

MicroRNAs: Multifaceted Regulators of Colorectal Cancer Metastasis and Clinical Applications

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Abstract: Colorectal cancer (CRC) is the third-commonest malignant cancer, and its metastasis is the major reason for cancer-related death. The process of metastasis is highly coordinated and involves a complex cascade of multiple steps. In recent years, miRNAs, as highly conserved, endogenous, noncoding, single-stranded RNA, has been confirmed to be involved in the development of various cancers. Considering that miRNA is also involved in a series of biological behaviors, regulating CRC occurrence and development, we review and summarize the role of miRNAs and related signaling pathways in several CRC-metastasis stages, including invasion and migration, mobility, metabolism, epithelial–mesenchymal transition, tumor-microenvironment communication, angiogenesis, anoikis, premetastatic-niche formation, and cancer stemness. In addition, we review the application of miRNAs as diagnostic CRC markers and in clinical treatment resistance. This review can contribute to understanding of the mechanism of miRNAs in CRC progression and provide a theoretical basis for clinical CRC treatment.

Keywords: colorectal cancer, miRNA, metastasis, invasion, migration, stemness

Introduction

Colorectal cancer (CRC) is the third-commonest of all cancers, with an estimated 145,600 new cases worldwide in 2019. Next only to lung cancer and breast cancer, CRC accounts for 8%–9% of all cancers. In terms of its mortality rate, it ranks third in males and second in females.¹ TNM stage is the main indicator of CRC prognosis, and early tumor stage indicates better survival. Unfortunately, due to lack of early symptoms, a considerable proportion of patients are diagnosed at an advanced stage and even coexist with metastasis. Comprehensive CRC-treatment therapy, including surgery, radiotherapy, chemotherapy and immunity therapy and neoadjuvant chemotherapy, has improved the 5-year survival rate significantly,² though many CRC patients still experience high risks of tumor recurrence and metastasis. Approximately 60% of patients with distant metastasis and even 20% patients were found the formation of multiple colorizations after comprehensive treatment in 5 years.³ The liver and peritoneum are the commonest sites of distant CRC metastasis.⁴ Therefore, understanding the mechanism of CRC metastasis can be of great importance.

The CRC-metastasis cascade is a set of complex and highly coordinated processes. First, CRC cells undergo a series of continuous evolution processes that endow more capacity for invasion and migration, and CRC cells are inclined to adopt an aggressive phenotype. These reprogramming processes including mobility

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alteration, metabolism regulation, and epithelial–mesenchymal transition (EMT) of CRC cells.⁵ Second, CRC cells destroy basement membrane and extracellular matrix (ECM), then interact with noncancer cells in the tumor microenvironment (TME).⁶ Third, the angiogenesis and lymphangiogenesis are induced, which work as an aisle for distant metastasis. CRC cells also promote vascular permeability boost cell leakage into the bloodstream and penetration in distant tissue.^{7–9} Above processes promote the generation of circulating tumor cells (CTCs). Fourth, the CTCs acquire anoikis resistance and survive the immune system during circulation. This acts as a precondition for distant primary cancer–cell metastasis. Then, the primary cancer cells promote the formation of a premetastatic niche (PMN) to facilitate the adhesion of CTCs to vascular endothelium and extravasation to distant organs and tissue. Finally, CRC cells reach metastatic sites and generate second colonization.¹⁰ The metastasis processes are not sequential. Instead, they intersect in time and spatial dimension. For example, primary tumor tissue continues to release CTCs into the circulation, which can even be detected in very early on in the TNM process, and vessel structure is also destroyed during the ECM-degradation process.^{11,12} Cancer stem cells (CSCs) are viewed as the instigators of growth, resistance to chemotherapy, and recurrence and metastasis of cancer. The stemness of CSCs is the major challenge in the fight against CRC recurrence and metastasis, and the elimination of CSCs is believed to be a potential method to overcome malignant disease.¹³

miRNAs are members of the endogenous noncoding RNA (ncRNA) family, with a length of approximately 22 nucleotides.¹⁴ The generation of miRNAs involves pri-miRNA catalysis by RNA polymerase II in the nucleus and a series of modifications by RNase III endonuclease and Dicer.¹⁵ They bind to the 3′-untranslated regions (3′-UTRs) of target protein-encoding mRNAs and form RNA–RNA complexes, resulting in translation suppression or mRNA degradation. One miRNA can regulate multiple target genes, and one gene can be regulated by many miRNAs synchronously. It is estimated that about 60% of protein-coding genes are controlled by various miRNAs.¹⁶ Accumulating evidence has revealed that dysregulation of miRNAs is associated with multiple biological processes, such as proliferation, differentiation, apoptosis, and autophagy.¹⁷ As for cancer, miRNAs participate in initiation, progression, and metastasis. In the CRC-metastasis cascade, miRNAs act as oncogenes or tumor-suppressive factors;

therefore, here we summarize state-of-the-art advances and explore the underlying miRNA-related molecular mechanisms of CRC metastasis. In addition, we review the application of miRNAs as diagnostic CRC markers and in drug resistance, hoping to provide a theoretical basis for clinical CRC treatment.

miRNAs, Invasion, and Migration miRNAs and Mobility

CRC cells undergo a series of distinct reprogramming processes to increase mobility, thus promoting cell invasion and migration.¹⁸ During these processes, CRC cells speed up cytoskeleton reconstruction and change cell morphology, which facilitate cell crawling, deforming, squeezing, through narrow tissue gaps, and crossing vessel walls.¹⁹ Connexins exist on cell surfaces and interact with the surrounding environment. After reprogramming processes, the adhesion pattern is altered and cells are able to detach from the primary tumor niche.²⁰ During cell movement, a polar foot protrusion termed lamellipodia or filopodia will be formed at the cell's leading edge.²¹ In an anoxic environment, through activating the RECK–FAK–Akt–Rac1 signaling pathway, the hypoxia-sensitive miR590-5p enhances CRC-cell sprouting and accelerates the formation of protrusions, and miR590-5p inhibitors can impact cell mobility conversely.²²

A remarkable rearrangement of cytoskeleton facilitates cell motility. The RhoA–ROCK signaling network is a critical signaling pathway in cytoskeleton regulation.^{19,23} miR133a-3p acts as an inhibitor, and its expression is reduced in CRC. Low expression of miR133a-3p in CRC cells activates the RhoA–ROCK signaling network, subsequently promoting cytoskeleton remodeling.²⁴ By inhibiting SLAIN2, miR106b-5p impairs mobility via blocking microtubule dynamics. Low miR106b-5p levels have been demonstrated to promote the mobility of CRC cells.²⁵ DLC1 is recognized as a member of Rho GTPase-activating protein family. CRC cell-derived exosomal miR106b-3p promotes cytoskeleton rearrangement by suppressing DLC1.²⁶

