Ther Adv Med Oncol
2020, Vol. 12: 1–28
DOI: 10.1177/1758835920947342

Molecular mechanisms and clinical implications of miRNAs in drug resistance of colorectal cancer

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***Abstract*:** Systemic chemotherapy is identified as a curative approach to prolong the survival time of patients with colorectal cancer (CRC). Although great progress in therapeutic approaches has been achieved during the last decades, drug resistance still extensively persists and serves as a major hurdle to effective anticancer therapy for CRC. The mechanism of multidrug resistance remains unclear. Recently, mounting evidence suggests that a great number of microRNAs (miRNAs) may contribute to drug resistance in CRC. Certain of these miRNAs may thus be used as promising biomarkers for predicting drug response to chemotherapy or serve as potential targets to develop personalized therapy for patients with CRC. This review mainly summarizes recent advances in miRNAs and the molecular mechanisms underlying miRNA-mediated chemoresistance in CRC. We also discuss the potential role of drug resistance-related miRNAs as potential biomarkers (diagnostic and prognostic value) and envisage the future orientation and challenges in translating the findings on miRNA-mediated chemoresistance of CRC into clinical applications.

Keywords: biomarkers, colorectal cancer, drug resistance, miRNAs, targeted therapy

Received: 13 November 2019; revised manuscript accepted: 13 July 2020.

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Introduction

Colorectal cancer (CRC) ranks the third for cancer incidence and fourth leading cause for cancer deaths worldwide.[1] In 2018, there will be over 1.8 million new cases of CRC with approximately 881,000 deaths in the same year across the world, accounting for about 10% of cancer cases and deaths.[2] CRC is a complex and heterogeneous disease with a multitude of genetic and epigenetic factors involved in the development of CRC.[3] Despite great progress having been made in the detection, surgical resection, and adjuvant therapy of CRC, the mortality of CRC patient still remains relatively high. Therefore, it is imperative for researchers to elucidate the pathogenesis of CRC, further to develop more effective therapeutic measures and improve prognosis.

Chemotherapy is an available curative approach for CRC since most advanced patients cannot benefit from surgical resection or radiotherapy.[4] However, the evolution of drug resistance contributes to therapy failure in CRC patients. Multidrug resistance (MDR), defined as the resistance of cancer cells to a variety of structurally and functionally unrelated drugs, can occur naturally or is acquired.[5] The main mechanisms of intrinsic or acquired MDR include, but are not limited to, overexpression of MDR transporters, alterations in the regulation of cell cycle and checkpoints, dysregulation on the apoptotic and autophagy machinery, alteration in DNA repair and drug targets, enhancing drug metabolism, etc.[6] In addition, cancer stem cells (CSCs) may also contribute to drug resistance.[7] Nevertheless, the concrete mechanisms refer to MDR have not been fully clarified. For the sake of reversing chemoresistance, many researchers fling themselves into exploring the concrete mechanisms underlying drug resistance. More recently, accumulating

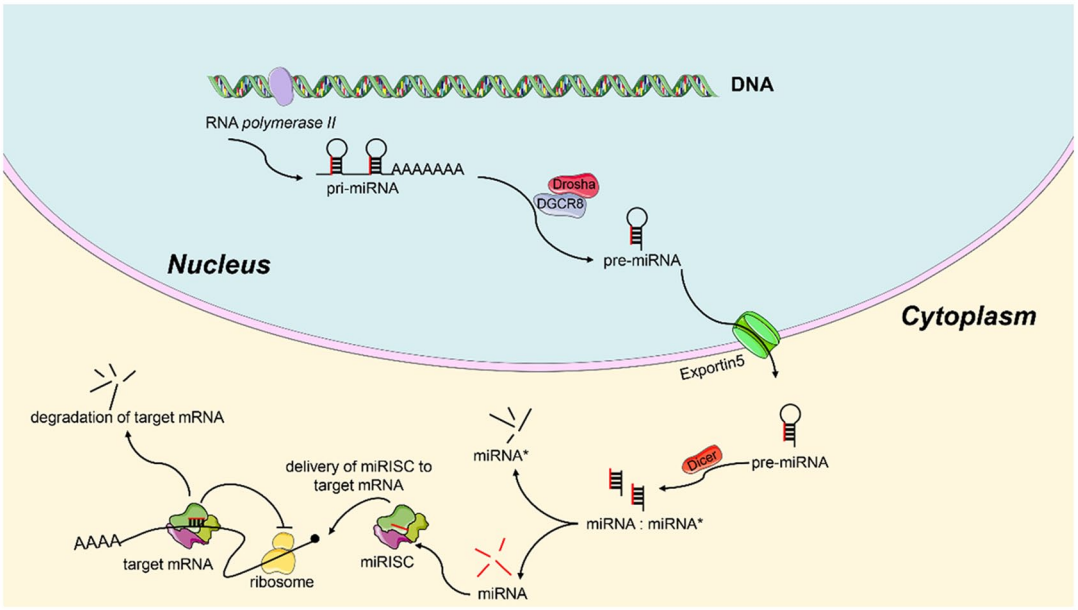

Figure 1. Schematic diagram of the biogenesis of miRNAs.
In the nucleus, the pri-miRNA transcript is firstly produced by RNA polymerase II. Then, the pri-miRNA is processed by the Drosha associates with DGCR8 and becomes pre-miRNA. Next, the pre-miRNA is transported into the cytoplasm by Exportin5. In the cytoplasm, the pre-miRNA further processed by the Dicer RNase III enzyme to form a mature miRNA.

evidence has reported that epigenetic modification such as miRNA dysregulation was significantly associated with the phenomenon of drug resistance.[8,9]

miRNAs, a subpopulation of noncoding RNAs, function as posttranscriptional regulatory elements consisting of 21–23 short nucleotides.[10] The biogenesis mechanism of miRNAs has been well understood (Figure1).[11] In brief, genes that encode miRNAs are transcribed primarily by RNA polymerase II in nucleus and create primary miRNA (pri-miRNA), which is subsequently processed by DiGeorge syndrome critical region 8 (DGCR8) protein associated with the Drosha ribonuclease III (Drosha) enzyme into a shorter stem-loop-structured precursor miRNA (pre-miRNA) (70–100 nucleotides).[12] Then, the pre-miRNA is transported into cytoplasm by exportin-5. Next, the Dicer RNase III enzyme processes the pre-miRNA and produces the dsRNAs (18~25 nucleotides in length). One strand of dsRNAs, termed miRNA*, is degraded, another strand of the dsRNAs that serves as the guide strand is incorporated into RNA-induced silencing complex (RISC) and forms miRISC, which then targets the 3′-untranslated regions (UTRs) of its target mRNAs and regulates genes expression either by attenuating RNA translation or by promoting mRNA degradation.[13,14] miRNAs play crucial roles in biological and pathological processes, encompassing metabolism, apoptosis, differentiation, cell proliferation, cell cycle as well as MDR, etc.[15–17] miRNAs exhibit differential expression in many malignancies, including CRC,[18] and function as either tumor suppressors or oncogenes.[19] Emerging evidence shed light on the role of miRNAs in drug resistance of CRC and revealed some critical mechanisms involved in MDR.[20] Aberrant expression of miRNAs can affect the expression and function of MDR-related mRNAs and proteins, further influencing the chemosensitivity of CRC cells. For example, miR-24, the first identification of chemoresistance-related miRNA, could contribute to methotrexate resistance *via* binding site polymorphism in the dihydrofolate reductase gene.[21] In addition, forced expression of miR-24 can also reverse paclitaxel (PTX) resistance of breast cancer by targeting ATP binding cassette subfamily B Member 9 (ABCB9), indicating that miR-24 may serve as a promising biomarker to predict drug response and an effective target for cancer treatment.[22] Therefore, miRNAs may serve as novel promising biomarkers and therapeutic targets in reversing chemoresistance of CRC.

