosis and therapeutics of this malignancy.

MIRNAS INVOLVED IN CRC METASTATIC CASCADE

Cancerous cells escape from the primary site, followed by local invasion of surrounding tissues into the circulatory or lymphatic system. After extravasation and survival of tumor cells, they proliferate and colonize into the secondary site. These are the multiple sequential steps of the metastatic cascade. MiRNAs that are associated with colorectal cancer metastasis^[24] have been identified by Hanahan *et al.*^[25] and others. The complex metastatic process can be broadly divided into two main stages, with the first being the migration of tumor cells from their primary tumor environment to various distant tissues and the second being the colonization of these tumor cells in their new location^[26]. Underlying these two main stages provides a number of cellular hallmarks taking place during the development and metastasis of human tumors^[27]. The expression patterns of miRNAs can also distinguish normal colonic mucosa, colon adenomas and colon carcinomas. These expression patterns are consistent with

Table 1 MicroRNAs involved in angiogenesis

MicroRNAs	Target genes/activators	Effect on angiogenesis	Ref.
miR-194	<i>THBS1</i>	↑ Enhance	[69]
miR-221, miR-222	c-Kit, Stat5A, ENOS, and ETS1	↓ Inhibit	[70]
miR-17-92 (Oncomir-1)	TSP-1 and CTGF	↑ Enhance	[71]
miR-126	SPRED1 and PIK3R2 p85beta	↑ Enhance	[72]
miR-210	Hypoxia-induced miR-210 activation accompanied by KRAS mutation	↑ Enhance	[73]
miR-497	<i>IGF1-R</i>	↓ Inhibit	[74]
miR-424	Hypoxia-induced activation of angiogenic genes	↑ Enhance	[75]

ENOS: Endothelial nitric oxide synthase; ETS1: V-ets erythroblastosis virus E26 oncogene homolog 1; Stat5A: Signal transducer and activator of transcription 5A; CTGF: Connective tissue growth factor; TSP-1: Encodes thrombospondin-1; SPRED1: Sprouty-related protein1; PIK3R2: Phosphatidylinositol-3-kinase regulatory subunit; KRAS: V-Ki-ras2 Kirsten rat sarcoma viral oncogene homolog; *IGF1-R*: Insulin-like growth factor 1 receptor gene.

the stepwise, multi-hit model for colon carcinogenesis and support a role for miRNAs in each step. MiR-21 is a good example of this in that it is elevated in both adenomas and colon carcinomas^[10]. Higher expression levels of miR-21 are associated with more advanced stages of CRC, indicating that miR-21 plays an important role in the initiation and progression of CRC^[28]. Moreover, the frequency and extent of miR-21 expression were found to be enhanced during the transition from adenoma to carcinoma. Another miRNA, miR-135b, may also have a role in the early stages of colon carcinogenesis. Various molecular, genetic, and epigenetic changes define the multistep dissemination process of the tumor, also known as the “metastatic cascade.” The steps involved in the cascade, schematically focusing particularly on miRNAs, will be discussed and described in detail below.

Angiogenesis

The generation of new blood vessels, also known as angiogenesis, is an essential physiological process that can be dysregulated in various pathological conditions, including cancer^[29]. Both primary and secondary (metastatic) tumor growth at any site are key components of angiogenesis^[30]. Regulated by pro- and anti-angiogenic factors, angiogenesis near the tumor is essential for its growth and contact with the bloodstream^[31]. Recent studies indicate that miRNAs may regulate angiogenesis by exerting pro-angiogenic or anti-angiogenic effects^[32,33]. It seems that miRNAs may play distinguishing roles in CRC angiogenesis through regulating the levels of mRNAs encoding inhibitors or activators of angiogenesis. Various miRNAs involved in angiogenesis are listed in Table 1.

