REVIEW

MicroRNAs in Colorectal Cancer: from Diagnosis to Targeted Therapy

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Abstract

Colorectal cancer (CRC) is one of the major healthcare problems worldwide and its processes of genesis include a sequence of molecular pathways from adenoma to carcinoma. The discovery of microRNAs, a subset of regulatory non-coding RNAs, has added new insights into CRC diagnosis and management. Together with several causes of colorectal neoplasia, aberrant expression of oncomiRs (oncogenic and tumor suppressor miRNAs) in cancer cells was found to be indirectly result in up- or down-regulation of targeted mRNAs specific to tumor promoter or inhibitor genes. The study of miRNAs as CRC biomarkers utilizes expression profiling methods from traditional tissue samples along with newly introduced non-invasive samples of faeces and body fluids. In addition, miRNAs could be employed to predict chemo- and radio-therapy responses and be manipulated in order to alleviate CRC characteristics. The scope of this article is to provide a comprehensive review of scientific literature describing aberrantly expressed miRNAs, and consequently dysregulation of targeted mRNAs along with the potential role of miRNAs in CRC diagnosis and prognosis, as well as to summarize the recent findings on miRNA-based manipulation methods with the aim of advancing in anti-CRC therapies.

Keywords: Colorectal cancer - microRNA - biomarker - cancer therapy

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Introduction

Colorectal cancer (CRC) is still one of the five most leading cancer-related death which have one million new cases every year (Pourhoseingholi, 2012; Siegel et al., 2012). Although since mid-1980's the number of CRC-related death has been decreasing due to the increased awareness and progresses in screening approaches, the prognosis of patients with metastatic CRC remains unknown (Terzic et al., 2010; Salimzadeh et al., 2012). Eventually, the study for early diagnosis and prognosis markers are still crucial and would allow selecting patients with early CRC stages for operative cancer management and developing novel targeted therapies.

The involvements of non-coding RNAs in carcinogenesis and tumor progression have been confirmed by numerous functional studies in the past decades (Seton-Rogers, 2013). Among the all types of ncRNAs, microRNAs (miRNAs) received the greatest attention due to their frequent dys-regulations in CRC. miRNAs compromise a large subsequent of endogenous small ncRNAs that regulate gene expression post-transcriptionally and control various cellular mechanisms including tissue development (Johnston and Hobert, 2003; Zhao et al., 2005), cell proliferation (Cheng et al., 2005; 2006), cell division (Hatfield et al., 2005; Croce and Calin, 2005), cell differentiation (Naguibneva et al., 2006), neuronal asymmetry (Bartel, 2004), metabolism (Filipowicz, 2005), stem cell properties (Jamshidi-Adegani et al., 2014), apoptosis (Matsushima et al., 2011), protein secretion (Poy et al., 2004) and viral infection (Mollaie et al., 2013). Each individual miRNA predicted to target multiple mRNAs based on the seed sequence matches in their 3'-UTRs and vice versa a single mRNA may be targeted by several miRNAs and have diverse outcomes (Lewis et al., 2005). Therefore, perturbation in miRNA expression may result in facilitating tumor initiation and proliferation and/ or inhibiting proliferation and invasion through targeting various mRNAs (Ahmed et al., 2009; Bandres et al., 2009a).

miRNAs have been reported to have pervasive effects on CRC tumorigenesis including, oncogenesis, progression, invasion, metastasis, and angiogenesis (Esquela-Kerscher and Slack, 2006; Huang et al., 2008; Zhang et al., 2012). Nevertheless, a comprehensive understanding of the functional role and thorough panel of target mRNAs for individual miRNAs are still in their infancy. Equally challenging or even more challenging is their applications in CRC diagnosis and prognosis, since clinical application of miRNAs have some drawbacks and some provocative reports directly contradict one or another outcomes of original assertions.