In the present review, a systematic electronic literature search of the Web of Science (http://apps.webofknowledge.com), PubMed (https://pubmed.ncbi.nlm.nih.gov), and EMBASE (http://www.embase.com) databases was conducted. Specific search strategies for each database were developed by using different combinations and variations of search terms, including 'colorectal cancer', 'colon cancer', 'rectal cancer', 'drug resistance', 'chemoresistance', 'microRNA', 'miRNA' and their variants. We summarize results from the published literatures on the role of miRNAs and their targets in drug-resistant CRC (Tables 1 and 2). Some of them even were regarded as potential biomarkers in CRC patients (Table 3). Furthermore, considering that 5-fluorouracil (5-FU) and oxaliplatin (L-OHP) are the most important first-line chemotherapeutic drugs for CRC, we summarize related miRNAs and their targets in Figure 2.

miRNA-mediated signaling pathways in drug resistance of CRC

MDR refers to resistance to a variety of anticancer drugs, and poses a great challenge to cancer treatment. Mounting evidence indicates that several signaling pathways, such as the phosphatidylinositol 3-kinase (PI3K)/Ser/Thr kinase (AKT) signaling pathway and Wnt/β-catenin signaling pathway, contribute to chemoresistance in CRC. Some miRNAs have been shown to affect the function/expression of various components of these pathways, thereby changing the chemosensitivity of CRC cells. The related cellular signaling pathways through which miRNAs modulate efficacy of chemotherapy regimens of CRC are summarized in the following (Table 1).

PI3K/AKT signaling pathway

The PI3K/Akt signaling pathway confers drug resistance to various malignancies including CRC.[122] The activity of the PI3K/AKT signaling pathway is regulated by various molecules, including phosphatase and tensin homolog (PTEN), epidermal growth factor receptor (EGFR), high mobility group protein A2 (HMGA2), and protein phosphatase 2 scaffold subunit A β (PPP2R1B), RAS, etc.[123]

PTEN functions as a lipid phosphatase to antagonize the PI3K/Akt pathway *via* dephosphorylating phosphatidylinositol 3,4,5-trisphosphate (PIP3). The decreased expression level of PTEN correlated with drug resistance to conventional therapy.[124] PTEN mRNA is a direct target of miRNA-17-5p, which is significantly upregulated in CRC patients. Enhanced expression of miR-17-5p contributes to the development of resistance to chemotherapeutic treatments (5-FU, L-OHP and Irinotecan) and correlates with distant metastases and poor clinical stages in CRC patients. Either antisense oligo against miR-17-5p or reconstruction of PTEN expression could effectively sensitize CRC cells to cytotoxic drug, inducing increased cellular apoptosis and cell death.[23] miR-21 also interacts with PTEN and is overexpressed in many malignancies, including CRC.[24] PTEN expression was downregulated in miR-21 overexpressing xenograft. Up-take of difluorinated curcumin (CDF), a novel nontoxic analog of the dietary ingredient curcumin,[125] has been shown to repressed miR-21expression and restored PTEN levels with subsequent reduction in Akt phosphorylation, contributing to inhibit the growth of 5-FU + L-OHP resistant colon cancer HCT116 and HT-29 cells. In short, Dysregulated of PTEN-Akt signaling mediated by miR-21 could be normalized by CDF in chemo-resistant CRC cells.[126] Of note, decreased expression of miR-200c in CRC can promote 5-FU resistance by inversely regulation of PTEN expression and caspase-3 activity and subsequently inhibiting the AKT signaling pathway.[25]

One class of upstream regulators of the PI3K/AKT pathway is EGFR, whose phosphorylation leads to the activation of PI3K/AKT pathway and extracellular signal-regulated kinase (ERK).[127] A recent study showed that 3′-UTRs of EGFR mRNA are direct functional targets of miR-7, the expression level of which was higher in CRC tissues than in adjacent normal tissues. miR-7 can promote cell proliferation and induce resistance to cetuximab in CRC cells *via* targeting EGFR. Therefore, miR-7 may serve as a promising biomarker for targeted therapy in CRC patients who exhibit resistance to EGFR-directed antibodies.[26] Interestingly, a disintegrin and metalloprotease 9 (ADAM9), involving in EGFR-AKT signaling and regulating cell proliferation, is a direct target of miR-20b. miR-20b expression was decreased in the 5-FU-resistant colon cancer tissues and cells and was inversely correlated with ADAM9 and EGFR expression. miR-20b can reverse 5-FU resistance of CRC both *in vitro* and *in vivo* through suppressing the ADAM9/EGFR signaling pathway.[27]

Table 1. miRNAs mediate drug resistance *via* cellular signaling pathways in CRC.

