Function and mechanisms of microRNA-20a in colorectal cancer (Review)

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Abstract. Colorectal cancer (CRC) is the third most common malignancy and the second leading cause of cancer-associated mortality worldwide. CRC currently has no specific biomarkers to promote its diagnosis and treatment and the underlying mechanisms regulating its pathogenesis have not yet been determined. MicroRNAs (miRs) are small, non-coding RNAs that exhibit regulatory functions and have been demonstrated to serve a crucial role in the post-transcriptional regulatory processes of gene expression that is associated with cell physiology and disease progression. Recently, abnormal miR-20a expression has been identified in a number of cancers types and this has become a novel focus within cancer research. High levels of miR-20a expression have been identified in CRC tissues, serum and plasma. In a recent study, miR-20a was indicated to be present in feces and to exhibit a high sensitivity to CRC. Therefore, miR-20a may be used as a marker for CRC and an indicator that can prevent the invasive examination of patients with this disease. Changes in the expression of miR-20a during chemotherapy can be used as a biomarker for monitoring resistance to treatment. In conclusion, miR-20a exhibits the potential for clinical application as a novel diagnostic biomarker and therapeutic target for use in patients with CRC. The present study focused on the role and mechanisms of miR-20a in CRC.

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1. Introduction

Colorectal cancer (CRC) is one of the most common cancers, causing the third highest cancer-associated morbidity and the second highest of cancer-associated mortality worldwide (1). According to a previous estimation, >1.8 million new cases of CRC and 881,000 cases of mortality occurred in 2018. According to current trends, in 2030, the incidence of colon and rectal cancers will increase by 90.0% and 124.2%, respectively (1). The 5-year survival rate for patients with CRC ranges from 12.5-70.4% and the prognosis for this disease is poor (2). Due to the fact clear clinical symptoms are not commonly seen in most CRC cases and diagnostic methods with high sensitivity and accuracy are lacking, the early detection of CRC is difficult. Currently, the main treatments for CRC surgery, radiotherapy and chemotherapy. However, one-third of patients exhibit recurrent issues following radical surgery and distant metastasis (3,4). Furthermore, the radiation dose is difficult to control during radiotherapy and the identification of the location of lesions in patients with CRC is required for an accurate dose to be administered (5). Additionally, resistance to chemotherapy can be easily ignored due to lack of monitoring indicators during treatment. The aforementioned issues highlight the requirement for the development of novel therapeutic treatments and the identification of predictive markers in CRC. The pathogenesis of CRC has been studied extensively, yet the mechanism governing the disease remains to be determined and this inhibits the research and development progress (6).

MicroRNA (miRNA/miR) are small noncoding RNAs that are 18-24 nucleotides (nt) in length and have been indicated to be associated with the post-transcriptional regulation of

Table I. miRNAs reported in colorectal cancer.

miRNAs	Expression	Target	Features	Reference
miR-17	↑	PTEN	Invasion and migration	(11)
miR-18a	↑	ATM	DNA repair	(12)
miR-19a	↑	TIA1	Proliferation and migration	(13)
miR-19b	↑	ITGB8	Growth and metastasis	(14)
miR-20a	↑	GABBR1,SMAD4, SENP1, BNIP2, etc.	Proliferation, apoptosis, invasion, migration, chemo-resistance	(15-17)
miR-21	↑	PDCD4	Invasion, migration, intravasation,	(18)
miR-30a	↓	Metadherin	Invasion and migration	(19)
miR-31	↑	RASA1	Growth and proliferation	(20)
miR-34a	↓	Sirt1 and E2F3	Chemo-resistance	(21)
miR-92a	↑	PTEN	Invasion and migration	(22)
miR-99a	↓	KRAS	Drug resistance	(23)
miR-128	↓	SIRT1	Apoptosis	(24)
miR-145	↓	MAP4K4	Migration	(25)
miR-149	↓	FOXM1	Invasion and migration	(26)
mR-198	↓	ADAM28	Proliferation	(27)
miR-296	↓	ARRB1	Cell growth and apoptosis	(28)
miR-383	↓	PAX6	Proliferation and invasion	(29)
miR-410	↑	DKK-1	Proliferation, migration and invasion	(30)
miR-452	↑	GSK3β	Proliferation and migration	(31)
miR-598	↑	INPP5E	Proliferation and cell cycle	(32)
miR-769	↓	CDK1	Proliferation, apoptosis, migration and invasion	(33)
miR 3666	↓	SATB2	Proliferation, migration and invasion	(34)
miR-7702	↓	TADA1	Invasion and migration	(35)

↑, up; ↓, down; miR, microRNA.

genes in CRC. Since October 2018, 38,589 miRNAs have been identified (miRBase Sequence Database). Studies have demonstrated that changes in the expression of miRNAs are associated with the majority of cellular processes within tumor pathology (7). miRNAs are regulatory RNA molecules in the genome and serve an important role in a number of physiological conditions, including cell differentiation, development, apoptosis, immune response, hematopoiesis, cell death and proliferation (8,9). miRNAs function by binding to complementary sequences on the 3'-untranslated regions, or the open reading frames, of target genes to regulate gene expression at the post-transcriptional level, leading to the degradation of target mRNAs or the inhibition of mRNA translation (10).

