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TOPIC HIGHLIGHT

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MicroRNAs in colorectal cancer as markers and targets: Recent advances

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Abstract

MicroRNAs are evolutionarily conserved small non-coding RNA molecules encoded by eukaryotic genomic DNA, and function in post-transcriptional regulation of gene expression *via* base-pairing with complementary sequences in target mRNAs, resulting in translational repression or degradation of target mRNAs. They represent one of the major types of epigenetic modification and play important roles in all aspects of cellular activities. Altered expression of microRNAs has been found in various human diseases including cancer. Many efforts have been made to discover the characteristic microRNA expression profiles, to understand the roles of aberrantly expressed microRNAs and underlying mechanisms in different cancers. With the application of DNA microarray, real-time quantitative polymerase chain reaction and other molecular biology techniques, increasing evidence has been accumulated which reveal that aberrant microRNAs can be detected not only intracellularly within the cancer cells, but also extracellularly in plasma of patients, postulating the potential of aberrant microRNAs as promising diagnostic/prognostic markers and attracting therapeutic targets. This review is intended to provide the most recent advances in microRNA studies in one of the most common cancers, colorectal cancer, especially the identification of those specifically altered microRNAs in colorectal cancer, validation for their relevance to clinical pathological parameters of patients, functional analyses and potential applications of these microRNAs.

Key words: MicroRNA; Epigenetic modification; Colorectal cancer; Marker; Therapy

Core tip: MicroRNAs represent one of the important epigenetic modifications for gene expression and play important roles in all aspects of cellular activities. Altered expression of microRNAs has been found in various human diseases including cancer. Aberrant microRNAs can be detected not only intracellularly within the cancer cells, but also extracellularly in plasma of patients, postulating the potential of aberrant microRNAs as promising diagnostic/prognostic markers and attracting therapeutic targets. This review focuses on recent advances in identification, validation and functional analyses for such microRNAs in colorectal cancer, and potential applications of these altered microRNAs.

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INTRODUCTION

Colorectal cancer is one of the most common malignancies worldwide, with 1233700 new cases and 608700 deaths estimated in 2008[1]. Prevention, early diagnosis

and treatment can greatly reduce the incidence and mortality. All these depend on the achievements in a comprehensive understanding of every aspect of colorectal cancer at molecular and cellular levels. More and more evidence shows that epigenetic modifications, such as hyper- or hypo-methylation at specific sites in DNAs or proteins, acetylation or de-acetylation of nucleosome histones and conditionally specifically expressed non-coding RNAs like microRNAs, are involved in the carcinogenesis of many types of cancer including colorectal cancer[2-4], and some of the epigenetic modifications can serve as markers for diagnosis, treatment efficacy monitoring and prognosis, or be developed into targets for therapeutic interventions.

MicroRNAs are evolutionarily conserved small non-coding RNA molecules that are encoded by eukaryotic genomic DNA. Located in the spacer regions between protein-coding genes or in the introns of protein-encoding genes, microRNA coding sequences have their own promoters or utilizes the same promoters as protein-coding genes, and are transcribed as primary microRNAs (pri-microRNAs) in the same manner as the messenger RNAs of the protein-coding genes do. Pri-microRNAs are processed into microRNA precursors (pre-microRNAs) in the nucleus and transported to the cytoplasm and further processed into mature microRNAs, and function in 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[5]. Both strands of a pre-microRNA may be processed into two mature microRNAs, with similar efficiencies which are discriminated by -5p and -3p, or with one dominantly processed and the recessive one star-labeled (*), which function differently against different target genes. This post-transcriptional regulation of expression of multiple genes represents one of the major types of epigenetic modification and exhibits important impacts in all aspects of cellular activities, under both physiological and pathological conditions. Many of the known microRNAs appear in clusters on a single polycistronic transcript[6], which may modulate the expression of genes whose products work together to fulfill the same task.

It is now well documented that microRNAs play important roles in the pathogenesis of many human diseases including cancer. Aberrant expression of microRNAs has been observed in cancers of various tissues such as lung, breast, liver, colon and rectum, and prostate. Up-regulation of certain specific microRNAs may suppress genes responsible for growth/proliferation inhibition, down-regulation of other specific microRNAs may augment genes responsible for growth/proliferation promotion, and either may result in the development and progression of cancer. The specifically altered microRNA expression patterns may serve as diagnostic/prognostic markers, and correction of these aberrant microRNAs may reverse the malignant phenotypes of cancer cells and therefore provide means for cancer treatment[7-9].