Mechanisms	Reported miRNA	Alteration	Validated miRNA targets	Corresponding drugs	Reference
PI3K/AKT signaling pathway	miR-17-5p	Up	PTEN	5-FU, L-OHP and Irinotecan	Fang *et al.*[23]
	miR-21	Up	PTEN	5-FU	Si *et al.*[24]
	miR-200c	Down	PTEN	5-FU	Heydari *et al.*[25]
	miR-7	Up	EGFR and RAF-1	Cetuximab	Suto *et al.*[26]
	miR-20b	Down	ADAM9	5-FU	Fu *et al.*[27]
	let-7	Down	Ras	5-FU	Salendo *et al.*[28]
	miR-224	Up	RKIP	5-FU	Amankwatia *et al.*[29]
	miR-204-5p	Down	RAB22A	L-OHP, 5-FU and CDDP	Yin *et al.*[30]
	miR-204	Down	HMGA2	5-FU	Wu *et al.*[31]
	miR-194	Down	VAPA	L-OHP, irinotecan	Chang *et al.*[32]
	miR-135b and miR-182	Up	ST6GALNAC2	5-FU	Liu *et al.*[33]
	miR-587	Up	PPP2R1B	5-FU	Zhang *et al.*[34]
	miR-199a-5p and miR-375	Up	PHLPP1	Cetuximab	Mussnich *et al.*[35]
Wnt/β-catenin signaling pathway	miR-181a-5p	Down	β-catenin/TCF4	5-FU	Han *et al.*[36]
	miR-149	Down	FOXM1	5-FU	Liu *et al.*[37]
	miR-320	Down	FOXM1	5-FU, L-OHP	Wan *et al.*[38]
	miR-203a-3p	Down	β-catenin, GRG5	CDDP, PTX	Xiao *et al.*[39]
	miR-224	Up	GSK-3beta	ADM	Liang *et al.*[40]
	miR-199a/b	Up	GSK-3β	CDDP	Chen *et al.*[41]
	miR-100	Up	DKK1 and ZNRF3	Cetuximab	Lu *et al.*[42]
	miR-125b	Up	ZNRF3, RNF43, DKK3 and APC2	Cetuximab	Lu *et al.*[42]
TGF-β signaling pathway	miR-19b-3p	Up	SMAD4	L-OHP	Jiang *et al.*[43]
	miR-34a	Down	SMAD4	L-OHP	Sun *et al.*[44]
Hippo signaling pathway	miR-874-3p	Down	YAP and TAZ	5-FU	Que *et al.*[45]
NF-κB signaling pathway	miR-15b-5p	Down	NF-κB1, IKK-α	5-FU	Zhao *et al.*[46]
Notch signaling pathway	miR-139-5p	Down	NOTCH-1	5-FU	Liu *et al.*[47]
	miR-195-5p	Down	Notch2 and RBPJ	5-FU	Xu *et al.*[48]
Raf/MEK/ERK signaling pathway	miR-497	Down	KSR1	5-FU	Wang *et al.*[49]

ADM, adriamycin; AKT, Ser/Thr kinase; CDDP, cisplatin; CRC, colorectal cancer; 5-FU, 5-fluorouracil; L-OHP, oxaliplatin; miRNAs, microRNAs; NF-κB, nuclear factor kappa B; PI3K, phosphatidylinositol 3-kinase; PTX, paclitaxel; TGF-β, transforming growth factor beta.

Table 2. Summary of reported drug resistance-related miRNAs and their target genes in CRC.

Mechanisms		Reported miRNA	Alteration	Validated miRNA targets	Corresponding drugs	Ref.
Aberrant metabolism	glucose metabolism	miR-122	Down	PKM2	5-FU	He *et al.*[50]
		miR-34a	Down	LDHA	5-FU	Li *et al.*[51]
	TS and dihydropyrimidine dehydrogenase	miR-218	Down	TYMS	5-FU	Li *et al.*[52]
		miR-197	Down	TYMS	5-FU	Sun *et al.*[53]
		miR-203	Down	TYMS	5-FU	Li *et al.*[54]
		miR-494	Down	DPYD	5-FU	Chai *et al.*[55]
DNA damage repair and MMR		miR-145	Down	RAD18	5-FU	Liu *et al.*[56]
		miR-21	Up	hMSH2	5-FU	Deng *et al.*[57]
		miR-203	Up	ATM	L-OHP	Zhou *et al.*[58]
ABC transporters family		miR200c	Down	JNK2	L-OHP,5-FU, CDDP, VCR	Sui *et al.*[59]
		miR-302c-5p	Down	ABCB1	L-OHP	Ghanbarian *et al.*[60]
		miR-451	Down	ABCB1	irinotecan	Bitarte *et al.*[61]
		miR-519c	Down	HuR	5-FU, irinotecan	To *et al.*[62]
		miR-21	Up	PDCD4	5-FU	Wu *et al.*[63]
		miR-23a	Up	ABCF1	5-FU	Li *et al.*[64]
		miR-761	Down	FOXM1	5-FU	Cao *et al.*[65]
		miR-522	Down	ABCB5	DOX	Yang *et al.*[66]
		miR-506	Down	MDR1/P-gp	L-OHP	Zhou *et al.*[67]
		miR-219-5p	Down	Sall4	L-OHP,5-FU	Cheng *et al.*[68]
		miR-297	Down	MRP-2	L-OHP, VCR	Xu *et al.*[69]
		miR-34a	Down	OAZ2	L-OHP	Li *et al.*[70]
Apoptosis-related pathway	BCL-2 family	miR-1915	Down	BCL2	L-OHP	Xu *et al.*[71]
		miR-139-5p	Down	BCL2	L-OHP,5-FU	Li *et al.*[72]
		miR-129	Down	BCL2	5-FU	Karaayvaz *et al.*[73]
		miR-206	Down	BCL2	5-FU	Meng *et al.*[74]
		miR-20a	Up	ASK1	CDDP	Zhang *et al.*[75]
		miR-195	Down	BCL2L2	DOX	Qu *et al.*[76]
		miR-20a	Up	BID	TRAIL	Huang *et al.*[77]
		miR-10b	Up	BIM	5-FU	Nishida *et al.*[78]

(Continued)

Table 2. (Continued)

Mechanisms		Reported miRNA	Alteration	Validated miRNA targets	Corresponding drugs	Ref.
	XIAP	miR-874	Down	XIAP	5-FU	Han *et al.*[79]
		miR-122	Down	XIAP	L-OHP	Hua *et al.*[80]
		miR-96	Up	XIAP	5-FU	Kim *et al.*[81]
	IGF1R pathway	miR-302a	Down	IGF-1R	5-FU	Liu *et al.*[82]
		miR-143	Down	IGF-1R	L-OHP	Qian *et al.*[83]
	Other apoptosis-related pathway	miR-27a	Up	Apaf-1	TRAIL	Zhang *et al.*[84]
		miR-23a	Up	APAF-1	5-FU	Shang *et al.*[85]
		miR-128	Down	SIRT1	TRAIL	Lian *et al.*[86]
		miR-425-5p	Up	PDCD10	L-OHP,5-FU	Zhang *et al.*[87]
		miR-153	Up	FOXO3a	L-OHP	Zhang *et al.*[88]
		miR-503-5p	Up	PUMA	L-OHP	Xu *et al.*[89]
Autophagy-related pathway		miR-218	Down	YEATS4	L-OHP	Fu *et al.*[90]
		miR-22	Down	ULK1	5-FU	Zhang *et al.*[91]
		miR-125b	Up	-	5-FU	Yu *et al.*[92]
		miR-409-3p	Down	Beclin-1	L-OHP	Tan *et al.*[93]
		miR-338-3p	Up	mTOR	5-FU	Han *et al.*[94]
		miR-18a* and	Down	BTG1	L-OHP,5-FU	Yu *et al.*[95]
		miR-4802	Down	ATG7		
		miR-34a	Down	Smad4	L-OHP	Sun *et al.*[44]
Cancer stem cells		miR-141	Down	Cyclin D2	5-FU	Ye *et al.*[96]
		miR-196b-5p	Up	SOCS1, SOCS3	5-FU	Ren *et al.*[97]
		miR-450b-5p	Down	SOX2	5-FU	Jin *et al.*[98]
		miR-106a	Up	DUSP2	5-FU	Qin *et al.*[99]
		miR-125a/b	Down	ALDH1, Mcl1	PTX	Chen *et al.*[100]
EMT		miR-223	Up	FBXW7	DOX	Ding *et al.*[101]
		miR-514b-3p	Down	-	CDDP, Irinotecan	Ren *et al.*[102]
		miR-200c	Down	SUZ12	L-OHP	Tanaka *et al.*[103]
Cell cycle		miR-195	Down	CHK1 and WEE1	5-FU	Kim *et al.*[104]
		miR-520g	Down	P21	5-FU	Zhang *et al.*[105]