As a critical downstream-signaling molecule of the RhoA–ROCK pathway, cofilin enhances actin-filament remodeling and promotes mobility.¹⁹ PAK4 is a serine/threonine kinase that regulates the LIMK1–cofilin pathway. miR145 impairs mobility of CRC cells by suppressing PAK4 and inactivating this pathway.²⁷ miR145 can also impair CRC-cell mobility via inhibiting the expression of MYO6.²⁸ CRC cells change adhesion pattern by regulating

connexin expression. Integrins are major molecules that mediate the connection between CRC cells and the ECM.^{29,30} In addition to being involved in EMT and proliferation, miR27b-3p in CRC cells promotes an aggressive morphology and intercellular junction pattern by suppressing HOXA10, thus increasing integrin β_1 expression. It also results in cytoskeleton remodeling and a spindle-shaped phenotype.³¹ Similarly, miR130b has been found to bind directly to the 3'-UTR of integrin β_1 mRNA.³² miR30e-5p suppresses metastasis by directly binding to mRNAs of integrin α_6 and integrin β_1 . However, controlled by p53, miR30e-5p is at a significantly low level in CRC cells.³³ The tumor-suppressive miR143-3p has also been found to directly inhibit the expression of integrin α_6 . miR330-5p and miR19b-3p inhibit integrin α_5 and integrin β_8 , respectively, to promote cancer metastasis.^{34,35}

miRNAs and Metabolism

Cancer cells undergo a form of metabolic reprogramming termed the Warburg effect. Even under conditions of sufficient oxygen supply, cancer cells incline to ingest a lot of glucose and undergo anaerobic sugar metabolism, produce lactic acid. This process sustains energy supply for cell migration, and the production of lactic acid creates a prometastasis environment.³⁶ Overexpression of miR27a relates to the silence of mitochondrial activity and exhibits great glycolysis potential. miR27a in CRC cells significantly enhances metabolic reprogramming via interacting with metabolism-related genes, including hexokinase, *GCK*, pyruvate dehydrogenase, *MAPK*, *PTEN*, and *PI3K*.³⁷ DKK2 is a kind of secreted protein and is highly expressed in metastatic cancer. DKK2 can accelerate aerobic glycolysis speed, and low levels of miR493-5p in CRC cells promote the production of lactic acid via activating the DKK2–PI3K–Akt–mTOR pathway. Reexpression of miR493-5p has been found to repress glucose uptake and reduce the production of lactic acid.³⁸ Expression of PKM2 is related to the dysregulation of miR122. By inhibiting the expression of PKM2, miR122 affects the glycolysis rate. In CRC, the expression of miR122 is repressed and results in an overexpression of PKM2, which induces anaerobic sugar metabolism.³⁹

miRNAs and EMT

EMT is a vital process in the cancer-metastasis cascade that endows cancer cells with great potential for metastasis. During EMT, cancer cells lose the epithelial phenotype and acquire the mesenchymal phenotype. In detail,

E-cadherin in cancer cells is downregulated, thus losing apical–basal polarity and the original tight connection of cells, whereas mesenchymal-associated markers are upregulated, mainly N-cadherin, vimentin, and fibronectin, and then obtain an invasive cell morphology.⁴⁰ EMT is triggered or silenced in response to diversity stimulation and intracellular components.⁵ In the TME, the expression of miRNAs is diverse. Through controlling the expression of the EMT-related core transcription factors, such as Snail, Slug, ZEB, and several signaling pathways, miRNAs orchestrate complex biological events.⁴¹ We summarize the miRNA-related EMT-regulating network in CRC cells in Figure 1 and give some new examples.

HIF1 α and *TP53* conversely control the EMT/MET process through miR34a. Under hypoxic conditions, HIF1 α in *TP53*-defective CRC cells directly represses the expression of miR34a, which promotes hypoxia-induced EMT via activating STAT3. In contrast, under hypoxic conditions but with the presence of sufficient *TP53* expression, expression of miR34a is enhanced, and overexpression of miR34a leads to the suppression of hypoxia-induced EMT.⁴² The suppression of miR34a and activation of the STAT3 pathway shift the cell phenotype toward a mesenchymal state and enhance the metastatic cascade. On the contrary, highly expressed miR34a and an inactivated STAT3 pathway switch back the cell phenotype to an epithelial state and allow colonization of metastases.

Endogenous miRNAs exist mainly in cytoplasm. They also present extracellularly via protein carriers, liposome carriers, and exosomes. Exosomes are small vesicles of 30–100 nm in size and often work as transport vesicles between various cells. They are enriched with signal molecules, including proteins, lipids, DNA, RNA, and miRNAs.⁴³ When they are released by cells and taken up by others, they participate in multiple biological events.⁴⁴ DLC1 is a member of the Rho GTPase-activated protein family and controls the expression of EMT-associated proteins.⁴⁵ Highly metastatic CRC cells release miR106b-3p-contained exosomes to less metastatic CRC cells. The oncogenic miR106b-3p in the latter increases N-cadherin and decreases E-cadherin at the protein level via suppressing DLC1. Collectively, oncogenic miR106b-3p-containing exosomes promote the invasive capacity of low invasive-potential cells and endow CRC cells in situ more capacity for metastasis. High levels of miR106b-3p exosomes in serum indicate poor prognosis, and miR106b-3p inhibitors impair cell-migration capacity.²⁶