Cancer cell invasion

Cancer cells exhibit properties consistent with a propensity to migrate and invade into surrounding tissues and

Table 2 MicroRNAs and invasion

MicroRNAs	Dysregulation	Remarks	Ref.
miR-31	↑	Contributed to the invasive nature of CRC cells <i>in vitro</i> and <i>in vivo</i>	[76]
miR-122	↑ ↓	Non-neoplastic tissue to dysplasia Dysplasia to inflammatory bowel disease-associated CRC	[77] [77]
miR-200 family	↑	Associated with acquiring an aggressive phenotype	[78]
miR-328	↓	Accompanied by a high fraction of side population (SP) cells showing cancer stem like properties	[79]
miR-143	↓	Stimulated cell growth, migration and invasion	[80]
miR-145, miR-103 and miR-107	↑	Promoted local invasion and liver metastasis in a mouse model	[81]
miR-29a	↑	Elevated in CRC tumor samples compared to normal epithelial tissue; a specific and sensitive marker discriminating CRC with liver metastases from non-metastatic CRC	[82,83]
miR-21, miR-17, miR-19a	↑	Favored cell proliferation and CRC metastasis	[84]

CRC: Colorectal cancer; miRNA: MicroRNA.

distal organs^[34,35] prior to the development of frank metastatic lesions. An early step in tumor progression is the invasion of the cancer cell from the tumor mass to the adjacent tissue. Increased potentials for malignant cells to spread to local and distant sites, including directional activation of proteolytic enzymes (including metalloproteases), degradation of extracellular matrix, transition of the cancer phenotype from epithelial to mesenchymal (EMT), and translocation of cancer cells, are known to be linked with a variety of cellular events. The role of miRNAs has been evaluated in the process of cancer cell invasion. Various miRNAs contributing to the process of invasion are listed in Table 2.

Intravasation, circulation and extravasation

The exact mechanism of how a cancer cell intravasates blood/lymph vessels by crossing the basement membrane is still elusive. The connection of miRNAs with tumor growth, invasion and intravasation has been illustrated by recently published studies, even though the complex mechanisms are still not fully understood. Degradation of cancer cells as they enter the bloodstream may occur due to shear stress and immune system attacks^[36]. A number of miRNAs have been discovered to play critical roles in modulation of T and B lymphocyte activation, innate and adaptive immune responses^[37]. It seems that miRNAs help cancer cells evade recognition by the immune system in the blood/lymph vessels, even though the exact role of miRNAs is still unknown. The escape of cancer cells from the capillaries to invade the parenchyma is a step before creating cancer cell colonies

Table 3 Intravasation, extravasation and colonization

MicroRNAs	Dysregulation	Effect	Ref.
	Intravasation and extravasation		
miR-21	↓ <i>Pdcd4</i>	↑ Intravasation and metastatic potential	[34,85]
miR-126	↓ <i>VCAM-1</i>	↓ Decreased cell-cell adhesion, leukocytes-epithelial cell adherence, inflammation	[86]
miR-155		Required for adaptive and innate immunity	[40]
miR-17-92		Adaptive differentiation of B cells and conventional T cells	[40]
	Colonization		
miR-328	↓ in SP cells	Low miR-328 expression correlated with high SP fraction	[79]
miR-26b	↓ HUES-17 and CRC cell line	↓ Cell growth and induction of apoptosis	[87]
miR-103/107	↓ <i>DAPK</i> and <i>KLF4</i>	↑ Colonization	[69]

in the site far from the primary tumor. Based on these miRNAs-regulated processes, it is hypothesized that miRNAs may influence cancer cell extravasation as illustrated in only a few studies^[38,39]. MiRNAs regulating the processes of intrasation, circulation and extravasation are listed in Table 3.

Metastatic colonization

The final step in cancer metastasis is colonization to the distant secondary sites. The circulating tumor cells or cancer cells in the bloodstream showing the affinity for the particular sites^[40] are explained by the “seed and soil” hypothesis, with the “seed” being the cancer cell and the specific organ microenvironment being the “soil”. Metastatic colonization to this microenvironment may be dependent on the ability of cancer cells to proliferate and to adapt to the new conditions. Characterized by the ability of self-renewal and multipotency, cancer stem cells are a subpopulation of cancer cells which may aid in the establishment of distant metastases^[41]. MiRNAs may control the pathways that are necessary for the phenotype of stem cells. The abnormal levels of miRNAs were observed in cancer stem cells compared to their non-stem counterpart. Given that these miRNAs may regulate the stem-cell properties of cancer cells, they may possibly play a role in CRC metastasis and enable the colonization (Table 3) of CRC cells at a metastatic site, but the precise mechanism of that action is unidentified^[42].