Studies have indicated that numerous miRNAs are aberrantly expressed in CRC and regulate multiple targets (Table I) (11-35). It has been revealed that all members of the miR-17-92 cluster participate in the process of CRC. The miR-17-92 family includes miR-17, miR-18, miR-19a, miR-19b, miR-20a and miR-92a. Currently, the miR-17-92 cluster is one of the most researched miRNA clusters and is an example of a multi-sequence miRNA gene that is associated with the development of a variety of malignancies (36). miR-17 has been indicated to be overexpressed in CRC and promote the invasion

and metastasis of tumors by targeting PTEN (11). High levels of miR-18a in CRC have been revealed to attenuate the repair function of DNA and induce carcinogenesis by targeting ATM to suppress ATM expression (12). The overexpression of miR-19a in CRC cells has been indicated to promote cell invasion and the epithelial-mesenchymal transition (EMT), and has been revealed to be associated with lymph node metastasis (37). In a previous study, miR-92a upregulated β-catenin and vimentin, and downregulated epithelial-cadherin, targeting PTEN induced EMT in CRC through the PTEN/phosphoinositide 3 kinase/protein kinase B pathway (22). Using the Integrating Gene Expression Omnibus DataSets portal (GEO DataSets) of 3 cohorts from different regions (GSE41655, GSE35834 and GSE48267), bioinformatics analysis has identified common changes in 14 differentially expressed miRNAs in CRC, including miR-145, miR-497, miR-30a, miR-31 and miR-20a. Target prediction of differentially expressed miRNAs has previously demonstrated that tumorigenesis is associated with a series of transcription factors. A previous study indicated that miR-20a may serve an important role in CRC, according to the network constructed by these microRNAs (38). Furthermore, miR-20a was revealed to be upregulated in the serum, plasma, tissue and fecal samples of patients with CRC, and was

indicated to serve a role in the development of CRC and the mechanisms regulating chemotherapy resistance (39-43). The aforementioned results provide novel information regarding CRC and can aid in the development of novel target drugs for use in the treatment of this disease. In the present review, miR-20a is introduced, the mechanisms of miR-20a in CRC are elaborated on and then the potential of miR-20a as a diagnostic indicator of CRC is described. Additionally, the expression of miR-20a in CRC during chemotherapy is described, explaining why miR-20a may be used as a biomarker for predicting drug resistance to CRC. Finally, the research prospects of miR-20a in CRC are discussed.

2. microRNA-20a overview

Human miR-20a, which is located at 13q31.3, is also known as MIR20, MIRH1, MIRHG1, MIRN20, miR-20, MIR17HG, MIRN20A, mir-20a, C13orf25, miRNA20A, hsa-mir-20 or hsa-mir-20a.

miR-20a is an important molecule in a variety of biological processes and in cancer progression. Previous studies have shown that the serum exhibits high miR-20a expression and has been indicated to be associated with poor prognosis in patients with nasopharyngeal carcinoma and gastric cancer (44,45). A study has shown that miR-20a can directly target run-related transcription factor 1 to attenuate cell-death in cervical cancer cells by preventing natural killer (NK) cells from releasing interferon-γ (IFN-γ) and tumor necrosis factor-α (TNF-α), which promote tumor growth (46). miR-20a can affect RB1CC1/FIP200 cellular levels, which are associated with autophagosome formation and the regulation of the autophagy pathway in breast cancer cells (47). miR-20a can also inhibit proliferation and induce the apoptosis of hepatocellular carcinoma cells *in vitro* by targeting the anti-apoptotic member myeloid cell leukemia sequence 1 protein of the Bcl-2 family (48). The expression of miR-20a in glioma, cervical cancer, gastric cancer, lung carcinoma, neuroblastoma and prostate cancer, and its corresponding target genes and their functions, are presented in Table II (46,49-68). However, the upregulation or downregulation of miR-20a expression in a number of tumors is not consistent in numerous previous studies due to the differences in cell lines and limited sample sizes (47,69-79). The current review article outlines the role of miR-20a in CRC and provides information that can be used in future research on miR-20a.

3. The mechanism of miR-20a in CRC

Increasing data has suggested that miR-20a serves a key role in CRC and its diverse functions in relation to carcinogenesis of CRC, including anti-apoptotic, EMT, migration, invasion and senescence, have recently been focused on (Fig. 1).

miR-20a participates in anti-apoptosis of CRC. A previous study demonstrated that TNF-related apoptosis-inducing ligand (TRAIL) -induced apoptosis is associated with a higher expression of miR-20a in CRC SW480 cells compared with the normal colorectal epithelial cell line FHC (15). Mitochondrial apoptosis, that is induced by a combination of the knockdown miR-20a and TRAIL, depends on the upregulation of BH3