(Continued)

Table 2. (Continued)

Mechanisms	Reported miRNA	Alteration	Validated miRNA targets	Corresponding drugs	Ref.
Other chemoresistance-related miRNAs	miR-505	Up	RASSF8	Methotrexate	Chen *et al.*[106]
	miR-519b-3p	Up	ARID4B	Cape,5-FU, L-OHP	Luo *et al.*[107]
	miR-124	Down	SGK1	DOX	Zhu *et al.*[108]
	miR-340	Down	RLIP76	L-OHP	Zhang *et al.*[109]
	miR-134	Up	CREB1	L-OHP	Ye *et al.*[110]
	let-7d-5p	Down	Aurora B	Trifluridine	Tsunekuni *et al.*[111]
	miR-33a/ let-7e	Down	ST8SIA1	5-FU	Shan *et al.*[112]
	miR-128	Down	Galectin-3	5-FU, L-OHP	Lu *et al.*[113]
	miR-200b-3p	Down	PRDX2	L-OHP	Lv *et al.*[114]
	miR-186	Down	CPEB2	Methotrexate	Li *et al.*[115]
	miR-137	Down	YBX1	L-OHP	Guo *et al.*[116]
	miR-203	Down	SIK2	Taxol	Liu *et al.*[117]
	miR-492	Down	CD147	L-OHP	Peng *et al.*[118]

ABC, ATP binding cassette; BCL-2, B-cell lymphoma-2; CDDP, cisplatin; CRC, colorectal cancer; DOX, doxorubicin; EMT, epithelial–mesenchymal transition; 5-FU, 5-fluorouracil; IGF1R, insulin-like growth factor 1 receptor; L-OHP, oxaliplatin; miRNAs, microRNAs; MMR, mismatch repair; TS, thymidylate synthase; VCR, vincristine; XIAP, X-linked inhibitor of apoptosis protein.

Another PI3K/AKT signaling pathway upstream is RAS, which also modulates drug resistance of CRC.[128] Ras activity was found to be increased *via* the inhibition of let-7, which targeted the 3′-untranslated region of Ras proteins and enhanced 5-FU resistance of CRC.[28] In addition, the let-7 family also contributed to enhance sensitivity of metastatic colorectal cancer (mCRC) to anti-EGFR agents by post-transcriptionally downregulating KRAS.[129] Indeed, higher Let-7a levels in KRAS-mutated mCRC patients treated with salvage cetuximab plus irinotecan correlated with favorable survival outcomes.[130] Let-7b and let-7e were downregulated in HCT-116 cells (with mutated KRAS) following cetuximab treatment. All of these miRNAs were identified as potential biomarkers to predict cetuximab resistance in KRAS-mutated CRC.[131] Interestingly, miR-146b-3p and miR-486-5p were also found to be up-regulated in KRAS-mutated CRC patients compared with wild-type KRAS,[131] and KRAS mutations were considered as negative predictor of anti-EGFR therapy response in CRC,[132] suggesting that these miRNAs may serve as predictive biomarkers of response to cetuximab in CRC. A recent study showed that mCRC patients who did not benefit from cetuximab treatment exhibited higher miR-31-5p/3p expression in comparison with responders, and miR-31-5p/3p were significantly associated with time to progression (TTP) in RAS wild-type (wt-RAS) mCRC patients who received cetuximab therapy.[133] Thus miR-31-5p/3p could be used as a promisingly predictive biomarkers of response to cetuximab in wt-RAS mCRC patients. It is notable that miR-17-3p was upregulated in HCT-116 (with mutated KRAS) cells and downregulated in Caco-2 (with wild-type KRAS) cells after cetuximab treatment, suggesting that it may be used as potential predictive markers of cetuximab resistance in KRAS-mutated CRC patients.[131] One study demonstrated that miR-224 made CRC cells exhibit a poor response to 5-FU-based chemotherapy *via* the RAS/PI3K/AKT signaling pathway.[29] In addition, RAB22A, a member of the RAS oncogene family, is also involved in

Table 3. Summary of key drug resistance-related miRNAs which are identified as biomarkers (diagnostic and prognostic value) in CRC.

miRNA	Alteration	Potential values	Ref
miR-17-5p	Up	High level of miR-17-5p predicts poorer survival and poor response to chemotherapy	Fang *et al.*[23]
miR-7	Down	Low level of miR-7 predicts poorer survival	Suto *et al.*[26]
miR-204-5p	Down	Low level of miR-204-5p predicts poorer survival	Yin *et al.*[30]
miR-182	Up	diagnostic marker for CRC	Liu *et al.*[33]
miR-199a/b	Up	High level of miR-199a/b predicts poorer survival	Chen *et al.*[41]
miR-19b-3p	Up	High level of miR-19b-3p predicts poorer survival	Jiang *et al.*[43]
miR-218	Down	Low level of miR-218 predicts poorer survival and poor response to chemotherapy	Li *et al.*[52]
miR-1290	Up	High level of miR-1290 predicts poorer survival	Ye *et al.*[119]
miR-506	Down	Low level of miR-506 predicts poorer survival	Zhou *et al.*[67]
miR-10b	Up	High level of miR-10b predicts poorer survival	Nishida *et al.*[78]
miR-143	Down	diagnostic marker for CRC; Low level of miR-143 predicts poor response to chemotherapy	Qian *et al.*[83]
miR-338-3p	Up	High level of miR-338-3p predicts poorer survival	Han *et al.*[94]
miR-196b-5p	Up	diagnostic marker for CRC	Ren *et al.*[97]
miR-128	Down	Low level of miR-128 predicts poorer survival	Lu *et al.*[113]
miR-1914* /1915	Down	diagnostic marker for CRC	Hu *et al.*[120]
miR-21	Up	High level of miR-21 predicts poorer survival and poor response to chemotherapy	Kulda *et al.*[121]

CRC, colorectal cancer; miRNAs, microRNAs.