MIRNAS ARE ASSOCIATED WITH VARIOUS OTHER FACTORS PROMOTING METASTATIC CASCADE

Macrophage migration inhibitory factor (MIF) is an innate cytokine which plays a critical role in the control of host inflammation and immunity; it also plays an impor-

tant role in the colorectal carcinogenesis and hypoxia-induced apoptosis^[12,43], due to the fact that MIF can inhibit p53 tumor suppressor activity^[13]. Bioinformatic analysis has shown that MIF is a potential target of miR-451. Over-expression of miR-451 in gastric cancer and CRC has been related to reduced cell proliferation, enhanced susceptibility to radiotherapy and downregulated expression of MIF at both mRNA and protein levels. In biopsies of gastric tumors, it was observed that there was an inverse connection between miR-451, a tumor suppressor, and MIF expression^[44]. It has been elucidated that miRNAs play a role in linking inflammation and tumorigenesis, and their close relationship with DNA methylation. Methylation of CpG islands in the miR-34b/c gene was repeatedly observed in CRC cell lines (9 of 9, 100%) and in primary CRC tumors (101 of 111, 90%) rather than in normal colonic mucosa^[45]. Five other miRNAs were downregulated in CRC samples, whose genes are located around/on a CpG island. Expression of miR-9, miR-129 and miR-137 was restored after treatment with a DNA methyltransferase inhibitor and a histone deacetylase inhibitor in three CRC cell lines. Methylation of their genes was frequently observed in CRC cell lines and in primary CRC tumors instead of normal colonic mucosa^[46]. Evidence has shown the acquisition of EMT (a process by which epithelial cells lose their cell-to-cell contacts and subsequently attain characteristics of mesenchymal phenotype) could be regulated by deregulated expression of miRNAs in the context of metastasis. The responsibility for tumor cell metastasis is believed to be due to the detachment of these cells from the primary tumor site and the entering into circulation^[47,48]. In the context of metastasis, the phenotype could be regulated by deregulation in the expression of miRNAs. Studies have shown that detection of circulating miRNAs can be associated with clinical parameters such as relapse with metastatic disease^[49]. It has been reported that the expression of KRAS is inversely regulated by miR-143 *in vivo*^[50]. Compared with their surrounding normal tissues, KRAS was downregulated in 87.5% (35 of 40) of CRC tissues and was inversely correlated with mRNA and protein expression of DNMT3A in CRC. After the restoration of miR-143 expression, tumor cell growth and soft-agar colony formation were inhibited, and DNMT3A expression at both mRNA and protein levels was downregulated^[51]. Thus, miRNAs have an impact on the expression of oncogenes^[52]. It has been suggested that c-Myc could encourage the growth of cancers *via* the miR-17-92 cluster^[53]. siRNA-mediated downregulation of microtubule-associated kinase (DCAMKL-1) resulted in a growth arrest of the HCT116 tumor, increased the level of pri-let-7a miRNA and decreased the expression of Myc in tumor cell lines. It is suggested that DCAMKL-1 may play a role in both stem cell differentiation and tumor growth^[54]. In colorectal adenomas and carcinomas^[55] an inverse correlation was observed between the level of APC mRNA and miR-135. In two of the eight human CRC samples based on stem-loop RT-PCR^[56], human let-

Table 4 MicroRNAs as diagnostic markers

MicroRNAs	Sensitivity	Specificity	Remarks	Ref.
Plasma				
miR-29a	69%	89.1%	Upregulated in CRC plasma, associated with advanced TNM stages	[82]
miR-92a	64%	70%	Upregulated in CRC plasma; could distinguish CRC from other GI cancers and IBD; not associated with TNM stages	[50]
miR-17-3p	89%	70%	Upregulated in CRC plasma	[51]
miR-92a	84%	71.2%	Upregulated in CRC plasma; not associated with TNM stages	[82]
Fecal				
miR-17-92 cluster	69.5%	81.5%	Upregulated in stool of CRC patients	[88]
miR-135	46.2%	95%	Upregulated in stool of CRC patients	[88]
miR-92a	50%	80%	Upregulated in stool of CRC patients	[89]
miR-21	50%	83%	Upregulated in stool of CRC patients	[89]

CRC: Colorectal cancer; miRNA: MicroRNA; TNM: Tumour-node-metastasis.