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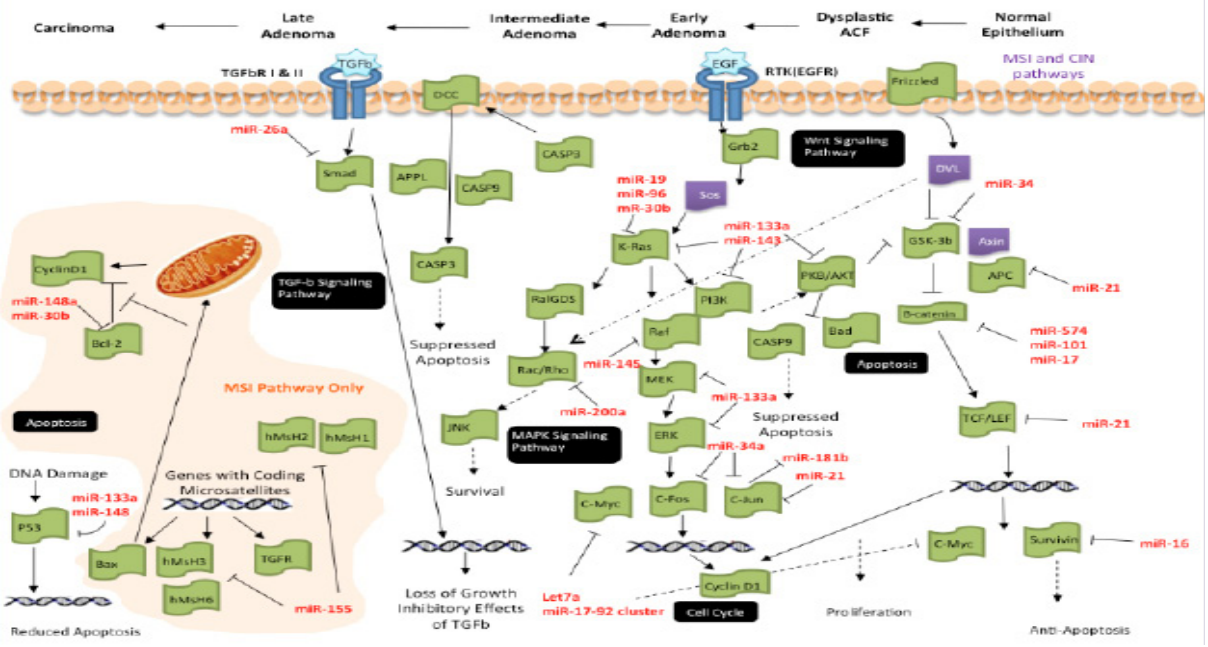

Figure 1. Regulation of CRC-Related Pathways by miRNAs. According to Vogelstein's model Colorectal cancer pathogenesis includes sequence of changes and mutations in normal epithelium from dysplasia to carcinoma. Several miRNAs have been reported to regulate the Wnt, TGF-b, and MAPK signalling pathways, along with cell cycle and apoptosis through direct and indirect mechanisms

These discrepancies between studies could be explained by different factors. First, the heterogeneities observed in results arise from different tumor locations (Colon or Rectum, proximal or distal colon tumor) (Slattery et al., 2011). Secondly, different population sampling bearing various genomic pools could lead to different gene expressions and regulations. Therefore, miRNA expression pattern could differ among populations. On the other hand, the subgroup of tumor is an important defining factor since it has been reported that miRNA deregulation could vary between MSI and CIMP tumors (Schepeler et al., 2008; Earle et al., 2010; Haghighi et al., 2010; Shemirani et al., 2011). In addition, several other factors affect miRNA expression profiling and may hand in different data and results. These factors include the type of the sample (blood, tissue, serum, and faces), the timing between sampling and extraction, methods and kits used for profiling experiments and sample storage.

Despite all aforementioned disadvantages, accumulating proofs demonstrating the potential role of miRNAs in carcinogenesis reflect the worthy advantages of miRNA implications as tumor markers and their potential role for cancer therapies. These advantages include the need of a small amount of sample, the possibility of extracting miRNAs from body fluids, their stability in FFPE tissues, and non-invasive and poisonousness nature of their sampling methods. In the following, we provide a comprehensive review of scientific literature describing the aberrantly expressed miRNAs, and consequently dysregulation of targeted mRNAs along with the potential role of miRNAs in CRC diagnosis, prognosis, and response prediction. We also summarize the recent findings on miRNA-based manipulation methods with the aim to enhance knowledge of anti-CRC therapies.