interacting domain death agonist (BID). The knockdown of miR-20a was indicated to inhibit the translocation of truncated BID (tBID) into the mitochondria, which induced the mitochondrial pathway of apoptosis. TRAIL is a TNF superfamily member that can selectively induce apoptosis in cancer cells and induce exogenous apoptosis, however TRAIL is associated with the activation of caspase-8 (80). BID, which is a pro-apoptotic member of the Bcl-2 family, serves as a bridge between death receptor signaling and mitochondrial apoptosis (81). Following the interaction between the death receptor and the ligand, BID is cleaved by cystatin-8 into an activated form, tBID (82). The translocation of tBID to the mitochondria is followed by mitochondrial outer membrane permeabilization and depolarization (83), leading to the activation of caspase-9, caspase-3 and apoptotic effects (80). Furthermore, the activation of caspase-9 and caspase-3 has been demonstrated to be initiated by caspase-8 activation. The knockdown of miR-20a in SW480 cells has been revealed to increase the antitumor effect of TRAIL through the caspase-8 dependent pathway (15). miR-20a regulates BID apoptotic genes that are associated with TRAIL sensitivity of CRC and therefore anti-miR-20a is a promising target to promote apoptosis.

miR-20a promotes EMT and the migration and invasion of CRC. During EMT, cancer cells lose epithelial characteristics to form migratory and invasive mesenchymal cell phenotypes, leading to the consideration that EMT is a prologue to cancer cell invasion and migration. By promoting EMT, miR-20a aids the detachment of CRC cells from the tissue parenchyma and their entry into systemic circulation during cancer metastasis. Studies have indicated that miR-20a induced EMT by inhibiting mothers against decapentaplegic homolog 4 (Smad4) expression via direct targeting of *Drosophila* Smad4 3'-untranslated region (UTR), whereas the overexpression of Smad4 abolished EMT that was mediated by miR-20a overexpression. Furthermore, among a variety of miRNAs, miR-20a has been indicated to exhibit the highest potential for binding to 3'-UTR of Smad4, which is a central signal transduction element of the transforming growth factor (TGF) superfamily and its mutation leads to a functional transition of TGF-β into a tumor promoter (84,85). Early carcinogenesis is caused by WNT signaling activation and TGF-β inactivation. Additionally, experiments have indicated that miR-20a interfered with the colonic epithelium homeostasis by disrupting the regulation of Myc/p21 via TGF-β. Research has also revealed that miR-20a enhances EMT by modulating the expression of tissue inhibitor of metalloproteinases-2 (TIMP2) and matrix metalloproteinase 9 (MMP9), and that the overexpression of miR-20a inhibits the expression of TIMP2 and induces the expression of MMP2 and MMP 9 to promote EMT (16).

However, EMT can also lead to decreased cell adhesion, cytoskeletal dynamics, morphological changes and increased invasion and migration ability (86). The overexpression of miR-20a has been revealed to promote migration and invasion in CRC cells and to be inversely correlated with Smad4 levels (85). Longqiu *et al* (87) demonstrated that miR-20a was upregulated in HCT116 and HT-29 cells (CRC lines). Through specifically binding to the 3'-UTR of γ-amino-butyric acid type B receptor 1 (GABBR1), miR-20a downregulated the expression of GABBR1 and promoted proliferation and invasion.

Table II. Expression of microRNA-20a in specific tumors.

Tumor	Cell lines	Expression	Target	Features	Year	Reference
Human glioma	T98G, U118, U251, NHA	↑	CELF2	Proliferation, invasion and apoptosis	2018	(49)
Cervical cancer	NK92	↑	RUNX1	Killing effect	2018	(46)
Cervical cancer	CaSki and SiHa cell (HPV16-positive)	↑	PDCD6	Growth	2018	(50)
Gastric cancer	multidrug-resistant variants SGC7901/VCR, SGC7901/ADR	↑	LRIG1	Chemotherapy resistance	2018	(51)
Non-small cell lung carcinoma	NSCLCA-549	↑	EGR2	Cell viability and motility	2018	(52)
Neuroblastoma	SH-SY5Y	↓	ATG7	Autophagy	2018	(53)
Nasopharyngeal cancer	SUNE1, HONE1, CNE-2 and CNE-1	↑	NPAS2	Radiation resistant	2017	(54)
Cervical cancer	HeLa and SiHa,	↑	FBXL5, BTG3	Chemotherapy resistance	2017	(55)
Nasopharyngeal cancer	CNE-1 and CNE-2	↑	Rab27B	Radiotherapy resistance	2017	(56)
Gastric cancer	SGC7901/DDP	↑	CYLD	Chemotherapy resistance	2016	(57)
Prostate cancer	DU145 and 22Rv1	↑	PTEN	Medical treatment	2015	(58)
Gastric cancer	SGC7901/DDP	↑	NFKBIB	Chemotherapy resistance	2016	(59)
Glioblastoma multiforme	U251/TMZ cell	↑	LRIG1	Drug resistance	2015	(60)
Cervical cancer	SiHa	↑	TIMP2, ATG7	Proliferation, migration and invasion	2015	(61)
Gastric cancer	BGC-823, SGC-7901 and 293T	↑	UBE2C	Growth	2015	(62)
Gastric cancer	BGC-823, HGC-27	↑	FBXO31	Tumor size, degree of tumor invasion, clinical grade and prognosis	2014	(63)
Cutaneous squamous	A431 and SCL-1	↓	LIMK1	Tumor suppression	2014	(64)
Thyroid cancer	TPC-1, XTC-1, FTC-133, and C643	↑	LIMK1	Proliferation, spheroid formation and invasion	2014	(65)
Ovarian cancer	SKOV3 and ES-2	↑	MICA/B	Metastatic ability and immune escape	2014	(66)
Prostate cancer	PC-3 and DU145	↑	ABL2	Invasion and migration	2014	(67)
Gallbladder carcinoma	GBC-SD and SGC-996	↑	SMAD7	Infiltration, metastasis, prognosis	2013	(68)
Breast carcinoma	MDA-MB-231, BT-20	↑	RUNX3	Invasion and migration	2018	(69)
Breast cancer	MCF7, SKBR3, MDAMB-231	↓	HMGA2	Growth, migration, invasion and apoptosis	2018	(70)
Breast cancer	BCap37	↓	MAPK1	Chemotherapy resistance	2018	(72)
Breast cancer	MDA-MB-231	↑	BECN1, ATG16L1, SQSTM1	Autophagy	2017	(74)
Breast cancer	BCap37	↑	MICA/B, NKG2DL	Immunogenicity, cytotoxicity	2017	(76)
Breast cancer	MCF7 and MDA-MB-231	↓	RB1CC1/FIP200	Autophagy	2016	(47)
Osteosarcoma	G-292, Saos2, MG-63, HOS, U2OS	↓	TAK1	Proliferation	2018	(71)
Osteosarcoma	G-292, SJSA-1	↑	SDC2	Chemotherapy resistance	2017	(73)