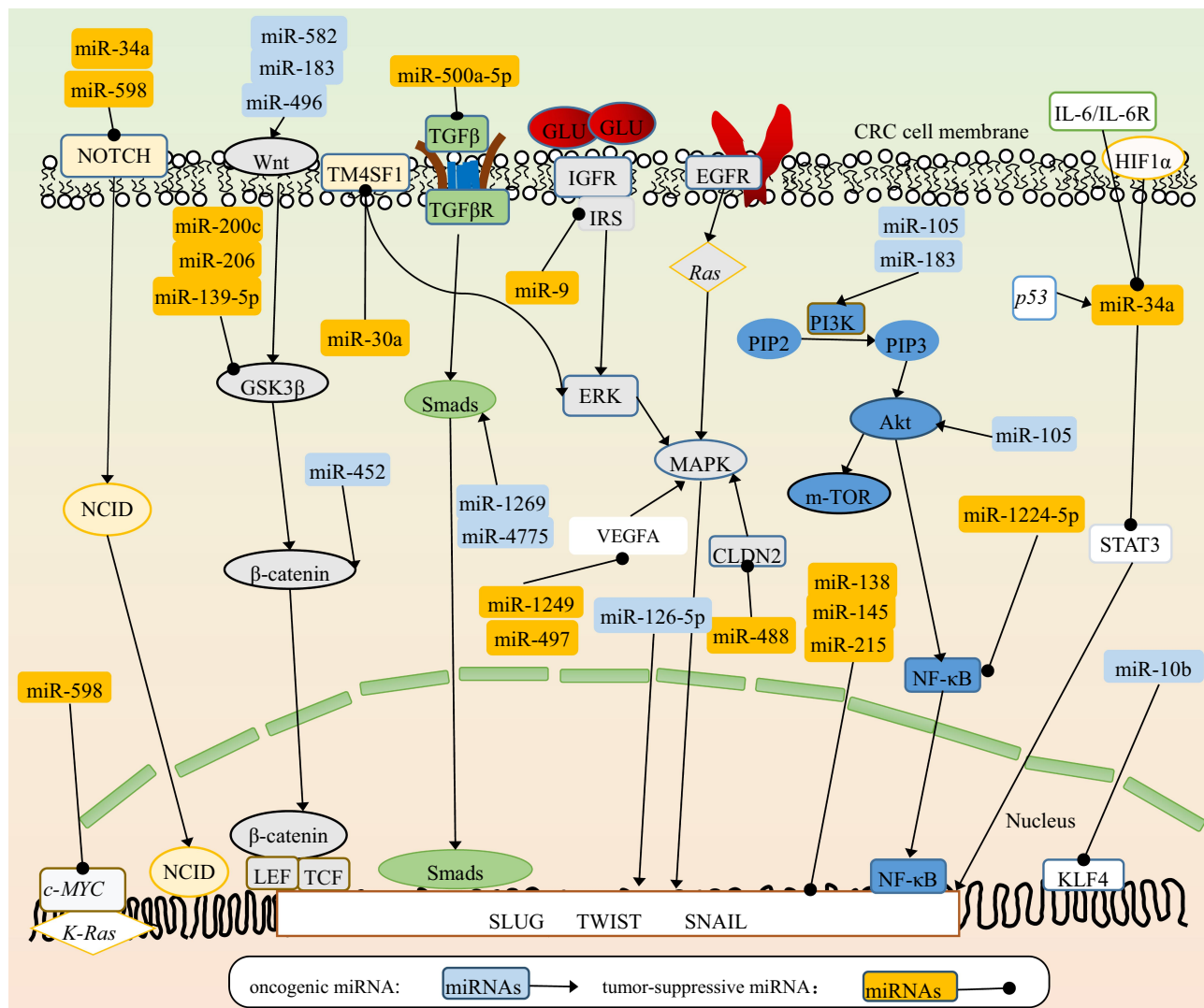


Figure 1 miRNA-related EMT-regulating network in CRC cells. The miRNAs in light-blue squares refer to oncogenic miRNAs. The miRNAs in orange squares refer to tumor-suppressive miRNAs. The round shapes on the end of arrows refer to the suppressive function on target molecules. The sharp arrows refer to the oncogenic function on target molecules. Most miRNAs work by regulating several signaling cascades, including Notch–NCID, Wnt– β -catenin, MAPK–ERK and PI3K–Akt–NF κ B, in various aspects. Also, some miRNAs work by interacting with proteins and genes. Above all, miRNAs finally target EMT-related core transcription factors (Slug, Twist and Snail) and regulate the EMT process of CRC.

miR126-5p works as a tumor-suppressive miRNA and is lowly expressed in CRC. It interacts with the 3'-UTRs of Slug, Twist, and VEGF α mRNAs, leading to inhibition of the EMT process and angiogenesis in CRC. Further exploration has demonstrated that the lncRNA, MALAT1 binds directly to miR126-5p and impairs its function. The potent oncogenic factor YAP1 promotes the EMT process and angiogenesis by inhibiting the tumor-suppressive miR126-5p.⁴⁶ A bulk of miRNAs are involved in the regulation of EMT. They work as oncogenes or tumor-suppressive regulators in tumor progression by controlling downstream targets. miR34a and miR598 suppress EMT by inhibiting the Notch pathway. miR598 and miR10b play

a negative role by regulating cMyc, K-Ras, and KLF4. miR582, miR183, miR496, and miR452 positively enhance EMT by directly or indirectly activating the Wnt– β -catenin pathway, while miR200c, miR206, and miR139-5p suppress EMT by inhibiting GSK3 β . Although miR30a, miR9, miR1249, miR497, and miR488 act on different proteins or receptors, they inhibit EMT by MAPK. Overexpression of miR4775 and miR1269 promotes EMT and induces an aggressive phenotype via activating the TGF β –Smads pathway, while miR500a-5p plays a negative role via this signaling pathway. miR105 and miR183 promote EMT by activating the PI3K–Akt pathway, while miR1224-5p inhibits EMT via this pathway. miR34a

plays a negative role in EMT via inhibiting the STAT3 pathway. To sum up, these signaling pathways, molecules, and some miRNAs, such as miR138, miR215, and miR145 target EMT-related core transcription factors and regulate EMT in CRC. In Table 1, some tumor-suppressive and oncogenic miRNAs and their direct targets are summarized. Those miRNAs promote or inhibit EMT by positively or negatively controlling downstream-signaling cascades. Relationships between miRNAs and signal cascades are depicted in Figure 1.

miRNAs and TME

The TME comprises the ECM, immune cells, fibroblasts, various signaling molecules, and blood vessels. The ECM consisted mainly of collagen, elastin, and proteoglycans and usually acts as a barrier to cancer metastasis.⁶ There are numerous types of non-TCs in the TME, including cancer-associated fibroblasts (CAFs), endothelial cells, and inflammatory cells. Cross talk between cancer cells and non-TCs participates in metastasis.^{6,76,77} CRC cells destroy the ECM and make passageways via secreting such substances as proteolytic enzymes in the form of MMP. For example, miR194 in CRC cells promotes metastasis via inducing the expression of MMP2.⁵⁴ High miR203 level can attenuate the metastatic potential of CRC by blocking the ERK–MMP9 pathway.⁷⁸ miR139-5p impairs metastasis of CRC via inhibiting the Notch pathway and suppressing the expression of MMP7 and MMP9.⁷⁹ ADAMTS5 shares the domains of MMP and possesses proteolytic enzyme-like functions. Due to downregulation of miR140-5p, the expression of ADAMTS5 is increased, leading to ECM destruction.⁸⁰