Clinical Applications

Cancer diagnosis

CRC diagnosis based on a molecular signature implies that a specific expression level is found in tumour cells compared to non-tumour counterpart. Increasing profiling experiments have revealed that miRNA expression patterns are unique to specific cancers, unlike other markers currently available, offering capability of cancer diagnosis in early stages (Zhou et al., 2013a; Li et al., 2014c). The most extensively applied techniques of studying miRNA profiles are microarray, real- time PCR- based methods, as well as sequencing and in situ hybridization (ISH) (Weng et al., 2010; Xie et al., 2011). Next Generation Sequencing (NGS) added a new layer of accuracy as new method for miRNA expression measurement and normalization and provided new knowledge of changes in genome and relevant disease for translational studies (Yadav et al., 2014).

The first miRNAs found to be aberrantly expressed in CRC were miR-143 and miR-145 that were consistently downregulated at the adenomatous and cancer stages of CRC neoplasia compared to normal colon mucosa (Michael et al., 2003; Akao et al., 2006b). Since then the literature dedicated to dysregulation of miRNAs in three different series including tumour samples, both fresh frozen and formalin-fixed paraffin-embedded (FFPE), circulating miRNAs, both in serum and plasma, and faecal samples has grown considerably.

Dysregulated miRNAs in tissue samples and CRC cell lines

After discovering miR-143 and miR-145, several studies have been performed in order to investigate other CRC-related miRNAs. miR-143 was then found to be down-regulated in colon but not in rectum related cancer

Table 1. A Comprehensive List of Dysregulated miRNAs in Colorectal Cancer Tissues and Cell Lines