Numerous investigations on screening for altered expression of microRNAs in various types of cancer have been conducted during the past decade, with more and more functional validations in recent years. The aberrantly expressed microRNAs exert their functions by modulating oncogenic or tumor-suppressive genes and play important roles in the development and progression of cancers, therefore exhibit their potentials as "oncogenic" or "tumor-suppressive" microRNAs. Some of the alterations are common among different cancers, while others are type-specific. MicroRNAs function in a multi-target manner that one microRNA may modulate the expression of multiple genes, and one target gene may also be modulated by multiple microRNAs. While the microRNA-modulated gene expression is one kind of epigenetic modification, the expression of microRNA itself is modulated by other epigenetic modifications such as hyper- or hypo-methylation. This review focuses on the most recent advances in studies on some extensively investigated microRNAs in colorectal cancer, especially with regards to the potentials as bio-markers or therapeutic targets.

ONCOGENIC MICRORNAS AS POTENTIAL MARKERS AND TARGETS IN COLORECTAL CANCER

MiR-21

MiR-21 is one of the most extensively investigated oncogenic microRNAs whose expression is frequently up-regulated in colorectal cancer. The identified target genes regulated by miR-21 include programmed cell death 4, RhoB and transforming growth factor beta receptor 2 (TGFBR2). MiR-21 regulates cell proliferation, invasion and apoptosis, and induces stemness. Through its pro-metastatic effect, ectopic stromal miR-21 expression associates with increased epithelial invasiveness. The expression level of miR-21 correlates with clinical stage, and increases with advanced disease, decreased recurrence-free cancer-specific survival and shorter overall survival (OS). There is higher stool level of miR-21 in patients with colorectal cancer but not polyps. Plasma/serum miR-21 can be served as a potential diagnostic and prognostic marker. The post-therapeutic miR-21 level in colorectal cancer is lower and can predict the pathological tumor response to chemotherapy. Down-regulation of miR-21 reduces cell proliferation, migration and invasion, induces apoptosis and inhibits cell cycle progression, up-regulates Spry2 and phosphatase and tensin homologue deleted on chromosome 10 and enhances the cytotoxic effects of 5-fluorouracil and metformin, and also leads to differentiation of chemoresistant cells, therefore inhibition of miR-21 may serve as a novel therapeutic approach[10-30].

MiR-155

Up-regulation of oncogenic miR-155 in colorectal cancer cells promotes cell proliferation, migration and inva-

sion, increases chemoresistance and correlates with poor prognosis. Claudin-1, a member of integral membrane proteins that constitute tight junctions, is the identified target gene modulated by miR-155[30-33]. Low expression of claudin-1 is associated with lymphatic involvement, histological differentiation, extent of poorly differentiated component, reduced disease-free and overall survival of colorectal cancer patients[34].

MiR-31

With rat sarcoma viral oncogene homolog (RAS) p21 Guanosine-5'-triphosphatase (GTPase) activating protein 1 (*RASA1*) gene as the target gene, miR-31 overexpression activates oncogene RAS by repressing RASA1, and elevated expression of miR-31[35-38] is associated with aggressive mucinous phenotype. For metastatic colorectal cancer patients with wild-type kirsten rat sarcoma viral oncogene homolog/v-raf murine sarcoma viral oncogene homolog B (KRAS/BRAF) who received anti-epidermal growth factor receptor (EGFR) monoclonal antibody (mAb) treatment, significant miR-31* up-regulation appeared in progressive disease *vs* disease control, and can be used to predict the benefits of anti-EGFR mAb treatment.

MiR-92a

The overexpression of miR-92a[14,26,39-43] correlates with tumor metastasis and poor prognosis. Higher miR-92a level in stool in patients with colorectal cancer and polyps can be detected. BCL-2-interacting mediator of Cell Death (BIM) is the target gene of miR-92a. As the down-regulation of *BIM* gene by over-expressed miR-92a in colon cancer cells may lead to the evasion of apoptosis, anti-miR-92a strategy effectively induces apoptosis of colorectal cancer cells, which suggests a potential new therapeutic approach.

MiR-17

Elevated in colon cancer, miR-17[18,42-45] expression is associated with poor survival and is an independent prognostic marker. By targeting tumor suppressor gene Rho family GTPase 3 (*RND3*), miR-17 promotes proliferation, growth and cell cycle progression. Moreover, elevated oncofoetal miR-17-5p expression resulted in shorter overall survival rates by repressing its target gene retinoblastoma-like protein 2 (*P130*), but caused a better response to adjuvant chemotherapy.