7a miRNA expression was significantly reduced. A low level of let-7a could activate multiple signaling pathways including c-Myc and KRAS and lead to the formation and development of CRC. Meanwhile, a high level of let-7a could restrain the drug-induced apoptosis of CRC cells. Cyclooxygenase-2 (COX-2), which has a significant effect on the growth and invasiveness of CRC cells, was inversely correlated with miR-101 expression in colon cancer cell lines and translation of COX-2 mRNA was directly inhibited by miR-101 *in vitro*.

CLINICAL PERSPECTIVES

In addition to DNA methylation, a large body of data support that miRNAs serve as biomarkers for early detection, determination of predictive responses to chemotherapy, and prognosis in patients with colorectal neoplasia. Along with DNA methylation, miRNA expression changes can be easily measured in archival tissues, as well as in blood, feces, urine, and so on. Moreover, miRNA expression and DNA methylation can be measured quantitatively, which might be useful for monitoring disease progression and the patient responses to various treatments.

MicroRNAs as diagnostic markers (blood and stool tests)

In the peripheral blood^[23], circulating miRNAs, as blood-based markers for cancer detection, have been discovered in a highly stable, cell-free form. Through mechanisms still unknown, circulating miRNAs are packed in complexes, either called exosomes or microvesicles, and released by normal and tumor cells. Such external miRNAs are also involved in cell-to-cell signal transduction and genetic information exchange^[57], as indicated by emerg-

ing evidence. These circulating miRNAs can potentially serve as noninvasive markers for CRC detection (Table 4). However, the false-positive and false-negative rates in diagnosis and lower specificity are problems still left to resolve. An optimized method of plasma/serum miRNA detection and data analysis has recently been described. The improved protocol can increase the detection accuracy and help uncover novel miRNA markers in the plasma^[58], as expected. A widely adopted noninvasive screening method for CRC diagnosis is stool-based test. Endogenous miRNAs are packed and protected from RNases, compared to mRNAs and proteins which are degraded rapidly. Therefore, they are more likely to be detected in the stools. Several criteria need to be met if stool miRNAs have to be developed as diagnostic markers, including predictability, reproducibility and measurability, due to complex and hostile stool environment as compared to plasma. Recently, a novel detection protocol including stool preparation, stool miRNA extraction and quantitative analysis has been developed^[28]. In comparison with blood, it has been postulated that tumor cells and most tumor markers can be readily detected in the stools at earlier stages of CRC. Thus, stool miRNA testing has the advantage for pre-cancerous lesion screening^[59]. For stool miRNA purification, a commercial miRNA extraction kit is also available, which can yield total RNA of high quality and integrity for further assays. The use of stool miRNAs as biomarkers is still in its infancy and none of the miRNAs discussed above has progressed beyond the preclinical stage; however, the obtainable data indicated that higher specificity, sensitivity and reproducibility can be achieved for stool miRNA detection. For CRC diagnosis, further studies of stool miRNA characterization and validation are required. A variety of known stool miRNAs are listed in Table 4.

MicroRNAs as therapeutic agents and prognostic markers

Since a single miRNA can modulate the expression of various genes^[60], applying miRNAs in anticancer therapy could be efficient. The use of miRNA-based therapies to treat cancer has been emphasized lately. There are two general strategies for miRNA-based therapies: to inhibit oncogenic miRNAs or to restore tumor suppressor miRNAs. Both of these strategies can be effective, as shown in preclinical models. Antisense oligonucleotides or miRNA sponges can be used to bind and sequester the target miRNA for direct inhibition of miRNAs. Antagomirs are modified antisense oligonucleotides which have been used to inhibit miRNAs *in vivo*^[61]. In a recent study, anti-miR-122 treatment in chimpanzees chronically infected with HCV has shown promising results in improving HCV-related liver pathology^[62]. This anti-miR-122 drug has progressed to phase II clinical trials to treat HCV in humans, suggesting that anti-sense based miRNA therapeutics may soon be available. Through treatments with various chemical compounds, indirect inhibition of miRNAs can also be achieved. In fact, through screening, various small molecule inhibitors that can inhibit the function of at least mir-21 have been