Studies have shown that CAFs can promote CRC metastasis by interacting with CRC cells through miRNAs. For example, miR92a-3p-contained exosomes are released by CAFs and taken up by CRC cells, thus activating the intracellular Wnt– β -catenin pathway by inhibiting FBXW7 and MOAP1.⁸¹ Also, CAFs can attenuate the inhibitor role of miR141 by releasing exosomal lncRNA H19. The lncRNA H19 from CAFs can activate the Wnt– β -catenin pathway and promote stemness by sponging miR141 in CRC cells.⁸² Tumor-associated macrophages (TAMs) are the most abundant immune cells in the TME, and M2 phenotype TAMs promote cancer progression and take part in ECM remodeling and immune response. On the one hand, TAMs can promote invasion and migration of CRC cells. TAMs inhibit the expression of miR506-3p in CRC, and in turn accelerate

EMT process by activating FoxQ1. Meanwhile, mesenchymal phenotype CRC cells enhance the recruitment of TAMs via secreting CCL12.⁷⁷ On the other hand, TAMs can also be stimulated by CRC cells. The tumor suppressor miR195-5p is decreased in CRC cells, and low miR195-5p levels induce EMT by activating the Notch2 pathway. Meanwhile, dysregulation of miR195-5p enhances the reprogramming of TAMs by stimulating CRC cells to secrete IL4.⁷⁶

miRNAs and Angiogenesis

With uncontrolled cell division and growth of cancer tissue, a hypoxic environment is formed inside the tumor. The key HIF1 is upregulated in response to hypoxia, which boosts the expression of angiogenesis-related genes, including *ANG2*, *HIF1*, *TGFB*, *VEGF*, and *PLGF*.⁸³ miRNAs control angiogenesis at multiple levels via suppressing antiangiogenesis genes or promoting proangiogenesis genes.⁷ miRNAs can affect the response to hypoxia of CRC through regulating the expression of HIF1. Induced by chemokine CCL19, miR206 inhibits the Met–ERK–Elk1 pathway and suppresses the expression of HIF1 α , leading to the inhibition of angiogenesis in CRC.⁸⁴ Similarly, miR107 regulates hypoxia signaling by inhibiting the expression of HIF1 β . Downregulation of miR107 has been found to accelerate neovascularization.⁸⁵ miRNAs mediate the regulation of VEGF expression and play a critical role in promoting CRC angiogenesis.⁸⁶ CRC cell-derived miR1229 accelerates angiogenesis through activating the HIPK2–VEGF α –VEGFR pathway, and high levels of exosomal miR1229 in serum have been demonstrated to enhance tube formation in vitro and accelerate angiogenesis in vivo.⁸⁷

CRC-derived miRNA-contained exosomes can facilitate metastasis by increasing vascular permeability. KLF4 is an oncogenic transcription factor of cell junction related protein which supports the integrity of endothelial barriers.⁸⁸ miR25-3p from CRC cells targets endothelial cells and significantly decreases the expression of cell-cell junction related protein (ZO-1, occludin, Cldn5) via suppression of KLF4. This results in a significant increase of CRC cells leakage to bloodstreams and facilitates distant metastasis. In further, miR25-3p makes a similar changing in the formation of PMN and accelerates extravasation.⁸ Analogously, miR92a from CRC cells decreases cell-cell tight connection components and cell adhesion. And it also stimulates cell mitosis and accelerates micro-tube formation to promote angiogenesis.⁸⁹ Lymphatic metastasis is also a common way of metastasis, therefore, lymphangiogenesis is also

Table 1 Dual effects of miRNAs in CRC EMT process

miRNAs	Biological behaviors	Direct targets	Signaling pathways	References
miR514b-3p miR514b-5p	Tumor-suppressive miRNA Oncogenic miRNA	FZD4, NTN1 CDH1, Cldn1	miR514-3p→FZD4, NTN1↓→EMT↓ miR514-5p→CDH1, Cldn1↓→EMT↑	47
miR10b	Oncogenic miRNA	KLF4	miR10b→KLF4↓→EMT↑	48
miR29a-3p	Oncogenic miRNA	KLF4, Pgrn	miR29a→Pgrn-Wnt-β-catenin and MMP2↑→EMT↑	49, 50
miR452	Oncogenic miRNA	GSK3β	miR452→TCF-LEF-GSK3β-Wnt-β-catenin↑→EMT↑	51
miR1269 miR4775	Oncogenic miRNA Oncogenic miRNA	Smad7	miR1269/miR4775→Smad7↓→TGFβ-Smad↑→EMT↑ TGFβ→Sox4→miR1269↓	52, 53
miR194	Oncogenic miRNA	MMP2	miR194→MMP2↑→EMT, ECM degeneration, cytoskeleton remodeling↑	54
miR600	Oncogenic miRNA	KIAA1199	miR600→KIAA1199↑→mobility↑	55
miR105	Oncogenic miRNA	RAP2C	miR105→RAP2C-NFκB↓→EMT↑	56
miR183	Oncogenic miRNA	β-catenin	miR183→PI3K-Akt-ERK↑→EMT↑ miR183→Wnt-β-catenin↑→EMT↑	57
miR582	Oncogenic miRNA	APC2	miR582→APC2-Wnt-β-catenin↑→EMT↑	58
miR496	Oncogenic miRNA	RASSF6	miR496→RASSF6-Wnt-β-catenin↑→EMT↑	59
miR126-5p	Oncogenic miRNA	Slug, Twist, VEGFα	miR126-5p→Slug, Twist, and VEGFα↑→EMT↑	46
miR500a-5p	Tumor-suppressive miRNA	TGFβ	miR500a-5p→TGFβ↓→EMT↓	60
miR1224-5p	Tumor-suppressive miRNA	SPI	miR1224-5p→SPI-NFκB↓→EMT↓	61
miR200c	Tumor-suppressive miRNA	ZEB1/2, β-catenin	miR200c→ZEB1/2 and Wnt-β-catenin↓→EMT↓	62
miR34a	Tumor-suppressive miRNA	PPP1R11, Notch, β-catenin, Snail	miR34a→Wnt-β-catenin, SATB3, and Notch↓→EMT↓	62
miR138	Tumor-suppressive miRNA	Twist2	ANGPTL1↑→miR138↑→Twist2↓→EMT↓	63
miR145	Tumor-suppressive miRNA	Twist1	miR145→Twist1↓→EMT↓	64
miR598	Tumor-suppressive miRNA	JAG1	miR598→JAG1-Notch2↓→EMT↓	65
miR488	Tumor-suppressive miRNA	Cldn2	miR488→Cldn2-MAPK↓→EMT↓	66
miR9	Tumor-suppressive miRNA	IGF1R	miR9→IGF1R-Src-STAT3 and MMP9-FOX4↓→EMT↓	67
miR143	Tumor-suppressive miRNA	K-Ras, cMyc, BCL2, MMP9	miR143→K-Ras, cMyc, BCL2 and MMP9↓→EMT↓	68
miR302c	Tumor-suppressive miRNA	AP4	miR302c→AP4↓→EMT↓	69
miR218	Tumor-suppressive miRNA	VEGFα ANGPT2	miR218→VEGFα-MAPK↓→EMT↓ miR218→VEGFα and ANGPT2↓→angiogenesis↓	70
miR206	Tumor-suppressive miRNA	TM4SF1	miR206→TM4SF1-Wnt-β-catenin, VEGF, MMP9, Snail↓→EMT↓	71
miR1249	Tumor-suppressive miRNA	VEGFα, HMGA2	miR1249→VEGFα-HMGA2↓→EMT↓ miR1249→VEGFα-Akt-mTOR↓→angiogenesis↓	72
miR30a	Tumor-suppressive miRNA	TM4SF1	miR30a→TM4SF1↓→EMT↓	73, 74
miR139-5p	Tumor-suppressive miRNA	CTNNB1, DVLI	miR139-5p→Wnt-β-catenin↓→EMT↓	75