MDR of CRC. RAB22A is a direct functional target of miR-204-5p, which was downregulated in CRC tissues. Functional analyses revealed that restoring miR-204-5p expression significantly represses cell proliferation and invasion both *in vitro* and *in vivo* and enhances the sensitivity of CRC cells to 5-FU, L-OHP, and cisplatin (CDDP). Mechanistic investigations showed that restoring miR-204-5p expression inhibited colorectal cancer invasion and migration and increased CRC sensitivity to chemotherapy *via* directly targeting RAB22A.[30]

HMGA2, a substantiated activator of PI3K/AKT signaling pathway, plays a vital role in regulating cell proliferation and differentiation, and its overexpression was identified as a poor prognostic factor for colon cancer.[134] A cross-section study showed that HMGA2 expression was associated with Dukes stages and metastasis of CRC patients.[135] miR-204 is significantly downregulated in CRC, can directly target HMGA2 mRNA. miR-204/HMGA2 axis mediated the resistance of CRC cells to 5-Fu through activation of the PI3K/AKT pathway.[31] Conversely, HMGA2 can bind to the promoters of miR-194 loci. Overexpression HMGA2 attenuated miR-194 expression and promoted cell growth, migration and drug resistance, whereas restoring miR-194 expression could compromise the previously mentioned biological activities.[32]

The PI3K/AKT signaling pathway is also associated with the sialyltransferases (STs). Aberrant expression of ST6GALNAC2 has been identified to correlate to proliferative potential and invasive property of cancer *via* the PI3K/AKT pathway. It was reported that the sialylation related gene

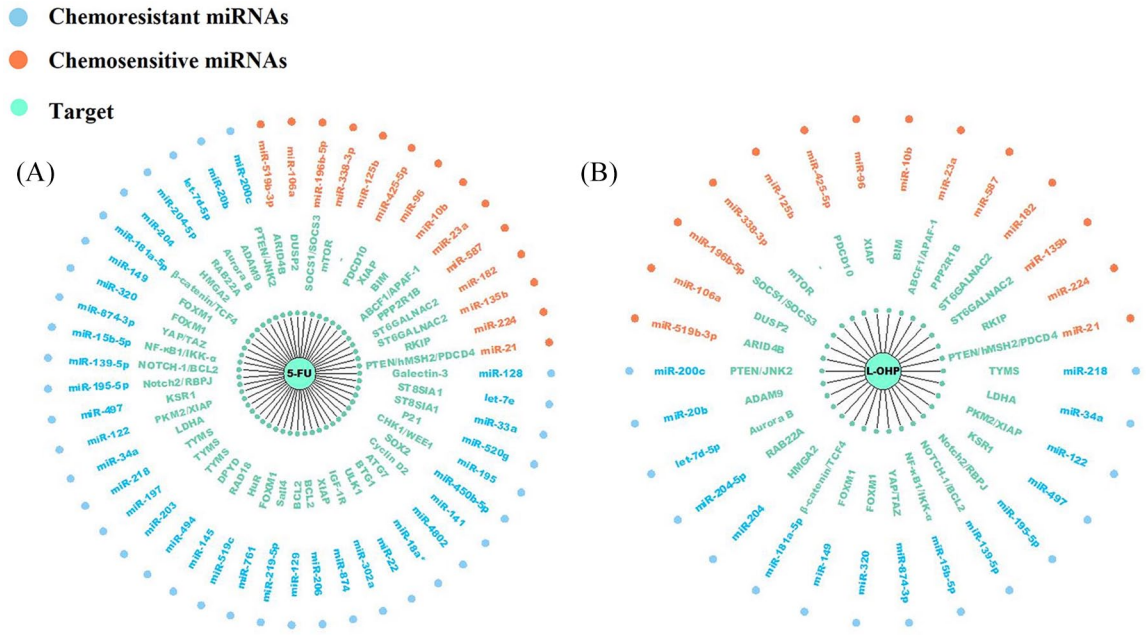

Figure 2. (A) Modulation of 5-FU chemoresensitivity by chemoresistant miRNAs and chemosensitive miRNAs in CRC; (B) Modulation of L-OHP chemoresensitivity by chemoresistant miRNAs and chemosensitive miRNAs in CRC.
CRC, colorectal cancer; 5-FU, 5-fluorouracil; L-OHP, oxaliplatin.

ST6GALNAC2 was a direct target of miR-135b and miR-182, expression of which were remarkably elevated in CRC samples and cell lines. Forced expression miR-135b or miR-182 induced the resistance of HCT-8 and LoVo cell lines to 5-FU and promoted cell proliferation *in vitro* and *in vivo*, whereas ST6GALNAC2 silencing attenuated the previously mentioned effects. Inhibition of miR-135b or miR-182 may function as potential therapy targets to enhance the chemosensitivity to 5-FU *via* activation of PI3K/AKT pathway.[33]

PPP2R1B, a regulatory subunit of the PP2A complex, was identified as a negative regulator of the PI3K/AKT signaling pathway.[136] Oncogenic miRNA, miR-587, was upregulated in 5-FU-resistant CRC patients, and its expression inversely correlated to PPP2R1B expression. Knockdown of PPP2R1B expression mediated by miR-587 leads to AKT phosphorylation, which gives rise to elevated XIAP expression and promotes 5-FU resistance. Of note, a specific and robust AKT inhibitor, MK2206 could attenuate miR-587-induced 5-FU resistance.[34]

Another negative regulator of the PI3K/AKT signaling pathway PHLPP1, is classified as a member of a phosphatase family.[137] PHLPP1 expression was found to be downregulated in CRC cells after transfecting miR-199a-5p and miR-375, which exhibited decreased expression in colon cancer cells. Of note, miR-375 directly targets PHLPP1 mRNA and degrades it, whereas miR-199-5p functions only at the translational level. Up-regulation of miR-199a-5p and miR-375 led to PHLPP1 degradation and enhanced phospho-AKT levels, resulting in significant chemoresistance of CRC cells to cetuximab treatment. Conversely, restoration of PHLPP1 expression *via* silencing of the same miRNAs was able to reduces phospho-AKT levels, thus resensitizing CRC cells to cetuximab.[35]

Wnt/β-catenin signaling pathway

Wnt/β-catenin signaling plays fundamental roles in biological processes such as tissue regeneration and morphogenesis.[138] Dysregulation of the Wnt/β-catenin pathway was identified as a central oncogenic driver in CRC *via* enhancing Wnt target genes, including Myc, cyclin D1, and so on.[139,140] These genes correlate with cell proliferation and survival, and thus might be involved in the development of CRC.[141] Emerging evidence indicated that miRNAs can affect chemotherapy resistance *via* the Wnt/β-catenin signaling

pathway.[142] The related miRNAs are summarized in the following.