miRNA	Dysregulation	Predicted target genes	References
Let-7a	Down	c-Myc, DLD1, KRAS	(Cummins et al., 2006, Akao et al., 2006a, Fang et al., 2007, Earle et al., 2010)
Let-7c	Down	MMP11, PBX3	(Han et al., 2012)
Let-7g	Up, Down	KRAS,MYS,E2F,CYC-1, HRAS,HMGA2, NF2, CCND,	(Akao et al., 2006a, Xi et al., 2007, Vogelstein et al., 1988)
miR-1	Down	MET	(Reid et al., 2012)
miR-7	Down, up	XRCC2, YY1,PAX6,	(Motoyama et al., 2009, Xu et al., 2014, Zhang et al., 2013c, Li et al., 2014b)
miR-9	Down	α-Catenin	(Cekaite et al., 2012, Zhu et al., 2012)
miR-10b	Down		(Nishida et al., 2012, Burk et al., 2008, Zhu et al., 2012)
miR-16	Down	Cdx2	(Ma et al., 2013, Volinia et al., 2006, Tagawa et al., 2012)
miR-17	Up	THBS1, MYC, CDKN1A,TMBIM1, E2F1	(Lanza et al., 2007, Arndt et al., 2009, Volinia et al., 2006, Motoyama et al., 2009, Diosdado et al., 2009, Cummins et al., 2006)
miR-18a	Up	ATM	(Cummins et al., 2006, Sarver et al., 2009, Arndt et al., 2009, Wang et al., 2010, Wu et al., 2013a)
miR-19a	Up	TF	(Diosdado et al., 2009, Yu et al., 2013a, Bandres et al., 2006, Cummins et al., 2006)
miR-19b	Up	SFPQ and MYBL2	(Cummins et al., 2006, Arndt et al., 2009, Kurokawa et al., 2012)
miR-20a	Up	PTEN, TMP1	(Tan et al., 2013, Bovell et al., 2013, Earle et al., 2010, Yantiss et al., 2009, Volinia et al., 2006)
miR-20	Up		(Bandres et al., 2006, Lanza et al., 2007, Earle et al., 2010)
miR-21	Up	PTEN, BCL2, PDCD4, CDC25A, TIMP1, SPRY2, SERPINB5, RECK, TIMP3, TIAM1, MSH2, MSH6	(Asangani et al., 2008, Schetter et al., 2008, Valeri et al., 2010a, Slattery et al., 2011 Arndt et al., 2009, Kulda et al., 2010, Yamamichi et al., 2009)
miR-23a	Up	MTSS1	(Rossi et al., 2007, Jahid et al., 2012)
miR-23b	Down		(Volinia et al., 2006)
miR-24	Down	DHFR	(Michael et al., 2003, Mishra et al., 2009)
miR-25	Up		(Lanza et al., 2007, Earle et al., 2010, Xi et al., 2007)
miR-26a	Down		(Michael et al., 2003)
miR-27a	Up	KITENIN	(Rossi et al., 2007, Park et al., 2014)
miR-27b	Up		(Rossi et al., 2007)
miR-26b	Down		(Earle et al., 2010)
miR-29a	Up	KLF4	(Tang et al., 2014)
miR-29b	Up	MMP-2	(Poudyal et al., 2013)
miR-30a	Down	DTL, PIK3CD	(Baraniskin et al., 2012, Zhong et al., 2013)
miR-30b	Down	KITENIN	(Park et al., 2014)
miR-30c	Down	RASA1, ERG, SEMA6D, SEMA3A	(Xi et al., 2007, Volinia et al., 2006, Cummins et al., 2006)
miR-30e	Up	HELZ, PIK3C2A	(Rossi et al., 2007, Schepeler et al., 2012)
miR-31	Up	TIAM1, FOXC2, FOXP3, HIF1A, FIH1	(Chen et al., 2014b, Cottonham et al., 2010, Earle et al., 2010, Olaru et al., 2011)
miR-32	Up	PTEN	(Wu et al., 2013b)
miR-33	Up	GABRB2	(Narasimhan., 2014)
miR-34	Down	AXL	(Mudduluru et al., 2011)
miR-92a	Up	DKK-3, BCL-2	(Yamada et al., 2013, Tsuchida et al., 2011)
miR-93	Down	HDAC8, TLE4, ERBB2, p21, VEGF	(Yu et al., 2011, Yang et al., 2012)
miR-95	Up	Nexin1	(Huang et al., 2011)
miR-96	Up		(Xu et al., 2012b)
miR-101	Down	EP4R	(Chandramouli et al., 2012)
miR-106a	Up	PTEN, E2F1, RB1, TGFBR2	(Catela Ivkovic et al., 2013, Feng et al., 2012, Diaz et al., 2008)
miR-106b	Up	p21/CDKN1A	(Ivanovska et al., 2008)
miR-107	Up	DAPK and KLF4	(Chen et al., 2012b)
miR-124a	Down	PRRX1, MYH9 and SOX9	(Zhang et al., 2014b, Park et al., 2014)
miR-125a	Down, Up	p53	(Nishida et al., 2011)
miR-126	Down	IRS-1	(Zhou et al., 2013b)
miR-127	Up	BCL6	(Saito et al., 2006)
miR-133a	Down, Up	LASP1, KRAS	(Wang et al., 2013)
miR-133b	Down	Met, TBPL1	(Hu et al., 2010, Xiang and Li, 2014)
miR-135a	Up	MTSS1	(Zhou et al., 2012)
miR-135b	Up	TGFRB2, DAPK1, APC, FIH, LATS2	(Valeri et al., 2014, Ragusa et al., 2012)
miR-137	Down	CDC42, LSD1	(Liu et al., 2011b, Balaguer et al., 2010)
miR-138	Down	TWIST2	(Long et al., 2013)
miR-139	Down	IGF-IR, RAP1B	(Guo et al., 2012, Shen et al., 2012)
miR-143	Down	KRAS, MAPK7, DNMT3A, ERK5	(Chen et al., 2009, Ng et al., 2009b)
miR-145	Down	TGFBRE, APC, IRS1, STAT1, YES1, FLI1, RAS, c-Myc, SOX52	(Arndt et al., 2009, Shi et al., 2007, Akao et al., 2006b)
miR-147	Up		(Rossi et al., 2007)
miR-148a	Down	TGIF2, Bcl-2	(Lujambio et al., 2008, Zhang et al., 2011a)
miR-151	Up		(Rossi et al., 2007)
miR-152	Up		(Rossi et al., 2007)
miR-155	Up	MSH2, MSH6, MLH1, Claudin-1, E2F2	(Zhang et al., 2013a, Li et al., 2014a, Valeri et al., 2010b)
miR-181	Down		(Pichler et al., 2014, Nakajima et al., 2006)
miR-182	Up	TSP1	(Amodeo et al., 2013)
miR-183	Up	EGR1	(Zhou et al., 2014, Sarver et al., 2010)
miR-185	Up	RhoA, Cdc42	(Rossi et al., 2007, Akcakaya et al., 2011, Liu et al., 2011a)
miR-191	Up, Down	TIMP3	(Qin et al., 2014, Xi et al., 2006, Earle et al., 2010)
miR-192	Down	CDKN1A, DHFR, Bcl-2, Zeb2, VEGFA	(Braun et al., 2008, Song et al., 2008, Geng et al., 2013)
miR-195	Down	BCL2	(Wang et al., 2012c, Liu et al., 2010)
miR-196a	Up, Down	HoxA7, HoxB8, HoxC8 and HoxD8	(Schimanski et al., 2009, Earle et al., 2010)
miR-199a	Down	AXI	(Mudduluru et al., 2011)
miR-200 family	Up, Down	SOX2, ZEB1, PTEN, ETS1, FLT1,	(Lu et al., 2014, Chen et al., 2008, Chen et al., 2014a, Hur et al., 2013)
miR-203	Down, Up	ATM, AKT2	(Chiang et al., 2011, Zhou et al., 2014, Li et al., 2011)
miR-205	Down, Up		(Orang et al., 2014b)
miR-210	Down	VMP1	(Rossi et al., 2007, Qu et al., 2014)
miR-215	Down	DTL	(Karaayvaz et al., 2011)
miR-218	Down	BMI1	(Yu et al., 2013b, He et al., 2012)
miR-221	Up	PTEN	(Pu et al., 2010)