MiR-106a and miR-106b

MiR-106a[46,47] is highly expressed in metastatic colorectal cancer cells and regulates migration and invasion. Tumor suppressor Rb1 is one of the target genes of miR-106a, and the regulatory role for Rb1 may happen in sporadic colorectal cancer. Similar to miR-21, miR-106a also inhibits the expression of TGFBR2, leading to increased colorectal cancercell migration and invasion.

Interestingly, miR-106b[42] is upregulated in cancer stromal tissues compared with normal stroma, and the stromal miR-106b expression level is associated with clinicopathologic factors, suggesting the possibility that miRNAs in cancer stroma are crucially involved in cancer progression, a similar phenomenon observed for stromal miR-21[10].

MiR-135a and miR-135b

Oncogenic miR-135a[24,48] promotes the growth and invasion of colorectal cancer cells *in vitro* by repressing its target gene metastasis suppressor 1. The level of miR-135b[17,20,49] is also elevated in colorectal cancer, which correlates with clinical stage, liver metastasis, and both disease-free survival (DFS) and cancer-specific survival of patients, and inhibition of miR-135b leads to decreased viability of colorectal cancer cells *in vitro*.

TUMOR SUPPRESSIVE MICRORNAS AS POTENTIAL MARKERS AND TARGETS IN COLORECTAL CANCER

Let-7

The let-7 family is one of the most ancient and conserved microRNAs, which functions as a well-recognized tumor suppressor targeting oncogenic KRAS and whose expression is deregulated in many types of cancer including colorectal cancer[50,51].

Recent studies on let-7 family members showed that: let-7a expression is elevated in metastatic colorectal cancer with KRAS mutation compared to normal mucosa or non-metastatic disease[24], and the high level of let-7a in KRAS-mutated colorectal cancer may rescue anti-EGFR therapy effects[52]; decreased expression of let-7b at tumor invasion front is an adverse prognostic marker for recurrence and OS of colorectal cancer patients[53]; let-7c is a metastasis suppressor in colorectal cancer by targeting matrix metalloproteinase 11 and pre-B-cell leukemia homeobox 3[54]; and let-7e is overexpressed in responders to neoadjuvant chemoradiotherapy[55].

Another current research focus is the correlation between a functional polymorphism in let-7 complementary site within the 3' untranslated region (3'-UTR) of KRAS (rs61764370) and the risk for development of colorectal cancer, pathological and clinical parameters, clinical outcome, progression-free survival (PFS) or OS in metastatic colorectal cancer patients[52,56-58].

All these novel findings for the Let-7 family member microRNAs provide us further predictive/prognostic markers in the management of colorectal cancer patients.

MiR-143

MiR-143[28,37,53,59-65] targets hexokinase 2 (*HK2*) gene and metastasis-associated in colon cancer-1 gene, and inhibit invasion/migration of colorectal cancer cells. Loss of miR-143-mediated repression of HK2 can promote glucose metabolism in cancer cells. The complementary strand miR-143* is down-regulated in colon cancer cells and forced expression significantly abrogated invasive potential.

MiR-143 is often down-regulated in colorectal cancer, especially at liver invasion front, and the reduced ex-

Table 1 Colorectal cancer-associated microRNAs with identified targets

MiR (family)	Role/ potential	Identified targets	Ref.
9	ON	E-cadherin	[36,81,82]
16	TS	COX-2, cyclin D1, survivin, CDK6	[84-86]
17	ON	RND3, P130	[18,42-45]
21	ON	PDCD4, RhoB, TGFBR2	[10-30]
22	TS	p21	[90-93]
31	ON	RASA1	[14,17,35-38]
33a	TS	Pim-1	[67]
34 family	TS	Axin2	[33,70,101-103]
92a	ON	BIM	[14,26,39,40-43]
95	ON	Nexin 1	[106]
139	TS	RAP1B, IGFR-1	[37,121,122]
143	TS	HK2, MACC1	[28,37,53,59-65]
145 family	TS	PAK4, NRAS, IRS1	[14,28,53,60,64,66-68]
148 family	TS	Bcl-2, CCK-2 receptor	[69-72]
155	ON	Claudin-1	[30-33]
215	TS	DTL	[20,55,73-75]
320a	TS	Neuropilin 1, β-catenin	[147,148]
339-5p	TS	PRL-1	[151]
342	TS	DNMT1	[152]
365	TS	Cyclin D1, Bcl-2	[155]
373	TS	RAB22A	[157]
499-5p	ON	FOXO4, PDCD4	[162]
506	ON	PPARα	[164]
1915	TS	Bcl-2	[170]
Let-7 family	TS	MMP11, PBX3	[24,38,52-57]