miR-181a-5p expression was decreased significantly in CRC. Enhanced expression of miR-181a-5p was associated with increased sensitivity of CRC cells to 5-FU treatment. Mechanically, β-catenin and TCF4 were direct targets of miR-181a-5p. Overexpression of miR-181a-5p could regulate the chemoresistance of CRC *via* modulating the activity of Wnt/β-catenin signaling.[36]

Another downregulated miRNA in 5-FU-resistant CRC cells was miR-149. Restoration of miR-149 could sensitize 5-FU-resistant CRC cells to 5-FU by increasing 5-FU-inducing apoptosis, while miR-149 silencing exhibits the opposite effect. Mechanistic investigations revealed that Forkhead box protein M1 (FOXM1) is a target of miR-149 in 5-FU-resistant CRC cells. FOXM1 could modulate β-catenin nuclear localization and regulate the Wnt/β-catenin signaling pathway.[143] Knockdown of FOXM1 expression could mimic the effect of miR-149 overexpression on the 5-FU resistance of 5-FU-resistant CRC cells. Taken together, upregulation of miR-149 could reverse the 5-FU resistance of CRC cells *via* inhibition of Wnt/β-catenin signaling pathway by targeting FOXM1, targeting miR-149/FOXM1 signaling may be a promising therapeutic strategy for 5-FU-resistant CRC patients.[37] Interestingly, another down-regulated miRNA in colon cancer, namely miR-320, can also directly bind to FOXM1, resulting in decreased expression of Wnt/β-catenin signing pathway associated molecules, including β-catenin, c-myc, and cyclin D1. Enhanced expression of miR-320 can inhibit CRC cell proliferation, invasion and increase sensitivity of CRC to 5-Fu and L-OHP by targeting FOXM1.[38] The miR-320–FOXM1 axis may widen our horizon of knowledge about the concrete mechanisms of chemo-resistance for CRC, and the re-expression of miR-320 may provide a new therapeutic target for CRC treatment.

miR-203a-3p acts as a tumor suppressor in CRC. Ectopic expression of miR-203a-3p is critical for cell proliferation repression and chemoresistance reduction. β-catenin and GRG5, the downstream genes of Wnt/β-catenin signaling pathway, were identified as direct targets of miR-203a-3p. Overexpression of miR-203a-3p sensitized CRC cells to CDDP and PTX *via* inhibition of the Wnt/β-catenin signing pathway by targeting β-catenin and GRG5.[39] miR-203a-3p-mediated Wnt/β-catenin signaling pathway may provide new insights into the mechanisms of drug resistance, and offer potential strategies for the treatment of CRC.

Enhanced expression of miR-224 is associated with adriamycin (ADM) resistance of CRC cells. Glycogen synthase kinase-3β (GSK-3β) is a target of miR-224. GSK-3β is able to phosphorylate and degrade β-catenin, and further inhibit the Wnt/β-catenin signal pathway. Suppression of miR-224 expression up-regulated GSK-3β expression, inhibited Wnt/β-catenin signal pathway activity and survivin expression, as well as reduced ADM resistance of CRC SW480 cells.[40] GSK-3β was also identified as the direct target of miR-199a/b. Enhanced expression of miR-199a/b was detected in colorectal cancer stem cells (CCSCs) and correlated with CDDP resistance. miR-199a/b regulated Wnt/β-catenin pathway by targeting Gsk3β in CCSCs, contributing to the resistance of CDDP in CRC.[41]

Up-regulation of miR-100 and miR-125b were detected in CRC tissues and cell lines with cetuximab resistance. miR-100 and miR-125b coordinately drive cetuximab resistance by targeting five negative regulators of Wnt signaling, of which DKK1 and ZNRF3 were targets of miR-100, ZNRF3, RNF43, DKK3 and APC2 were targets of miR-125b. Targeting Wnt signaling can attenuate this mode of cetuximab resistance.[42]

TGF-β signaling pathway

Accumulating evidence has reported that the activation of the transforming growth factor (TGF)-β signaling pathway could promote tumorigenesis, including metastasis and chemoresistance.[144] As a key mediator of the TGF-β signaling pathway, SMAD4 plays a pivotal role in promoting apoptosis and suppressing tumor progression. SMAD4 deficiency is associated with poor response to chemotherapeutic drugs and worse prognosis of patients with colon cancer.[145] A study conducted by Jiang *et al.* reported that SMAD4 is a direct target of miR-19b-3p. High expression of miR-19b-3p promoted proliferation and mediated resistance to L-OHP-based chemotherapy *via* targeting SMAD4.[43] In addition, SMAD4 is also identified as a direct target of miR-34a, which expression was inversely associated with TGF-β and SMAD4 in the blood samples of CRC patients following L-OHP treatment. miR-34a mediated the resistance of CRC patients to

L-OHP by directly targeting SMAD4 through the TGF-β/SMAD4 pathway.[44]

Other signaling pathways and transcription factors

Apart from the previously mentioned cellular signaling pathways, aberrant activation or inactivation of the Hippo, NF-κB, Notch, Raf/MEK/ERK signing pathway, etc., have been reported to be implicated in chemotherapeutic resistance of CRC.[146]

The transcriptional co-activators YAP and TAZ of the Hippo signaling pathway play a fundamental role in the development and progression of CRC,[147] were identified as direct targets of miR-874-3p, which was significantly downregulated in CRC. Enhanced expression of miR-874-3p can decrease the mitochondrial potential and increase the apoptosis ratio of CRC cells following 5-FU treatment *in vitro* and attenuated the chemoresistance of CRC cells treated with 5-FU *in vivo*, whereas knockdown of miR-874-3p exhibited opposite effects. Mechanically, miR-874-3p directly targeted YAP and TAZ, leading to the downregulation of Hippo signing pathway downstream genes, including BCL2L1, CTGF and cyclin A, and further attenuating 5-FU resistance of CRC cells.[45]

miR-15b-5p is regarded as a NF-κB-dependent gene, and its decreased expression was detected in CRC tissues and cell lines. Enhanced expression of miR-15b-5p increased cellular apoptosis rate of CRC cells treated with 5-FU and sensitized CRC to 5-FU. Mechanistic investigations indicated that miR-15b-5p modulates therapeutic effects *via* influencing the activity of NF-κB signaling pathway by negatively regulating the expression of NF-κB1 and IKK-α.[46] Given this insight into the miRNA regulation of the drug-resistant phenotype, targeting miR-15b-5p might be a promising alternative for 5-FU-resistant CRC patients.