Table 1 (Continue). A Comprehensive List of Dysregulated miRNAs in Colorectal Cancer Tissues and Cell Lines

miRNA	Dysregulation	Predicted target genes	References
miR-222	Up	PTEN, ADAM-17	(Tsunoda et al., 2011, Xu et al., 2012a)
miR-223	Up	FOXO1, IGF-1R	(Wu et al., 2012b, Josse et al., 2014)
miR-224	Up, Down	MBD2	(Zhang et al., 2013b, Yuan et al., 2013)
miR-296	Down		(Kunte et al., 2012)
miR-320	Up		(Schepeler et al., 2008)
miR-342	Down	DNMT1, EVL	(Grady et al., 2008, Wang et al., 2011)
miR-372	Up	TXNIP	(Yamashita et al., 2012, Ragusa et al., 2012)
miR-375	Down	PIK3CA	(Cummins et al., 2006, Sarver et al., 2009)
miR-378	Up, Down	Vimentin	(Sarver et al., 2009, Wang et al., 2010, Arndt et al., 2009, Zhang et al., 2014a)
miR-422a	Down		(Arndt et al., 2009)
miR-451	Down	COX-2, CAB39, LKB1, AMPK, AKT, PI3K and Bcl2	(Bandres et al., 2009b, Bitarte et al., 2011, Li et al., 2013)
miR-497	Down	IGF1-R	(Guo et al., 2013)
miR-622	Up		(Balaguer et al., 2011)
miR-941	Down	ADAM15	(Yan et al., 2011)
miR-1238	Up		(Balaguer et al., 2011)
miR-1247	Down		(Yan et al., 2011)

and it acts as a tumour suppressor by inhibiting KRAS (Slaby et al., 2007; Chen et al., 2009; Motoyama et al., 2009; Wang et al., 2009). Subsequently, high expression levels of miR-21 were found to be correlated with distant metastatic CRC samples and poor survival prognosis and therapeutic outcomes via targeting PDCD4, a tumour suppressor protein (Asangani et al., 2008; Schetter et al., 2008). Let-7 family members that include 14 isomers were of the most studied miRNAs that act as a tumour suppressor through targeting growth suppressors such as RAS and MMP11, and oncogenes such as PBX3 and NIRF (Akao et al., 2006a; Han et al., 2012; Wang et al., 2012a). Another important miRNA is the miR-200 family which found to be associated with metastasis inhibition by targeting the transcriptional repressor zinc-finger E-box binding homeobox 1 (ZEB1) in CRC and shortly after that miR-200c found to be downreglated in CRC cells (Burk et al., 2008; Chen et al., 2012a; 2012c).