critical.⁹ VEGFC/D/VEGFR3 is considered as an inducer of lymphangiogenesis.⁸⁶ By activating Smad4/TGFβ/VEGFC pathway, high level of miR27a accelerates lymphatic tube formation and lymphatic metastasis.⁹⁰

miRNAs and Anoikis

Cancer generates mobile cells termed CTCs that immigrate from the primary environment and seep into the circulatory system.⁹¹ A type of programmed cell death termed anoikis is triggered when they leave the primary niche. CTCs must acquire the ability to resist anoikis and survive in the new background. Some malignant cells are equipped with the ability to resist anoikis or are less sensitive to anoikis.⁹² Itgα₃ signaling pathway has been demonstrated to be critical in regulating sensitivity of colorectal CTCs to anoikis. High miR124 levels activate caspase 3 and induce anoikis by reducing the expression of Itgα₃. High levels of Itgα₃ or reduced miR124 indicate poor CRC prognosis.⁹³ The expression of miR10a is upregulated in primary CRC tissues in SW480 cells compared to metastatic cancer tissue with lymph-node metastasis in SW620 cells. High miR10a levels induce cell mobility and decrease cell adhesion in primary CRC cells. When CRC cells detach from the primary niche, the expression of miR10a in CRC CTCs is decreased. Low miR10a levels enhance cell adhesion and promote anoikis resistance by increasing the expression of integrin and *BCL2*.⁹⁴ Tumor immunoescape refers to TCs escaping from immune-system attack and surviving in metastasis cascades. High PDL1 levels on the tumor surface can bind to PD1 on T lymphocytes, leading to immunosuppression and contributing to tumor survival.⁹⁵ The endogenous tumor suppressor miR93-5p directly suppresses the expression of PDL1. miR93-5p in CRC cells contributes to inhibition of immunoescape by inhibiting PDL1–PD1 interaction and improving the production of anti-inflammatory factors. High expression of PDL1 or low levels of miR93-5p indicate more CRC-metastasis potential.⁹⁶

miRNAs and PMN

Cancer metastasis is organ- and tissue-specific rather than random, according to the seed–soil theory and PMN theory, and the site of metastasis is related to the integrin type on the cell surface.⁹⁷ The PMN theory refers to primary cancer promoting a suitable microenvironment in distant organs or tissue for cancer-cells settlement.⁹⁸ As for CRC, the liver and peritoneum are the two commonest sites of metastasis. Studies have found that primary CRC cells can

facilitate PMN formation in the liver by releasing various miRNA-contained exosomes.⁴

miR21-contained exosomes are released from primary CRC cells and identified by macrophages in the liver, then miR21 stimulates polarization of macrophages and enhances the production of IL6. The secreted IL6 in turn enhances miR21 recruitment, which further expands the inflammatory response in the liver and consequently forms an inflammatory PMN site to facilitate liver metastasis for CRC.⁹⁹ Similarly, the expression of miR25-3p, miR130b-3p, and miR425-5p stimulated by CXCL12 and CXCR4 is upregulated in CRC cells. When these miRNAs are secreted by CRC cells in exosomes and taken up by TAMs, they enhance the infiltration of TAMs and induce an inflammatory environment in the liver via inhibiting *PTEN* and activating the PI3K–Akt pathway.¹⁰⁰

The reverse process of EMT, MET is also essential for metastasis. EMT allows emigration from primary tumor tissues. The MET process shifts the cancer cells to a less aggressive phenotype and allows cancer cells to settle in a distant location to go on to further proliferation.¹⁰¹ miR200c also expresses contrastingly between primary and metastatic tissue. The level of miR200c in primary tissue is lower than in metastatic tissue. Lowly expressed miR200c triggers EMT in the invasive margin of primary CRC tissue. When cells reach a suitable distant metastatic location, such as lymph nodes or the liver, the expression of miR200c is increased. High levels of miR200c promote MET and allow CRC cells to regain epithelial features and decrease mobility.¹⁰² Collectively, EMT triggered by low levels of miR200c in primary CRC tissue allows cancer-cell emigration and MET process allows the settlement of CTCs in distant tissues.

miRNAs and Stemness

CSCs are subpopulation cancer-cell clusters that express specific markers, including CD44, CD24, CD133, LGR5, Pgp, and ABCG2. CSCs are equipped with abilities of self-renewal, multilineage-differentiation, tumorsphere formation, and conventional treatment resistance. A small group of CSCs can be activated and form complete tumor tissue. They are also considered the seeds of metastasis and treatment resistance.¹⁰³ CRC-derived miRNAs regulate the stemness of CSCs via various signaling pathways (Figure 2).¹⁰⁴ CSCs undergo asymmetric division to retain stem traits. This process produces partially differentiated cells and SCs.¹³ Epigenetically silenced miR34a accelerates the asymmetric division process of CRC SCs, enhances self-renewal ability,