Table II. Continued. Expression of microRNA-20a in specific tumors.

Tumor	Cell lines	Expression	Target	Features	Year	Reference
Hepatocellular carcinoma	HepG2	↓	Cyclin D1	Cell cycle	2017	(75)
Hepatocellular carcinoma	SMMC-7721	↑	RUNX3	Proliferation and migration	2016	(77)
Osteosarcoma	SJSA-1	↓	KIF26B	Chemotherapy resistance	2016	(78)
Hepatocellular carcinoma	Bel-7402 and SMMC-7721	↑	PTEN	Radiation resistant	2015	(79)

↑, up; ↓, down.

GABBR1 is a 7-transmembrane receptor and its expression is indicated to be decreased in CRC tissues (88,89). A study has shown that the overexpression or activation of GABBR1 inhibited the proliferation and invasion of CRC HCT116 cells, indicating GABBR1 may be a target for use in CRC treatment. These results indicated that miR-20a may function through the downregulation of GABBR1 to promote cell proliferation and invasion, leading to CRC. However, the validity of this mechanism requires verification in several other CRC cell lines.

In conclusion, miR-20a has been revealed to participate in EMT by regulating Smad4 and TIMP2. During the EMT process, miR-20a can also regulate GABBR1 to increase CRC invasion and metastasis. Further study of miR-20a in CRC may provide new research prospects for the mechanisms regulating EMT.

miR-20a induces cells senescence of CRC. In colibactin-producing Escherichia coli (pks + *E. coli*) infected intestinal epithelial cells, miR-20a has been indicated to be significantly upregulated and to induce cell senescence through targeting Sentrin-specific protease 1 (SENP1), thereby enhancing the invasiveness of CRC cells (90). miR-20a has been revealed to bind to the 3'-UTR of SENP1 mRNA and this was indicated using a reporter gene assay in pks + *E. coli* infected cells. SENP1 is a key enzyme that controls the process of small ubiquitin-like modifier (SUMO) (90). SENP1 overexpression significantly reduces the number of senescent cells induced by pks + *E. coli* infection. Long-term symbiotic bacteria, which produce metabolites or toxins, directly damage host DNA and cause chronic inflammatory stress, serve a role in epithelial cell chronic injury and constitute a potential etiological component of sporadic CRC (91). *E. coli* (pks + *E. coli*) is a component of the gut microbiota that stimulates inflammation and DNA damage and causes mutations and chromosomal instability to promote cancer development. Pks + *E. coli* induce intestinal epithelial cell senescence as a result of the accumulation of SUMO-conjugated p53, which is associated with the decreased expression of SENP1. The modification of p53 by SUMO can promote the transcriptional activity of p53, facilitating p53-mediated cell senescence and the abnormal reduction of p53 SUMO in cells can lead to abnormalities of p53 tumor suppressor function, leading to tumorigenesis (92). PksC + *E. coli* induced growth factor secretion is present in senescent cells. Growth factors are a key determinant of colon cancer progression and serve as a marker of poor prognosis, in addition to serving as a target for CRC treatment and leading to the proliferation of cancer cells. PksC + *E. coli* infection induces DNA damage and subsequently induces an increase in c-Myc expression, leading to c-Myc binding to the miR-20a promoter to regulate miR-20a. These senescent cells produce growth factors that can stimulate tumor growth (17). Therefore, even though miR-20a negatively regulates SENP1, the accumulation of SUMO binding p53 induces senile cells to produce growth factors, resulting in the proliferation of tumor cells.