Whereas several miRNAs have been found to be over-expressed or under-expressed in CRC samples compared to normal adjacent colorectal tissues, the role of the differentially expressed miRNAs in colorectal tumorigenesis is not fully understood. Moreover, there are some discrepancies between studies that may arise from different factors such as different tumour locations and genetic backgrounds (Schepeler et al., 2008; Slattery et al., 2011). In Table 1, the studies on dysregulated miRNAs and their cognate mRNAs are summarized.

Dysregulated miRNAs in serum or plasma samples

Recent studies have revealed that dysregulated miRNAs are present in body fluids carried by small micelles and therefore, are protected from hostile ribonuclease activity (Chim et al., 2008; Lawrie et al., 2008; Mitchell et al., 2008). Many groups evaluated the feasibility of using circulating miRNAs as non-invasive biomarkers for CRC (Slattery et al., 2011). Chen et al. reported the existence of circulating miRNA in the serum of CRC patients for the first time (Chen et al., 2008). Since then, dysregulated miRNAs were found to be in plasma or serum of CRC patients at detectable levels and are capable of distinguishing normal samples from CRC samples (Huang et al., 2010; Wang and Zhang, 2012; Wang et al., 2012b; Kanaan et al., 2012). Furthermore, the discovery of miRNA transport, mediated by exosomes, opened a new research area of isolating tissue specific circulating exosome and their contained miRNAs to better analysis of their expression (Taylor and Gercel-Taylor, 2008). These dysregulated circulating miRNAs are summarized in Table 2.

Dysregulated miRNAs in stool samples

Stool-based test is a widely used non-invasive screening method of CRC patients (Lee et al., 2014). However, due to their poor sensitivity and specificity these tests were losing their significance. Nevertheless, reporting miRNAs as screening markers found in faecal specimens by Ahmad et al in 2009, elevated the practicability of using miRNAs as non-invasive diagnostic biomarkers (Ahmed et al., 2009). Surprisingly, analysed miRNAs in stool samples showed relatively high sensitivity and specificity (Link et al., 2010; Koga et al., 2010; Kalimutho et al., 2011; Li et al., 2012; Wu et al., 2012a). Studies were summarized in Table 3. These studies confirmed the hypothesis that miRNAs hold a potential of being used in a stool-based assay for early CRC detection. However, the capability of profiling such miRNAs for adenomatous polyposis is remained to be explored.

miRNA as Marker for Treatment Response Predictions

Aberrant expression of some miRNAs has been shown to be associated with treatment response and outcomes in patients with colorectal cancer. An increasing number of dysregulated miRNAs were revealed to have association with drug resistance or sensitivity which indicate their capability of predicting patients' responses to some anticancer agents (Hummel et al., 2010). For instance the upregulated miR-10b and miR-192/215 were reported to hold a potential to indicate chemosensitivity to the common 5-FU-based chemotherapy regimen (Boni et al., 2010; Nishida et al., 2012) as well as miR-19a which predicts resistance to FOLFOX chemotherapy in advanced CRC cases (Chen et al., 2013). Pichler et al. showed that miR-18a downregulation is associated with poor survival in patients with CRC and its expression could predict progression-free survival (PFS) in EGFR-targeted therapy (Pichler et al., 2014). Moreover, miR-203 was demonstrated to induce oxaliplatin, a common component