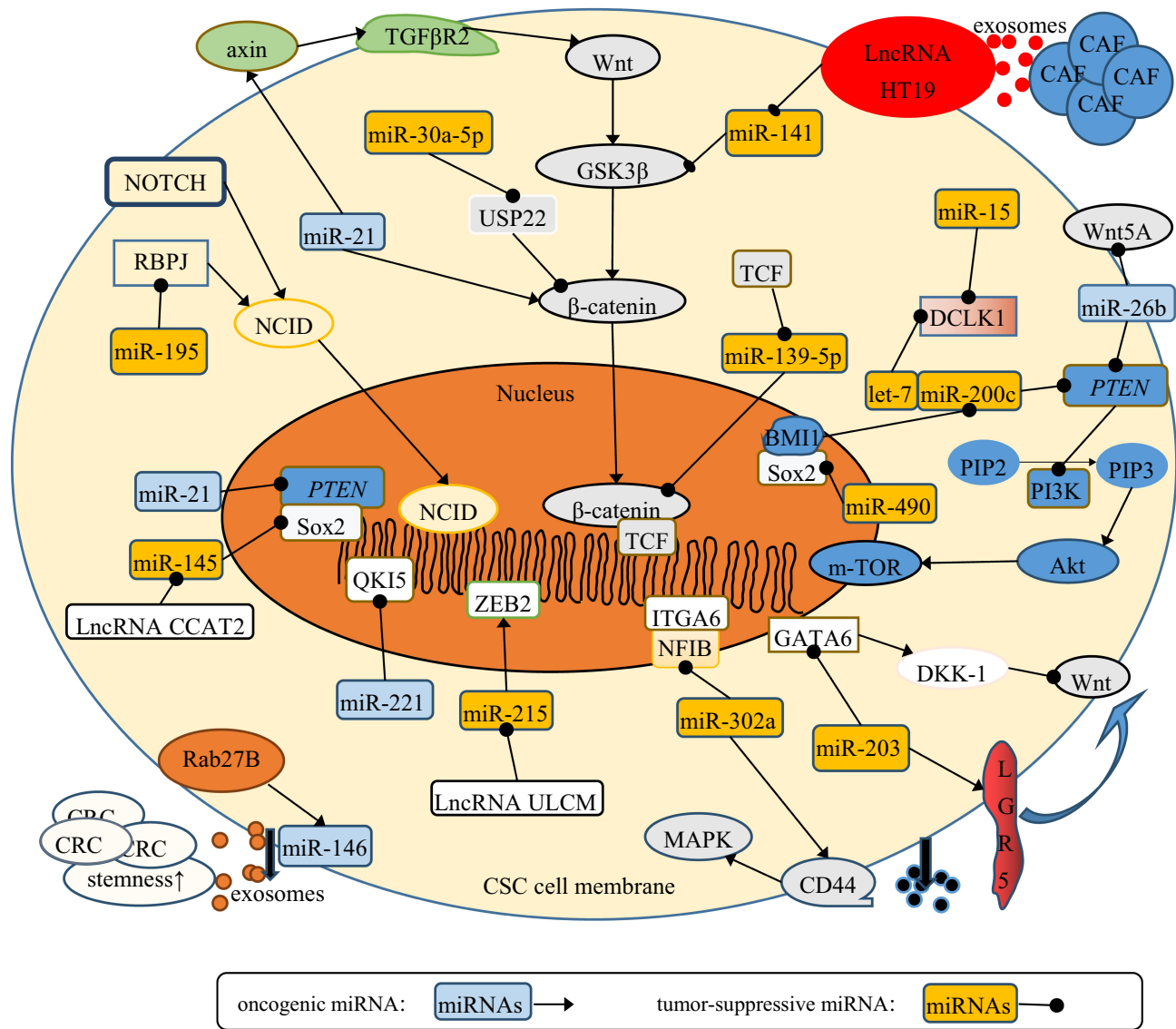


Figure 2 Signaling pathways related to miRNA regulation of CRC stemness. The miRNAs in light-blue squares refer to oncogenic miRNAs. The miRNAs in orange squares refer to tumor-suppressive miRNAs. The round shapes on the end of arrows refer to the suppressive function on target genes. The sharp arrows refer to the oncogenic function on target genes. Most miRNAs work by regulating several signaling cascades, including Notch–NCID, Wnt–β-catenin and PI3K–Akt–NFκB, in various aspects. Also, some miRNAs work by interacting with proteins and genes. lncRNAs can inhibit the effects of miRNAs on CRC stemness. Above all, miRNAs finally target stem markers (CD44, Sox, and LGR5), and regulate stemness of CRC.

and increases the expression of stem markers by activating Notch and the Wnt–β-catenin pathway.¹⁰⁵

The reverse process of differentiation happens in cancer when differentiated cancer cells reacquire stemness properties. CSCs interact with differentiated cancer cells and endow them with SC-like traits. Specifically, parent CSCs release exosomal miR146a to differentiated CRC cells and promote them to regain SC-like properties. The activated Wnt–β-catenin–TCF4–Rab27B pathway enhances the secretion of miR146a-encapsulated exosomes, which increases the expression of stem markers and self-renewal ability in recipient CRC cells.¹⁰⁶ Stem markers mainly help

to distinguish SCs and non-SCs. Some markers also contribute to conventional drug resistance, eg, Pgp, ABCG2, and CD44. CD44 is a stem marker, and high levels result in attenuated sensitivity to cetuximab. Ectopic expression of miR302 accelerates drug efflux in CRC chemotherapy by increasing the expression of CD44.¹⁰⁷

miRNAs, Tumor Markers, and Treatment Resistance

miRNA expression in cancer patients is correlated with tumor burden, and dysregulation of miRNAs in cancer patients can act as a clinical diagnostic biomarker. They

are detectable in blood, and levels correspond with the progression of cancer (Table 3). For example, levels of miR183-5p, miR365a-3p, and miR302a in CRC patients have been shown to be related to tumor size, extent of lymph-node metastasis, and whether distant metastasis has occurred.¹²¹ For a lack of symptoms in early stages, CRC patients often miss the opportunity for early diagnosis. Also, in the process of postoperative tumor review, miRNAs may serve as an important supplementary examination method to provide new detection methods for early diagnosis and postoperative review (Table 3).