4. miR-20a can be used as a diagnostic marker in CRC

To reduce the high morbidity and mortality observed in patients with CRC, the identification of novel biomarkers is urgently required. Observing the expression of miRNAs in CRC and the development of diagnostic markers has become a priority
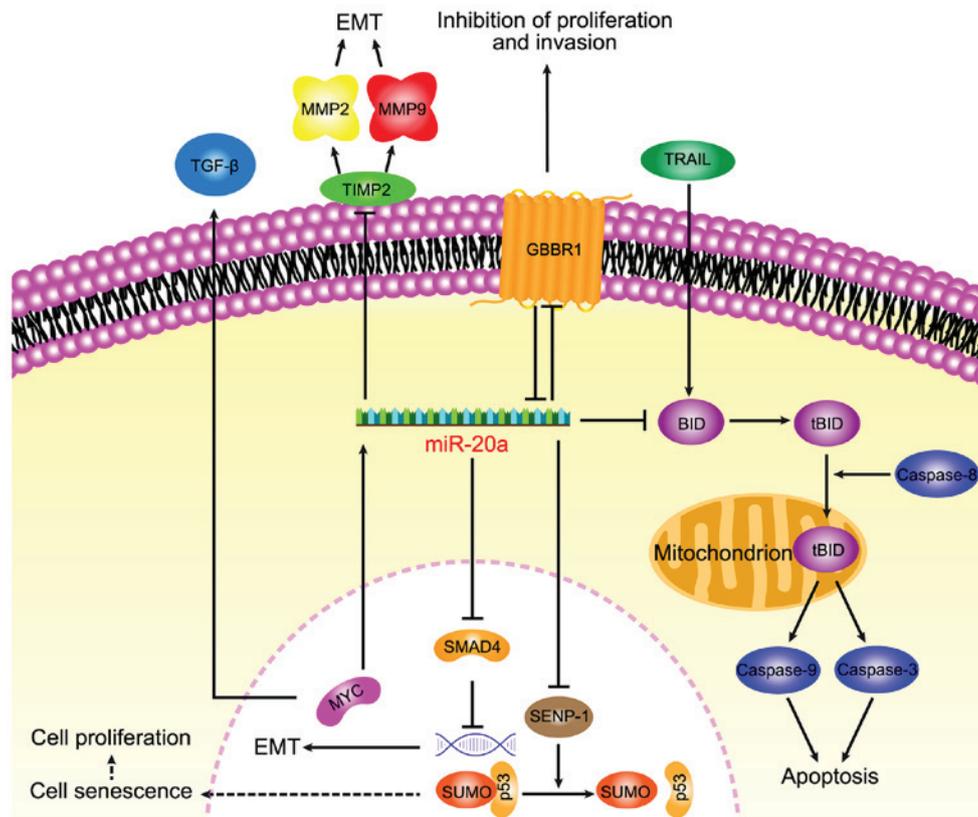
Figure 1. miR-20a downregulates GABBR1 to promote colorectal cancer proliferation and invasion and miR-20a is associated with TRAIL-induced apoptosis by targeting BID; miR-20a promotes epithelial mesenchymal transition by targeting SMAD4 and TIMP; miR-20a targets SENP1 induce cell senescence to stimulate tumor growth. miR, microRNA; SMAD4, mothers against decapentaplegic homolog 4; tBID, truncated BH3 interacting domain death agonist; SENP-1, Sentrin-specific protease 1; MMP, matrix metalloproteinase; TGF-β, transforming growth factor; TIMP, metalloproteinase inhibitor 1; TRAIL, TNF-related apoptosis-inducing ligand; GABBR1, γ-amino-butyric acid type B receptor 1.

in current research (93). Slattery *et al* (94) analyzed large sample data and demonstrated that >86% of the differentially expressed miRNAs between CRC tissues and normal mucosa are present in 80% of the population. Tan *et al* (95) indicated that although the difference in miRNA levels in ulcerative colitis was not significant in mouse experiments, in CRC significant changes were observed in miRNAs and the upregulation of miR-20a in CRC tissues was higher compared with normal tissues. Analysis of the expression profiles of miRNAs between tissues from patients with CRC and normal mucosa revealed that miR-20a was an important miRNA with a high predictive value for cancer (94,96,97). Analysis of 20 pairs of CRC tissues and adjacent tissues also indicated that miR-20a was differentially expressed between tissues (98). The level of miR-20a is enhanced in CRC tissues and its expression level has been indicated to be positively correlated with histological markers (including Ki-67 and cluster of differentiation 34) (99). High levels of miR-20a predict poor prognosis in patients with CRC and particularly in patients with tumor recurrence (85).

Previously, studies have indicated that the level of miR-20a in the serum and plasma of patients with CRC increased and was associated with late stage CRC (100,101). The results of custom miScript miRNA PCR array analysis of 100 CRC cases, performed by Zekri *et al* (102), demonstrated that miR-20a was significantly increased in the serum of female patients with CRC. The selective detection of small RNA expression in blood samples from 74 patients with stage

II-IV CRC and 32 healthy controls indicated that miR-20a increased significantly in patients with CRC, and plasma levels increased in accordance with the extent of malignancy (103). Liu *et al* (98) demonstrated that miR-20a exhibits a diagnostic value for CRC following the comprehensive analysis of GEOs and The Cancer Genome Atlas databases. miR-20a in the serum of patients with CRC is increased compared with healthy patient serum. Furthermore, reverse transcription quantitative (RT-q)-PCR analysis of samples from 15 patients with CRC indicated that the levels of circulating miR-20a in plasma samples were significantly reduced following surgical resection. Despite these outcomes not supporting the results of a previous study (104), the staging and grading of tumors should be taken into consideration to determine whether miR-20 is a novel marker for CRC. A larger sample size is required for future research. These aforementioned studies provided new insight for use in the diagnosis and monitoring of CRC, and indicated that miR-20a is a promising serum and plasma marker in CRC.