TS: Tumor suppressor; ON: Oncogene; COX-2: Cyclooxygenase-2; CDK6: Cyclin-dependent kinase 6; RND3: Rho family GTPase 3; PDCD4: Programmed cell death 4; TGFBR2: Transforming growth factor beta receptor 2; RASA1: RAS p21 protein activator 1; BIM: Bcl-2 interacting mediator of cell death; RAP1B: RAS related protein 1b; IGFR-1: Insulin-like growth factor receptor-1; HK2: Hexokinase 2; MACC1: Metastasis associated in colon cancer 1; PAK4: p21 protein-activated kinase 4; NRAS: Neuroblastoma RAS viral oncogene homolog; IRS1: Insulin receptor substrate 1; CCK-2: Cholecystokinin-2; DTL: Denticleless E3 ubiquitin protein ligase homolog; PRL-1: Phosphatases of regenerating liver-1; DNMT1: DNA methyltransferase 1; FOXO4: Forkhead box O4; PDCD4: Programmed cell death 4; PPARα: Peroxisome proliferator-activated receptor alpha; Bcl-2: B-cell leukemia/lymphoma 2; MMP11: Matrix metallopeptidase 11; PBX3: Pre-B-cell leukemia homeobox 3.

pression correlates with aggressive mucinous phenotype. MiR-143 also inhibits tumor growth and angiogenesis and sensitizes chemosensitivity to oxaliplatin. The post-therapeutic level of miR-143 increases and can be used for predicting response to treatment and prognosis. Down-regulation of fecal miR-143 is a potentional marker for colorectal cancer, and the miR-143 level in blood and tissue can be used as a new diagnostic marker and therapeutic target as well.

MiR-145

MiR-145[14,28,53,60,64,66-68] exerts its tumor suppressive function by modulating several target genes: it can block the activation of AKT and ERK1/2 pathways and the expression of HIF-1 and vascular endothelial growth factor *via* directly targeting neuroblastoma RAS viral oncogene homolog and insulin receptor substrate 1, down-regulate phosphorylated-extracellular signal-regulated kinase 1 level and lead to inhibition of tumor growth by targeting p21 protein-activated kinase 4.

MiR-145 is down-regulated in plasma and cancer tissues and liver invasion front of colorectal cancer patients. Down-regulation of fecal miR-145 is proposed as a potential marker for colorectal cancer. Decreased expression of miR-145 occurs before the mutation of APC gene and is involved in the initiation step of colorectal cancer. Similar to miR-143, the post-therapeutic level of miR-145 increases, predicting the response to treatment and prognosis. Overexpression of miR-145 inhibits cell proliferation, migration and invasion due to its proapoptotic and antiproliferative role, showing its potential in miRNA-replacement therapy of colorectal cancer.

MiR-148a and 148b

Tumor suppressive miR-148a[69-71] promotes apoptosis *via* repressing anti-apoptotic Bcl-2 expression. Hypermethylation leads to down-regulation of miR-148a in advanced CRC. Low miR-148a expression is associated with significantly shorter DFS, a worse therapeutic response, and poor OS. The miR-148a level can serve as a disease progression follow-up marker, and has prognostic/predictive value in chemotherapy as well.

MiR-148b[72] also acts as a tumor suppressor in colorectal cancer by targeting the choecystokinin-2 receptor which functions depending on the gastrin in colorectal cancer, and suppresses the growth of cancer cells. The expression of miR-148b is significantly down-regulated in human colorectal cancer tissues and correlates with tumor size, and is important in the cancer transformation process. Forced expression of miR-148b in colorectal cancer cells inhibits cell proliferation *in vitro* and suppresses tumorigenicity *in vivo*. miR-148b can be further evaluated as a biomarker and therapeutic tool against colorectal cancer.

MiR-215

As a tumor suppressor candidate, miR-215[20,73-75] level is decreased in cancer tissues of colorectal cancer patients, especially those relapsed patients. The expression level of miR-215 is an independent predictive marker for relapse and associated with poor OS. However, overexpressed miR-215 can be observed in non-responders to neoadjuvant chemoradiotherapy, and the high miR-215 level confers chemoresistance due to cell cycle arrest and reduced proliferation by targeted inhibition of thymidylate synthase, dihydrofolate reductase and denticleless protein homolog, genes that play essential roles in DNA synthesis, cell cycle progression, proliferation, and differentiation.