Treatment resistance of malignant tumors often indicates poor prognosis, and the unregulated expression of some miRNAs is directly related to chemotherapy resistance. In certain cell lines with stem markers highly expressed, there is abnormal expression of miRNAs associated with resistance to fluorochemical and platinum-based chemotherapy.¹²² These miRNAs are related to drug efflux, DNA-damage repair, and drug metabolism. For example, thymidylate synthase is one of the metabolic enzymes of 5FU, and miR375-3p enhances the sensitivity of CRC cells to 5FU by regulating the expression of thymidylate synthase.¹²³ Downregulation of miR4454 is related to drug resistance of CRC. Artificial induction of miR4454 expression leads to reduction in tumor tissue and increases sensitivity to 5FU, CPT11, and oxaliplatin.¹²⁴ A drug transporter, MRP5 decreases sensitivity to oxaliplatin by increasing drug efflux and reducing intracellular oxaliplatin accumulation. miR128-3p is a direct inhibitor of MRP5. Expression of miR128-3p is reduced in oxaliplatin-resistant cell lines (HCT116OxR and HT29OxR). Increasing the level of miR128-3p can improve sensitivity to oxaliplatin by suppressing the expression of MRP5.¹²⁵

Conclusion

CRC is the third-commonest cancer worldwide and metastasis the main cause of cancer-related death. Various proteins, lipids, and nucleotides including DNA and RNA regulate CRC metastasis in different aspects. Increasing evidence demonstrates that miRNAs participate in cancer metastasis at the epigenetic level. As a member of the ncRNA family, miRNAs have been found to participate in occurrence and development of CRC. miRNAs suppress posttranslational expression of metastasis-related genes or cause degradation of various mRNAs through an miRNA-mRNA interference model.

Firstly, miRNAs induce reprogramming of CRC cells to acquire mobility and generate mobile cells. Different

miRNAs accelerate morphological changes in CRC cells and detachment from the ECM by affecting cytoskeleton remodeling, adhesion, and metabolism. miRNAs mediate the expression of EMT-related proteins (E-cadherin, N-cadherin, vimentin, and fibronectin) in CRC cells to attenuate polarity and acquire an aggressive phenotype during EMT-MET conversion.¹³⁸ During this process, the deformed CRC cells accelerate degradation of the ECM and interact with other noncancer cells in the TME to promote invasion and migration. Secondly, miRNAs regulate angiogenesis, destroy endothelial barriers, and increase vascular permeability in primary CRC tissue by regulating several angiogenesis-associated factors (Ang2, HIF1, TGF β , and VEGF), leading to the leakage of CRC cells into the bloodstream and the formation of CTCs. Thirdly, miRNAs endow CRC CTCs with anoikis resistance and facilitate their survival in the bloodstream. miRNAs regulate the expression of PDL1 on the CRC cell surface and free CRC cells from immune harm. Then, miRNAs-contained exosomes from primary CRC can educate distant sites to establish a favorable PMN and facilitate CTCs to settle there, and the miRNAs induce angiogenesis, MET, and inflammatory reactions in the distant site for further settlement. Finally, miRNAs maintain CRC stemness. CSCs are considered the seeds of metastasis and recurrence. Conventional treatment fails to eliminate CSCs completely, which leaves the potential for metastasis. There are special clusters in CRC with specific makers expressed on the cell surface (CD44, CD24, CD133, and LGR5), and they are long-lived in the body, with self-renewal ability, great cell populations, tumor initiation, and multilineage-differentiation potential.¹³⁹ Clinically, miRNAs may be novel makers for early diagnosis and indicators for prognosis. They may also be potential methods to overcome CRC-treatment resistance.

We found that the level of miRNAs is in a dynamic state and has dual effects in CRC. miRNA levels in CRC alter in response to different microenvironments. They are regulated by various factors, such as TGF β , EGFs, hypoxia, hyperglycemia, and inflammatory factors. Expression of miRNAs is affected by cell state. For example, the level of miR200c and miR10a differs in primary and metastatic CRC cells. miRNAs exist in various forms. miRNAs exist intracellularly and regulate the expression of various genes. In addition, miRNAs can also be secreted by CRC cells via lipid carriers, such as exosomes or protein carriers. miRNAs can work as oncogenic or tumor-suppressive factors in CRC progression (Tables 1 and 2).

Though the genesis of CSCs is unknown, retention of self-renewal ability and stem-related markers are upregulated when cells undergo EMT. Some studies have regarded the stemness as a consequence of EMT and miRNAs regulating EMT and stem properties synchronously.^{140,141} In normal tissue, with different stages and different types of tumors, patterns of miRNA expression exhibit different features. Firstly, expression profiles of miRNAs are different between the normal and tumor tissues. Secondly, miRNA expression

shows tissue-specificity. Thirdly, expression profiles of miRNAs show significant difference among different cancers.¹⁴² There have been studies showing that expression differs between poorly differentiated and well-differentiated tumor tissue. In metastatic cancers with unknown primary origins or poorly differentiated malignant tumors, specific miRNA-expression profiles may help to determine tumor origin, including in CRC.^{143,144} The corresponding relationship between tumor stages and miRNA-expression levels

Table 2 Effects of miRNAs on the regulation of CRC stemness

miRNAs	Biological behaviors	Cell lines	Signaling pathways and effects	Stem markers	References
miR26b	Oncogenic miRNA	Caco2 DLD1	miR26b↑→PETN↓→PI3K–Akt↑→EMT↑ miR26b↑→Wnt5A↓→β-catenin↑→stem-like cell population↑	LGR5, ALDH1, CD44, CD133	¹⁰⁸
miR372 miR373	Oncogenic miRNA	HCT15 Caco2	miR372/373→expression of differentiation-related genes: NFKB, MAPK, ERK, VDR↓	CD24, CD26, CD44, CD133	¹⁰⁹
miR221	Oncogenic miRNA	HCT116	miR221↑→QKI5↓→proliferation and self-renewal↑	LGR5, Sox2, Oct4	¹¹⁰
miR21	Oncogenic miRNA	HCT116 HT29	miR21↑→Axin↓→Wnt–β-catenin–TCF–LEF↑→self-renewal↑	CD44, CD166, CD133	¹¹¹
miR302a	Tumor-suppressive miRNA	DLD1 Caco2 SW1463	miR302a↓→CD44↑→EGFR–MAPK–Akt↑→cetuximab resistance and tumorsphere formation↑ miR302a↓→NFIB and Itgα6↑→invasion and migration↑	CD44, Sox2, Oct4, Nanog, KLF4	¹⁰⁷
miR203	Tumor-suppressive miRNA	HCT116 HT29	miR203↓→GATA6, LGR5↑→(DKK1)↑→Wnt–β-catenin pathway↑→self-renewal and mobility↑	CD44, LGR5	¹¹²
miR30-5p	Tumor-suppressive miRNA	Caco2 HCT15	miR30-5p↓→(USP22)↑→GSK3β↑→Wnt–β-catenin↑→tumorsphere formation and proliferation↑	CD133, Sox2	¹¹³
miR139-5p	Tumor-suppressive miRNA	HCT116 HT29	miR139-5p↓→E2-2↑→Wnt–β-catenin–TCF7L2↑→EMT and self-renewal↑	Oct4, KLF4, Nanog, CD44	¹¹⁴
miR195	Tumor-suppressive miRNA	SW620/480 HT29/116	miR195-5p↓→Notch2 and RBPJ↑→Wnt–β-catenin↑→self-renewal and cell population↑ miR195-5p↓→Pgp, ABCG2↑→drug resistance↑	CD133, Sox2, Pgp,	¹¹⁵
miR145 miR21	Tumor-suppressive miRNA Oncogenic miRNA	HCT116 HT29	lncRNA CCAT2↑→miR145↓(miR21↑)→Sox2, TGFβR2, and KLF4→self-renewal and differentiation ability↑	CD44, Oct4, Sox2, Nanog	¹¹⁶
miR141	Tumor-suppressive miRNA	SW480 HCT116	CAFs→exosomal lncRNA HT19↑→miR141↓→Wnt–β-catenin↑→tumorsphere formation and cell population↑	ALDH	⁸²
miR20b-5p	Tumor-suppressive miRNA	HCT116	lncRNA MALAT1↑→miR20b-5p↓→Oct4↑→tumorsphere formation, self-renewal, and cell population↑	Oct4, Nanog	¹¹⁷
miR215-5p	Tumor-suppressive miRNA	SW620 DLD1	lncRNA UICLM↑→miR20b-5p↓→ZEB2↑→self-renewal and tumorsphere formation↑	LGR5, CD24, CD44, CD133, CD155, CD166	¹¹⁸
Let7 miR15	Tumor-suppressive miRNA	HCT116	Let7↓→DCLK1↑→EMT, proliferation and self-renewal↑ Let7↓→Akt and β-catenin↑ miR15↓→DCLK1↑→self-renewal and chemo/radioresistance↑	CD44, CD133, ALDH1, BMI1	^{119, 120}