The fecal immunochemical test is a new technique that is used to detect CRC (105). miRNAs identified in fecal samples are stable at 4˚C and at room temperature (76). Quantitative changes in the expression of several mature miRNAs in feces may provide a more sensitive and specific non-invasive diagnostic method for CRC. In a previous study, miR-20a was selected in a total of 40 CRC tissues and 595 fecal samples were analyzed using TaqMan probe-based RT-qPCR. miR-20a

exhibited a significant increase in CRC fecal samples and the levels of miR-20a in feces exhibited no significant difference regardless of the proximal or distal location of cancer tissue. Additionally, the use of antibiotics did not affect fecal miR-20a levels. Therefore, fecal miR-20a can be used as a potentially non-invasive screening biomarker for CRC (42,106).

5. miR-20a may be used as a monitoring indicator during chemotherapy

Chemotherapy is the widely used treatment for patients with CRC, especially in patients with metastatic CRC. Adjuvant chemoradiotherapy following surgery is also a widely used treatment, leading to a high cure rate and increased positive patient prognosis. The association between miRNA and chemotherapy has been reported in a variety of diseases, for example miR-21 antisense oligonucleotide has been indicated to increase the sensitivity of cholangiocarcinoma cells to gemcitabine (107), miR-15b and miR-16 have been revealed to regulate multidrug resistance by targeting Bcl2 in gastric cancer cells (108) and miR-451 has been demonstrated to downregulates multidrug resistance 1 and induces breast cancer cell resistance to doxorubicin (109). Furthermore, miRNAs are associated with the expression of a number of target genes that are related to chemosensitivity or the sensitivity of drugs to cancer cells (110). Therefore, identifying an indicator to monitor CRC chemotherapy is important and recent studies have indicated that miR-20a can be used as a monitoring indicator for chemotherapy (111,112).

miR-20a is differentially expressed before and after chemotherapy. Due to the difference in the location of colon cancer and rectal cancer, the corresponding treatment will often differ. A study has demonstrated that miR-20a and a number of miRNAs are reliable prognostic predictors for patients with stage II colon cancer (101). For advanced rectal cancer, preoperative chemoradiotherapy (CRT) can improve overall survival and reduce the local recurrence rate. The reduced expression of circulating miR-20a is inversely associated with negative postoperative lymph nodes, which may contribute to the stratification of the entire mesorectal surgery. Preoperative CRT blood circulating miR-20a can be used as a marker to indicate lymph node status of patients with locally advanced rectal cancer following neoadjuvant CRT. Additionally, the differential regulation of miR-20a before and after radiotherapy and chemotherapy, in patients with rectal cancer, may be used as a marker for monitoring tumor response before and after radiotherapy and chemotherapy (113-115).

miR-20a can be used as a marker to predict and improve chemotherapy resistance of CRC. Chemotherapy resistance is the main cause of treatment failure in patients with cancer, especially in patients with advanced cancer. miRNAs can serve as potential biomarkers for predicting therapeutic responses in CRC and are major regulators of CRC drug resistance (116). miR-20a is associated with resistance to chemotherapy in a variety of cancer types, including in cancers of the digestive system (113). A previous study demonstrated that the expression of miR-20a in patients exhibiting chemoresistant CRC was significantly upregulated compared with patients that exhibited chemosensitive CRC (117). Therefore, miR-20a may be used as a biomarker for predicting the chemical sensitivity of CRC.

Platinum-based chemotherapy is one of the most important strategies for the treatment of CRC. Cisplatin is widely used in the treatment of CRC and exhibits a number of anticancer activities (118). However, the chemotherapy resistance of CRC cells is challenge in the treatment of patients with CRC (119). Studies have indicated that miR-20a induces cisplatin resistance in numerous cancers, potentially including in CRC (55,57,111,112). The miR-20a inhibitor can sensitize cisplatin-induced CRC cytotoxicity via the reactive oxygen species (ROS) pathway. ROS induce apoptosis during drug treatments and can also exhibit an effect on the chemosensitivity of cancer cells (111). In combination therapy with an miR-20a inhibitor and cisplatin, ROS production is important for the death of CRC cells. ASK1 is a key mediator in the ROS-dependent cell death pathway and the knockdown of miR-20a upregulates ASK1 expression and promotes cisplatin-dependent phosphorylation of ASK1. Treatment to knockdown miR-20a can increase the expression of ASK1 to enhance ROS-dependent cell death. A combination of cisplatin and anti-miR-20a have been revealed to significantly increased JNK activation and subsequent mitochondrial apoptosis in CRC cells. Therefore, cisplatin-induced mitochondrial apoptosis is promoted by the ROS/ASK1/JNK pathway through combination with anti-miR-20a in CRC. Furthermore, the introduction of an miR-20a inhibitor eliminates cisplatin resistance and enhances the anti-tumor effect of cisplatin *in vivo* (112).