Dysregulation of Notch signaling pathway contributed to CRC progression, metastasis and inhibition of apoptosis. It was reported that enforced expression of miR-139-5p drove 5-FU sensitivity of CRC cells *via* regulating Notch signaling pathway. Mechanistic investigations revealed that miR-139-5p exerted its therapeutic effects by targeting NOTCH1 and influencing the expression of MRP-1 and BCL-2. Knockdown NOTCH-1 expression exerted an effect similar to miR-139-5p overexpression, whereas up-regulation of NOTCH-1 promoted the drug-resistant phenotype.[47] Similar results have been duplicated in other studies.[48] Therefore, miR-139-5p has the potential to enrich standard therapeutic approaches to CRC. The other two Notch signaling proteins Notch2 and RBPJ, which played key roles in CRC cell stemness and chemoresistance, and their 3′UTR possessed binding sites of miR-195-5p. Functional assays further confirmed that miR-195-5p could inhibit tumor sphere formation and increase CRC cells apoptosis following 5-FU treatment by targeting Notch2 and RBPJ.[148] miR-195-5p could serve as a promising therapeutic target for CRC treatment.

Furthermore, Raf/MEK/ERK signaling pathway has effects on induction of drug resistance as well.[149] Kinase suppressor of ras 1 (KSR1) acts as a molecular scaffold for the Raf/MEK/ERK phosphorylation cascade, binding to Raf, MEK, and ERK and further positively inducing ERK activation.[150] KSR1 was found to be a direct target of miR-497, which was downregulated in CRC tissues. Forced expression of miR-497 inhibited malignant phenotypes and increased chemosensitivity of CRC cells to 5-FU treatment *via* attenuating KSR1 protein expression and ERK activation, whereas KSR1 overexpression abrogated the previously mentioned effects.[49]

Specific mechanisms of drug resistance mediated by miRNA in CRC

Emerging studies have demonstrated that drug resistance of CRC is attributed to various mechanisms including aberrant metabolism, enhanced DNA damage repair, dysregulation of ATP-binding cassette transporters (ABC transporters) activity, resistance to apoptosis, induction of autophagy, regulating properties of cancer stem cells, promoting epithelial-mesenchymal transition (EMT), alternations of cell cycle and checkpoints and so forth. We discuss the role of miRNAs in modulating efficacy of anticancer drugs through the mentioned mechanisms in CRC as follow (Figure 3; Table 2).

Aberrant metabolism

Abnormal metabolism, such as enhanced glycolysis and reduced mitochondrial oxidative phosphorylation, is characterized as a hallmark of cancer cells.[151] Mounting evidence has shown

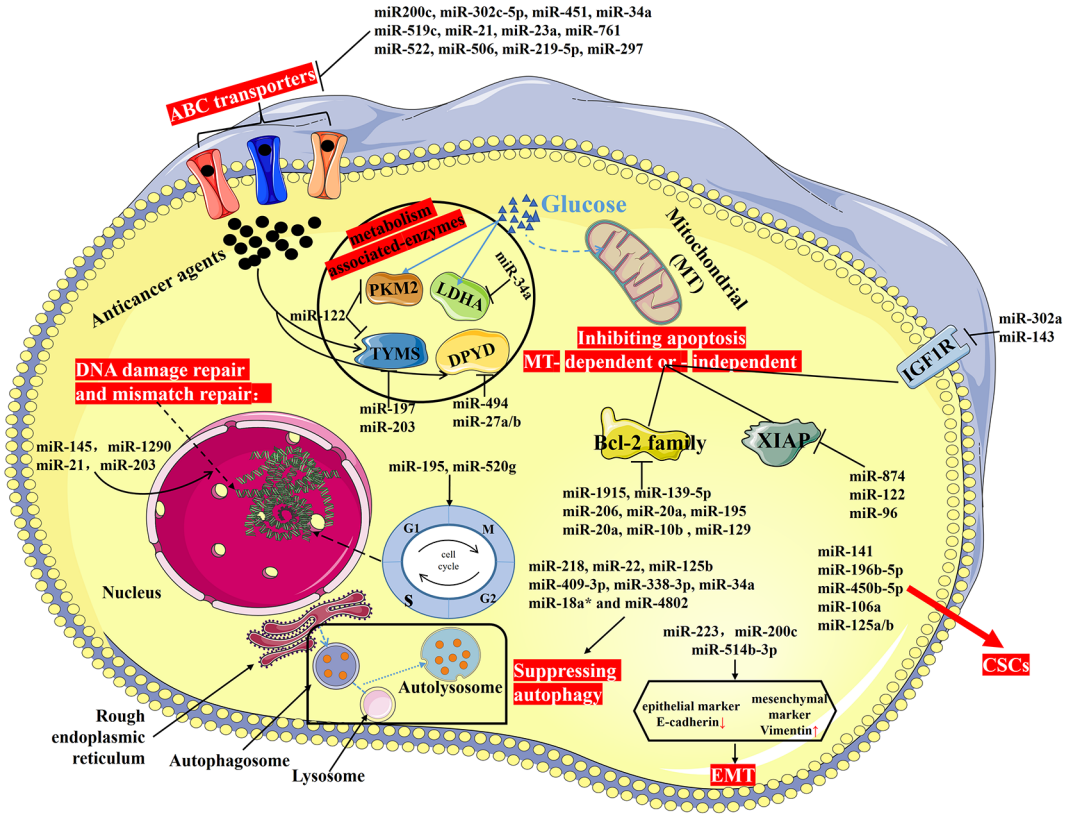

Figure 3. Drug resistance (or MDR) of CRC. Drug resistance of CRC is attributed to various mechanisms including aberrant metabolism, enhanced DNA damage repair, dysregulation of ABC transporter activity, resistance to apoptosis, induction of autophagy, regulating properties of CSCs, promoting EMT, alternations of cell cycle and checkpoints, and so forth.
ABC, ATP-binding cassette; CRC, colorectal cancer; CSCs, cancer stem cells; EMT, epithelial–mesenchymal transition; MDR, multidrug resistance.

that dysregulated cellular metabolism may also drive chemoresistance.[152]

Pyruvate kinase type M2 (PKM2) is considered to be one of key regulatory enzymes in glucose metabolism, catalyzing the final step of glycolysis and facilitating lactate production in cancer cells.[153] Luciferase reporter assay showed that the 3′UTR region of PKM2 could interact with miR122, which was downregulated in 5-FU-resistant CRC cells. miR-122 overexpression sensitized CRC cells to 5-FU *in vitro* and *in vivo* through the inhibition of PKM2.[50]

In addition, another glucose metabolism-associated enzyme – lactate dehydrogenase A (LDHA), an isoenzyme of LDH enzymes – catalyzes the conversion of pyruvate to lactate during the glycolytic process and plays a pivotal role in the growth, invasion, and metastasis of various tumors including CRC.[154] LDHA was found to be a direct target of miR-34a. Enhanced expression of miR-34a decreased the expression of LDHA through directly binding to its 3′UTR, resulting in the re-sensitization of 5-FU-resistant CRC cells to 5-FU treatment.[51]