Table 3 Effects of miRNAs in clinical applications

miRNAs	Direct targets	Clinical significances	Cell lines or detection methods	Clinical applications	References
miR320d	—	Exosomal miR320d in serum distinguishes metastatic from nonmetastatic CRC.	Serum	Biomarker	¹²⁶
miR30a-5p	—	Serum miR30a-5p works for early diagnosis and prognosis of CRC.	Serum	Biomarker/ prognostic indicator	¹²⁷
miR210, miR21, miR126	—	miR210 and miR21 associate with TNM stage and sensitivity/specificity: 88.6%/90.1%, 91.4%/95.0%, respectively. miR126 is downregulated in CRC.	Serum	Biomarker	¹²⁸
miR92a miR144*	—	These are detected in stool and may work as noninvasive biomarkers for CRC screening.	Stool	Biomarker	¹²⁹
miR20b, miR29b, miR155	miR29b→MMP2, PTEN miR155→HIF1 α	High levels of the three circulating miRNAs correlate with longer PFS and OS.	Plasma	Prognostic indicator	¹³⁰
miR19a	PTEN	Decreased expression of miR19a resensitizes cells to oxaliplatin.	SW480/R, HT29/R	Chemoresistance	¹³¹
miR483-3p	FAM171B	Overexpression of miR483-3p restores sensitivity to oxaliplatin.	HCT116/L	Chemoresistance	¹³²
miR302a	IGF1R	Overexpression of miR302a increases sensitivity to 5FU.	HCT116, HT29	Chemoresistance	¹³³
miR206	BCL2	Downregulation of miR206 promotes resistance to 5FU.	HCT116/FR, RKO/FR	Chemoresistance	¹³⁴
miR31-5p	LATS2	Overexpression of miR31-5p reduces sensitivity to oxaliplatin.	OR-LoVo	Chemoresistance	¹³⁵
miR194-5p	SIRT1	Low level of miR194-5p results in 5FU resistance.	HCT8FU	Chemoresistance	¹³⁶
miR125b	APC	High level of miR125b induces EMT process and reduces sensitivity to 5FU.	HCT116, SW620	Chemoresistance	¹³⁷
miR128-3p	BMII, MRP5	Exosomal miR128-3p decreases drug efflux and increases sensitivity to oxaliplatin.	HCT116OxR, HT29OxR	Chemoresistance	¹²⁵

ensures the possibility of miRNAs working as indicators for CRC prognosis. miRNA-expression profiles are informative, reflecting the developmental lineages and differentiation states of the tumors. A study has demonstrated that 48 miRNA markers encode 22 tissue types, with accuracy reaching 90%.¹⁴³

Expression profiles of miRNAs differ among species. At the cellular level, they are regulated in nuclei and cytoplasm. The expression process of miRNAs includes miRNA transcription, procession by Drosha and Dicer, and then the most miRNAs mature in cytoplasm. Transcription factors, such as

p53, Myc, ZEB1, and ZEB2, positively or negatively regulate the expression of miRNAs.¹⁴⁵ The transcription miR34a is regulated by p53 in the nucleus.⁴² Drosha forms a complex called a microprocessor that determines the specificity of miRNAs. The level of Dicer also determines the level of miRNAs. Expression of Dicer increases as the density of cancer cells increases, which leads to increased expression of miR590-5p (density-sensitive miRNA).¹⁴⁶

Cell-cell communication is a foundation of cellular biological phenomena. Differently from various signaling molecules, miRNAs act as signaling molecules and shuttle

between CRC cells and other noncancer cells, providing new insight.¹⁴⁷ miRNAs in the TME mediate signal exchange between cancer cells and noncancer cells and differentiated and undifferentiated cancer cells.^{148,149} They are even secreted into the bloodstreams by exosome, and can function in distant sites. In terms of chemotherapy resistance, fluorine and platinum drugs are first-line chemotherapeutics in CRC treatment. The dysregulation of miRNAs in CRC, such as in miR141, Let7, and miR375-3p, are involved in conventional chemotherapy resistance and poor survival. Levels of miRNAs in serum are related to CRC stage, and as biomarkers, miRNAs can be critical diagnostic and metastasis indicators. The quantitative detection of conservational miRNA markers may provide the possibility of detecting CRC recurrence and metastasis.^{150,151} It has been found that by artificially regulating the expression of miRNA in cancer cell, delivering miRNAs or their regulatory molecules to cancer cells can affect the rate of cancer progression. For example, artificial intracellular miR21 inhibitors can significantly increase the sensitivity of CRC cells to chemotherapy.¹⁵² In conclusion, reviewing the role of different miRNAs in CRC metastasis could benefit us tremendously in the field of CRC research and clinical therapy.

Abbreviations

5FU, 5-fluorouracil; Cdh, cadherin; Cld, claudin; CPT11, irinotecan; CXCR, chemokine receptor; Itg α , integrin α ; Itg β , integrin β ; OS, overall survival; PFS, progression-free survival; TCF, T-cell factor.

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