Fluorouracil, oxaliplatin and teniposide are additional chemotherapeutic agents that are used for CRC therapy and miR-20a has been indicated to regulate the sensitivity of these drugs. The overexpression of miR-20a exhibits resistance to these drugs in CRC. Furthermore, miR-20a directly downregulates BNIP2 mRNA and BNIP2 protein levels by binding to BNIP2 3' UTR to increase the resistance of CRC cells. BNIP2 is a proapoptosis factor, which is a member of the BCL-2 protein family (120). Therefore, miR-20a serves a role in multidrug resistance in CRC cells and may be a therapeutic target for anti-chemotherapeutic drug resistance in CRC (121).

6. Conclusion and prospects

The incidence of CRC has been increasing in recent years and many patients are in advanced stages of the disease. The early detection and treatment of CRC is important for controlling the progression of the disease. A number of studies have demonstrated that miRNA can be used as a biomarker for the diagnosis and prognosis of CRC, and this can provide information on tumor initiation, development, invasion, metastasis and response to chemotherapy (16,39,111,112,122,123). A number of studies have also confirmed that miR-20a is significantly upregulated and serves an important role in the development, progression and therapeutic response of CRC, and it can be used as a biomarker for CRC in tissues, serum and fecal samples (124). miR-20a has indicated efficacy in predicting risk of CRC recurrence and is associated with low survival rates (125,126). Furthermore, miR-20a has been revealed to promote CRC through an association with anti-apoptosis mechanisms, EMT, migration, invasion and senescence, indi-
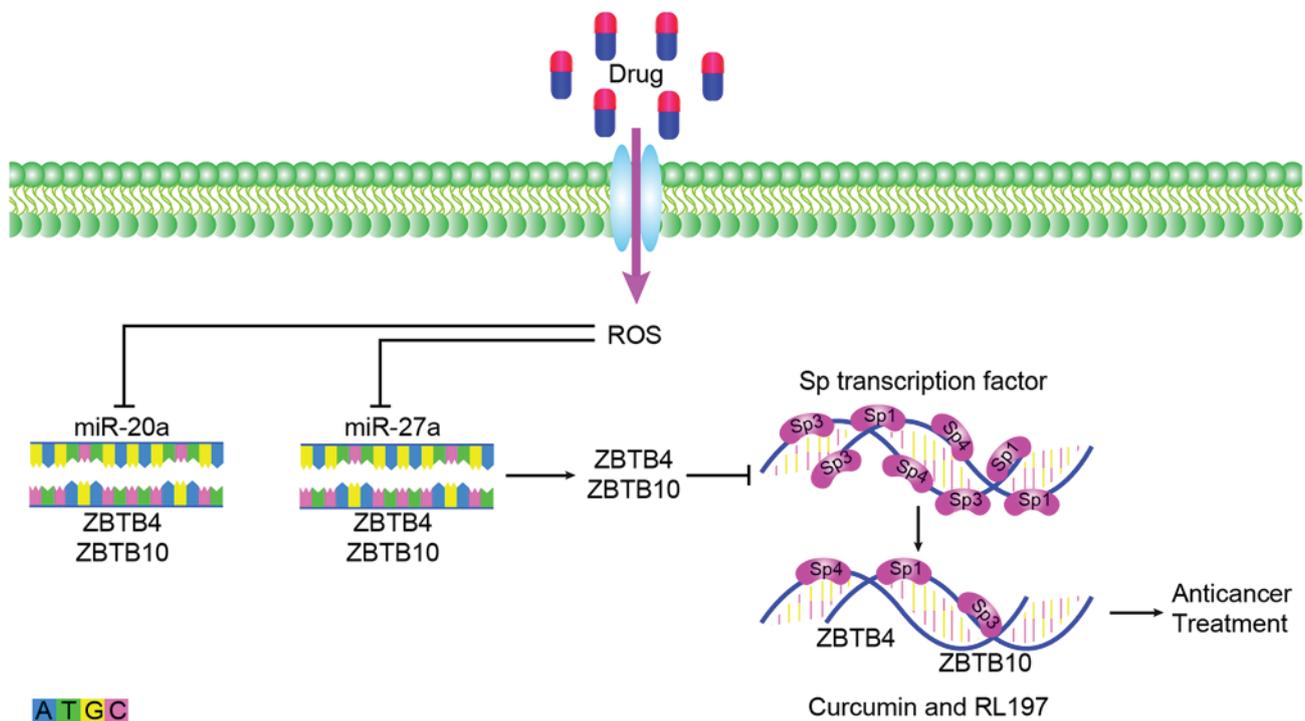
Figure 2. Drugs downregulate miR-27a and miR-20a, disrupt miR-ZBTB10 and miR-ZBTB4 axes in the colon, reduce SP regulatory proteins, and exert anticancer effects. miR, microRNA; ROS, reactive oxygen species.

cating it to be a promising therapeutic target for use in the treatment of CRC. Chemotherapy is a widely used treatment in patients with CRC, however resistance can occur and the mechanisms behind this are undetermined. miR-20a has been indicated to be an effective indicator in monitoring response to treatment (112-115,121). Furthermore, carcinoembryonic antigen (CEA) is a common tumor marker in gastrointestinal cancer, but its specificity and sensitivity are low. The combination of miR-20a with CEA and CA19-9 can improve the sensitivity and specificity of CEA, allowing patients to obtain the most accurate prognosis (127).