Table 5 MicroRNAs as therapeutic, potential prognostic and predictive markers for colorectal cancer

MicroRNAs	Dysregulation	Clinical phenotypes	Ref.
miR-221	Upregulated in CRC	Prognostic factors for poor overall survival in CRC patients	[90]
miR-141	Upregulated in CRC	Higher level associated with poor survival; an independent prognostic factor for advanced CRC	[71]
pre-miR-423	Upregulated in CRC	SNPs in these miRNAs were significantly associated with	[91]
pre-miR-608	Upregulated in CRC	recurrence-free survival in CRC	[91]
miR-222	Upregulated in CRC	Played a role in the development of MDR by modulation of ADAM-17 in CRC	[79,92]
miR-328	Upregulated in CRC	Chemotherapeutic insensitive CRC cells, carrying stem cell-like properties, could be reversed by restoring miR-328 to normal	[79]
let-7g	Upregulated in CRC	Higher level associated with poor S-1 response; was prognostic in early-stage CRC	[10,93]
miR-18a	Upregulated in CRC	Higher level associated with poor overall survival	[94]
miR-21	Upregulated in adenoma, CRC, and liver metastases	Higher level associated with lymph node metastasis, poor survival, poor therapeutic outcomes, rapid recurrence, and shorter disease-free interval	[88]
miR-31	Upregulated in CRC	Higher level associated with higher TNM stages and local invasion	[91]
miR-106a	Upregulated in colon cancer	Higher level associated with longer disease-free survival and overall survival	[10]
miR-143	Downregulated in colon cancer and liver metastases	Lower level associated with larger tumour size and longer disease-free interval; expression levels served as an independent prognostic biomarker for KRAS wild-type CRC	[65,91]
miR-145	Downregulated in CRC	Lower level associated with large tumour size and tumour location	[65,91]
miR-181b	Upregulated in CRC	Higher level associated with poor S-1 response	[10]
miR-320	Downregulated in MSS tumour	Lower level associated with shorter progression-free survival	[94]
miR-498	Downregulated in MSS tumour	Lower level associated with shorter progression-free survival	[94]

Up- or downregulation is stated as miRNA expression relative to normal colon tissue, or MSS relative to MS. CRC: Colorectal cancer; miRNA: MicroRNA; MSS: Microsatellite stable tumour; TNM: Tumour-node-metastasis.

found^[63,64]. In addition, miRNAs are also known as highly promising prognostic markers (Table 5)^[65], as several preclinical and clinical studies have illustrated. In human pancreatic, colorectal, ovarian, and breast cancers, as well as glioblastoma and other cancer types^[24,66-68], miRNA expression profiling has proven to be useful. Thereafter, a larger scale study using miRNA array was conducted with two independent cohorts with dissimilar races and geographical distributions. Skog *et al.*^[16] recognized 37

aberrantly expressed miRNAs in CRC, among which 5 highly expressed miRNAs (miR-20a, miR-21, miR-106a, miR-181b and miR-203) were related with poor survival in the test cohort. The statistically significant association between poor prognosis and high tumor level of miR-21 in Asian CRC patients was validated and confirmed. Prognostic and therapeutic perspectives related to miRNAs are mentioned in Table 5.

CONCLUSION

Although miRNAs have a crucial role throughout the metastatic cascade and an important role in the diagnosis and treatment of CRC, further large-scale evaluation in multiple independent cohorts is indispensable for determining their realistic expectation. It is expected to develop novel therapeutics in the near future to re-normalize the altered miRNAs in CRC by directly restoring down-regulated miRNAs and knocking down the upregulated miRNAs.

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