Table 2. miRNA Dysregulation in Body Fluids

miRNA	Dysregulation	Reference
Let-7a	Down	(Wang et al., 2012b)
Let-7d	Down	(Hofsli et al., 2013)
Let-7e	Up	(Wang et al., 2012b)
miR-10a	Down	(Wang et al., 2012b)
miR-16	Up	(Zheng et al., 2013)
miR-17	Up	(Ng et al., 2009a)
miR-18a	Up	(Zheng et al., 2013)
miR-19a	Up	(Wang et al., 2012b)
miR-21	Up	(Wang and Zhang, 2012, Kanaan et al., 2012)
miR-22	Up	(Wang et al., 2012b)
miR-23a	Up	(Chen et al., 2008)
miR-24	Up	(Wang et al., 2012b)
miR-29a	Up	(Hofsli et al., 2013, Huang et al., 2010)
miR-34a	Down	(Nugent et al., 2012)
miR-92a	Up	(Wang et al., 2012b, Ng et al., 2009a, Hofsli et al., 2013, Pu et al., 2010, Huang et al., 2010)
miR-95	Up	(Ng et al., 2009a)
miR-103	Down	(Hofsli et al., 2013)
miR-106a	Down	(Koga et al., 2013)
miR-107	Down	(Hofsli et al., 2013)
miR-125	Up	(Wang et al., 2012b)
miR-134	Up	(Chen et al., 2008)
miR-135	Up	(Ng et al., 2009a)
miR-141	Up, Down	(Wang et al., 2012b, Cheng et al., 2011)
miR-143	Down	(Hofsli et al., 2013)
miR-146	Up	(Chen et al., 2008)
miR-150	Down	(Wang et al., 2012b)
miR-151	Down	(Hofsli et al., 2013)
miR-155	Up	(Hofsli et al., 2013)
miR-188	Down	(Wang et al., 2012b)
miR-191	Down	(Hofsli et al., 2013, Zheng et al., 2013)
miR-192	Down	(Wang et al., 2012b)
miR-199a	Down	(Hofsli et al., 2013)
miR-210	Up	(Wang et al., 2012b, Hofsli et al., 2013)
miR-221	Down	(Wang et al., 2012b, Chen et al., 2008, Pu et al., 2010, Hofsli et al., 2013)
miR-222	Up	(Chen et al., 2008, Ng et al., 2009a)
miR-223	Up	(Ogata-Kawata et al., 2014)
miR-224	Down	(Wang et al., 2012b)
miR-296	Down	(Shivapurkar et al., 2013)
miR-320a	Up	(Hofsli et al., 2013)
miR-376a	Up	(Wang et al., 2012b)
miR-378	Up	(Hofsli et al., 2013)
miR-382	Down	(Hofsli et al., 2013)
miR-409	Down	(Hofsli et al., 2013)
miR-423-5p	Up	(Hofsli et al., 2013)
miR-423-3p	Down	(Hofsli et al., 2013)
miR-426	Down	(Wang et al., 2012b)
miR-484	Up	(Zheng et al., 2013)
miR-495	Down	(Wang et al., 2012b)
miR-572	Down	(Wang et al., 2012b)
miR-601	Down	(Wang et al., 2012b)
miR-652	Down	(Hofsli et al., 2013)
miR-720	Up, Down	(Hofsli et al., 2013, Wang et al., 2012b)
miR-760	Down	(Wang et al., 2012b)

combination therapeutic regimen for use in patients with metastatic CRC, and reverse chemoresistance by negatively regulating ATM kinase and Akt, respectively (Li et al., 2011; Zhou et al., 2014).

Besides, experimental and clinical studies have cleared that hsa-let-7g and hsa-miR-181b are potential indicators for chemoresponse to S-1 based chemotherapy and miR-200a, miR-200c, miR-141, and miR-429 expression levels may identify CRC patients, including those with stage II disease, who are most likely to benefit from fluropyrimidine, an adjuvant chemotherapy agent (Nakajima et al., 2006; Diaz et al., 2014).

Table 3. Dysregulated miRNAs Found in Fecal Samples of CRC Patients

miRNA	Dysregulation	Reference
miR-16	Down	(Ahmed et al., 2009)
miR-17	Up	(Koga et al., 2010)
miR-18a	Up	(Koga et al., 2010)
miR-19a	Up	(Koga et al., 2010)
miR-19b	Up	(Koga et al., 2010)
miR-20a	Up	(Ahmed et al., 2009)
miR-21	Up	(Ahmed et al., 2009, Koga et al., 2010, Link et al., 2010, Wu et al., 2012a)
miR-92	Up	(Ahmed et al., 2009)
miR-92a	Up	(Wu et al., 2012a)
miR-96	Up	(Ahmed et al., 2009)
miR-106a	Up	(Ahmed et al., 2009, Link et al., 2010)
miR-106b	Up	(Link et al., 2010)
miR-125b	Down	(Ahmed et al., 2009)
miR126	Down	(Ahmed et al., 2009)
miR-135	Up	(Koga et al., 2010)
miR-143	Down	(Ahmed et al., 2009, Li et al., 2012)
miR-144	Up	(Kalimutho et al., 2011)
miR-145	Down	(Ahmed et al., 2009, Li et al., 2012)
miR-203	Up	(Ahmed et al., 2009)
miR-320	Down	(Ahmed et al., 2009)
miR-326	Up	(Ahmed et al., 2009)
miR-484	Down	(Ahmed et al., 2009)