Currently, the targeted therapeutic drugs for CRC, which are used clinically, can be classified into two types. One is cetuximab and panitumumab, which target epidermal growth factor receptor and bevacizumab, regorafenib, aflibercept and ramucirumab, which target vascular endothelial growth factor. Although research into molecular targeted therapies is increasing, a large number of genes have been associated with tumor development and it is difficult to determine the genes that serve a leading role in a number of different stages in development. Molecular targeted therapy also exhibits the problem of multi-target combination therapy. Currently, the types of drugs available for clinical use are limited but exhibit great development potential. miR-20a serves an important role in the treatment and drug resistance of CRC. In anticancer therapy, miR-20a can inhibit the Sp repressor ZBTB4 and enhance the expression of Sp transcription factor. Anti-colon cancer drugs have been revealed to eradicate the miR-20a-ZBTB4 and miR-ZBTB10 axes within the colon by targeting SP regulators and SP transcription factors. Subsequently, Sp transcription factors and Sp-regulated genes competitively bind to GC-rich sites on their promoter sequences and induce the downregulation of Sp proteins and

Sp-dependent genes. After disruption of the miR-20a-ZBTB4 axis, ZBTB10 and ZBTB4 serve as transcriptional inhibitors of the SP regulatory gene, which can reduce Sp1, Sp3, Sp4 and SP regulatory proteins to inhibit the growth, proliferation, survival, angiogenesis and metastasis of cancer (Fig. 2). These regulatory proteins include curcumin and a synthetic analog of curcumin, (3E,5E)-3,5-bis (2,5-dimethoxybenzylidene)-1-tert-butoxycarbonylpiperidin-4-one (RL197) (128,129). Sorafenib is a multi-kinase inhibitor that is currently approved for the treatment of liver, kidney and thyroid cancer. Studies have indicated that miR-20ain CRC cell lines exhibit significant changes before and after treatment with sorafenib and may become an inhibitor of CRC (130). miR-20a is associated with chemoresistance, which provides a new direction for studying anti-transformation resistance (121). Therefore, the development of drugs for the treatment of CRC based on miR-20a is promising. In CRC, over-expression and knocking down of miR-20a followed by high-throughput screening could be applied to discover downstream target genes. This method can identify molecules that regulate the expression of miR-20a in CRC cells and thus find drug targeting molecules for the CRC. Part of mechanisms of CRC indicated that miR-20a induces high expression of certain proteins and low expression of some proteins, making high expression protein inhibitors a promising treatment for CRC. As mentioned above, miR-20a can inhibit TIMP2 expression, induce expression of both MMP2 and MMP9 to promote the occurrence of EMT (16). Whether CRC can be treated by inhibiting MMP2 and MMP9 is also worth discussing. Since miR-20a is a cancer-promoting factor in CRC, specific inhibition could be considered as a potential method for the treatment of CRC. However, specifically targeting miR-20a is technically difficult. Recent studies have found that circular (circ) RNA can selectively bind to miRNA

as a sponge (131,132). circRNA binding to miRNA can be predicted by bioinformatics analysis and the screened circRNA can be used as a therapeutic strategy for miRNA (133). For example, circ_0009910 inhibits cell proliferation and promotes apoptosis through negative regulation of miR-20a in acute myeloid leukemia (AML) cells, which may become a potential therapeutic target for future AML treatment (134). In addition, long noncoding (lnc) RNA can interact with miRNA as an competitive endogenous RNA to participate in the regulation of target gene expression (135). For example, lncRNA MEG3 can competently bind to miR-23a to regulate the expression of apoptotic protease activating factor-1 and thus regulate the progression of laryngeal cancer (136). Therefore, the establishment of lncRNA-miRNA-mRNA or circRNA-miRNA-RNA pathway in CRC is expected to provide a new direction for the treatment of CRC in the future (137).

Therefore, further study into the molecular mechanisms and functions of the miR-20a network is required for use in clinical practice. Elucidating the mechanism of elevated miR-20a expression in cancer, of miR-20a's association with chemotherapy resistance, the mechanism network of miR-20a promoting cancer, systemic effects and the side effects of anti-miRNA therapy, require further investigation. Furthermore, the presence of miRNAs in serum, plasma and other body fluids (including the saliva, urine and amniotic fluid) encourages the study of miRNAs, and the detection of miR-20a in these indicates that this miRNA may be used as a non-invasive biomarker for early detection and monitoring of disease progression. An increased amount of data is required to identify miR-20a in fecal, blood and other screenings, and this will provide evidence that will increase attention and lead to the assessment of the potential utility of miRNAs in clinical practice.

Availability of data and materials

Not applicable.

Authors' contributions

XZ and YZ designed the present study. ZX and SC prepared and wrote the manuscript. SF and YL revised the manuscript. JZ and HL performed a literature search and selected the studies to be included. All authors approved the final version of the article.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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