OTHER COLORECTAL CANCER-ASSOCIATED MICRORNAS

In addition to the above microRNAs, there are other microRNAs that have been identified to be involved in the development/progression of colorectal cancer. A

Table 2 Colorectal cancer-associated microRNAs without identified target

MiR (family)	Role/potential	Ref.
1	TS	[76-78]
7	TS	[79,80]
10b	Marker, +, chemo	[83]
15a	TS	[84]
18a	ON	[87,88]
19 family	Marker, +, chemo	[18,53,89]
23a	ON	[94,95]
27b	TS	[96]
29 family	Marker, +	[55,87,97,98]
30a-5p	TS	[99]
32	ON	[100]
93	TS	[79,104,105]
96	Marker, +	[17]
101	TS	[14,107,108]
103/107	ON	[109]
106 family	ON	[14,42,46,47]
122	ON	[110]
124	TS	[111-113]
125 family	TS	[114]
126	Marker, +	[115]
127-3p	Marker, +	[40]
129	TS	[116]
130a/301a/454	ON	[117]
133 family	Marker, -	[78,118]
135 family	ON	[17,20,24,48,49]
137	TS	[112,119,120]
140	Marker, +	[38,123]
141	Circ, Marker, +	[124]
144	Marker, -	[125,126]
146a	SNP	[127,128]
149	Marker, -	[129]
150	Marker, -	[130]
181a	ON	[131]
182	Marker, +	[36,132]
185	Marker, +	[118]
186, 216b, 337-3p	TS	[133]
190b	Marker, +, chemo	[55]
192	Marker, -	[74]
193a-3p, 338-5p	Circ, Marker, +	[94]
194	Marker	[53,74]
19, 512, 801, 246	Marker, +	[123]
196a2	SNP	[134-138]
199a-5p	TS	[139]
206	Marker, +	[24]
211	ON	[140]
212	TS	[141]
218	TS	[142]
221*, 224	TS	[143]
222	TS	[144]
223	TS	[145]
297	TS	[146]
328	TS	[149]
330	TS	[150]
340	TS	[112]
345	TS	[153]
362-3p	TS	[154]
367	SNP	[156]
372	Marker, +	[21]
375, 422a	TS	[20]
378	Marker, -	[20,40]
409-3p	Cirl, Marker, +	[79]
424*	TS	[65]
429	ON	[158]
450 family, 99a*	Marker, -, chemo	[55]
451	TS	[159]
486-3p	Marker, +	[40]
493, 493*	TS	[160]
497	TS	[161]
502	TS	[163]
574-5p	ON	[165]
592	Marker, +	[38]
601	Marker, +	[166]
608	SNP	[167]
625-3p	Marker, +, chemo	[168]
627	TS	[169]
638	Marker, -	[53]
760	Marker, +	[133, 66]
1224-5p	Marker, -	[38]
1275	Marker, -	[53]

TS: Tumor suppressor; ON: Oncogene; Marker, +: Up-regulated marker; Marker, -: Down-regulated marker; Chemo: Chemosensitivity-associated; SNP: Single nucleotide polymorphism-associated.

collection of the most recently investigated/concluded colorectal cancer-associated microRNAs are listed in Tables 1 and 2 for reference.

CONCLUSION

As discussed above, a number of alterations of microRNAs play important roles in the development and progression of colorectal cancer, and even alterations of the microRNA processing machinery components are of prognostic values[171,172]. The expression of microRNAs is regulated not only by other epigenetic modifications such as hyper- or hypomethylation, but also by other interacting molecules, *i.e.*, LIN28 and let-7[173], and in a clustered manner. Moreover, the polymorphisms of either microRNAs or targeted genes have a significant impact on colorectal cancer risk[174,175], even in population-based studies[176-178], and the responses to chemotherapy and prognosis[179,180] as well.

We can expect that the altered expression of microRNAs detection will serve as effective biomarkers for screening, diagnosis, monitoring therapy and prognosis of colorectal cancer in the future, as they can be detected from various kinds of samples including cell-free plasma/serum[181-184], circulating tumor cells[185], mucosal wash fluid[186], feces[187,188] and formalin-fixed paraffin-embedded tissues[189].

Based on the achievements in this field, we can also expect that novel therapeutics be developed to re-normalize the altered microRNAs in colorectal cancer[190], not only by directly restoring down-regulated microRNAs or knocking down the up-regulated microRNAs, but also by epigenetic therapy[191].

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