miRNA-Based Targeted CRC Therapy

The principle that miRNAs play important roles in CRC development and progression provide a rationale for CRC therapeutic investigations. Tumor suppressor and oncogenic miRNAs, which are so called oncomiRs, hold a promising potential to be manipulated for clinical trials such as CRC treatment, blocking the progression of precursor lesions, prevention of distant metastasis, and improving responses to chemo- and radio-therapies (Tong and Nemunaitis, 2008).

miRNAs interact with different cancer signalling pathways and control cellular homeostasis. Hence, silencing overexpressed oncogenic miRNAs as well as restoring downregulated tumor suppressor miRNAs may eventually lead to the tumor growth and progression inhibition, apoptosis, and reduced cell viability (Du et al., 2014; Orang et al., 2014a).

A wealth of published experiments, some of which have been referenced here, utilized tumor suppressor miRNA recovery methods of CRC treatment (Hu et al., 2010; Liu et al., 2011b; Zhang et al., 2011b). These methods include delivery of miRNA mimics, miRNA precursor, pre-miRNA and chemically modified oligonucleotides which consequently, abrogate some cancerous characteristics of CRC cell lines (Akao et al., 2006a; Shi et al., 2007; Ng et al., 2009b; Schimanski et al., 2009; Liu et al., 2010, , Nakano et al., 2010; Liu et al., 2011a; Mudduluru et al., 2011). However, in vivo experimental proof is lacking for majority of them.

Negative manipulation of oncogenic miRNAs'

expression has some similarities with siRNAs in principle and could be achieved through introducing silencing molecules into the cell. Antisense oligonucleotides along with some bearing anchored group, sponge and masking molecules, locked nucleic acid (LNA) are of important miRNA-based therapies. Elaboration of these methods could replace current anticancer therapies and find their ways into daily clinical practices.

On the other hand, the fact that miRNAs need partial sequence complementarity to target mRNA, and consequently could target plethora of mRNAs in a context of a network makes a hindrance to miRNA-based gene therapies, which may lead to toxic phenotype formations in unfavourable cells, off-target effects, and immune system responses. Moreover, rapid degradation of miRNAs or anti-miRNAs by cellular nucleases and poor cellular uptake are another drawback of theses clinical approaches. Therefore, using the lowest optimum concentration of miRNAs along with effective delivery systems such as viral and non-viral vectors and nanoparticles may minimize such side effects and provide dose-dependent accumulation of targeted vectors and nanoparticles in CRC cells.

Considering all together, the miRNA-based gene therapy depends mostly on both positive and negative miRNA expression manipulation. Although there are some administrative obstacles, these therapeutic tools should face a promising future.

Concluding Remarks and Future Challenges

miRNAs are attracting considerable interest and there are accumulating evidences that aberrant expression of miRNAs plays an important role in CRC development and progression by indirectly changing their plethora of cognate mRNAs, which act either as an oncogene via facilitating tumor initiation and proliferation, or in some cases as a tumor suppressor through inhibiting proliferation and invasion. Significant strengths of miRNA related research are the potential for an important complementary approach to assessing CRC risk, measurement of responses to traditional chemo-and radio-therapies and pharmacologic interventions, and as therapeutic targets for CRC risk and recurrence reduction.

Recently, miRNAs have gained substantial attention as therapeutic targets. Nevertheless, the complexity of gene networks that a single miRNA may control and the potential adverse effects of the miRNA and/or anti-miRNA in vivo deliveries remained to be deeply explored.

In summary, given the ever-expanding number of miRNAs, understanding their functional aspects represents a promising mission. Technologies that integrate RNA sequencing, proteomics, and system biology of gene network will allow a more comprehensive assessment and understanding of miRNA effects and provide exciting opportunities for new pathogenetic and treatment insights into colorectal cancer management. Novel therapeutic strategies will face the major challenge of developing standardized methods for miRNA inhibition that combine high transfection efficiency with targeted delivery.

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