Furthermore, it is well known that thymidylate synthase (TYMS), a critical enzyme of 5-FU metabolism, is significantly associated with the response to 5-FU-based therapy. One study has shown that overexpression of miR-122 re-sensitized 5-FU-resistant CRC cells to the drug through inhibition of TYMS expression. Of note, miR-218 was significantly downregulated in CRC tissues, and re-expression of miR-218 inhibited cell proliferation, promoted apoptosis and caused cell cycle arrest by suppressing BIRC5 expression.[52] In addition, luciferase assay and western blot analysis confirmed that miR-197 can bind

directly to TYMS and downregulate its expression. Upregulation of miR-197 increases the sensitivity of CRC cells to the cytotoxic effect of 5-FU by suppressing TYMS expression.[53] Furthermore, miR-203 can also directly bind to the site of 3′UTR of TYMS mRNA and suppress its expression both *in vitro* and *in vivo*. Cytotoxicity assay confirmed that miR-203 overexpression enhanced 5-FU chemosensitivity in CRC cells *via* regulating TYMS expression. Knockdown of TYMS expression increased 5-FU chemosensitivity, similar to the effects of miR-203 overexpression.[54] Taken together, downregulation of TYMS induced by miRNAs may provide a promising approach to overcome 5-FU resistance for CRC patients.

Apart from TYMS, dihydropyrimidine dehydrogenase (DPYD) also functions as a regulatory enzyme in the 5-FU catabolic pathway.[155] 3′UTR of DPYD could interact with miR-494, which was downregulated in 5-FU-resistant CRC cells. High miR-494 expression promoted apoptosis of CRC cells *in vitro* and repressed xenograft tumors growth *in vivo* in the presence of 5-Fu *via* directly suppressing DPYD expression, whereas upregulation of DPYD could abrogate miR-494-mediated 5-Fu sensitivity regulation.[55] In silico analysis indicated that the 3′UTR of DPYD also has two conserved recognition sites interacting with miR-27a and miR-27b. Ectopic expression of miR-27a and miR-27b could sensitize CRC cells to 5-FU by directly targeting DPYD.[156]

MiRNAs and regulation of DNA damage repair and mismatch repair

Cell-inherent DNA repair pathways could abrogate the DNA-damaging effect of cytotoxic agents. Though the effects of DNA damage repair on drug resistance is not well appreciated, certain miRNAs have been identified to play a key role in DNA damage repair-mediated drug resistance. Tumor-suppressor miR-145 enhanced re-sensitivity of CRC cells to 5-FU *in vitro* and *in vivo* by downregulating the expression of RAD18, which is a DNA damage-activated E3 ubiquitin ligase and plays an important role in DNA damage repair.[56]

The mismatch repair (MMR) system is critical for the recognition and repair of DNA base mismatches. Dysregulation expression of MMR proteins induced deficient MMR (dMMR). Interestingly, miR-1290 was positively associated with dMMR status. Human mutS homolog 2 (hMSH2), a core mismatch repair (MMR) protein, was shown to be a direct target of miR-1290. Forced expression of miR-1290 promoted the resistance of CRC cells to 5-FU by directly targeting hMSH2.[119] In addition, miR-21 also negatively regulated hMSH2 expression at transcriptional and protein level.[57] High level of miR-21 expression significantly promoted cell proliferation and reduces 5-FU-induced G2/M arrest and apoptosis *via* downregulating hMSH2 and hMSH6. Furthermore, miR-21 overexpression attenuated the therapeutic efficacy of 5-FU in xenograft tumors.[157] *In silico* analysis indicated that ataxia telangiectasia mutated (ATM) kinase – a primary mediator of the DNA damage response – was a potential target of miR-203. Upregulation of miR-203 expression is detected in L-OHP-resistant CRC cells. miR-203 silencing sensitized chemo-resistant CRC cells to L-OHP through regulating ATM protein expression.[58]

MiRNAs and regulation of ABC transporters

ATP-binding cassette (ABC) transporters) are members of P-type membrane ATPases that are involved in MDR.[158] To date, 48 ATP-binding cassettes (ABC) transporters have been identified in the human genome, subdivided into seven families (A–G). ABC transporters facilitate the efflux of excessive intracellular drugs, thus giving rise to a significant impairment of chemotherapeutic effects. Growing evidence indicates that miRNAs play a pivotal role in regulating ABC transporters, contributing to the sensitivity or resistance to anticancer drugs.

Permeability glycoprotein (P-gp), also known as ATP binding cassette subfamily B Member 1 (ABCB1), was the first identified ABC transporter that contributed to chemoresistance.[159] For example, ABCB1/P-gp expression correlated inversely with miR-200c expression, which was downregulated in MDR colorectal cancer cells [L-OHP, 5-Fu, CDDP and vincristine (VCR)]. JNK2 was shown to be a direct target of miR-200c. miR-200c overexpression downregulated the levels of ABCB1/P-gp specifically *via* the JNK2-mediated JNK signaling pathway, resulting in increased sensitivity to anticancer drugs and inhibition of metastasis *in vitro* and *in vivo*.[59] It was reported that the level of ABCB1 level was also inversely correlated with the level of miR-302c-5p level in CRC cells. Reduced miR-302c-5p expression

was detected in L-OHP-resistant CRC cells. Enhanced miR-302c-5p expression could increase the sensitivity of CRC cells to L-OHP *via* regulating ABCB1 expression.[60] In addition, miR-451 was also reported to regulate ABCB1 expression in drug-resistant CRC. miR-451 restoration significantly reduced the expression of ABCB1 and reversed drug resistance of CRC cells to irinotecan.[61]

Another ABC transporter that is significantly associated with MDR is ABCG2. It has been shown that miR-519c downregulated the expression of ABCG2 directly or indirectly *via* modulating mRNA binding protein HuR expression, causing increased sensitivity of CRC to 5-FU.[62] A recent study revealed that miR-21 remarkably elevated the expression of ABC transporter ABCC5 and the stem cell marker CD44 *via* negatively regulating programmed cell death protein 4 (PDCD4) expression (a target gene of miR-21), resulting in increased 5-FU resistance to CRC. miR-21 silencing significantly reduced the IC50 of 5-FU in CRC cells and increased the apoptosis ratio.[63] One study that focused on the role of miR-23a in chemosensitivity of microsatellite instability (MSI) CRC cells provided evidence that reduced miR-23a could increase 5-FU-induced apoptosis *via* directly targeting ABCF1.[64] In addition, miR-761 overexpression increased the sensitivity of CRC cells to 5-FU and ectopic expression of miR-761 suppressed CR cell proliferation, invasion, cell cycle, and colony formation partly *via* targeting FOXM1 expression.[65] FOXM1 silencing overcame 5-FU resistance of CRC cells through regulating ABCC10 expression.[160] In the case of miR-522, the authors showed that miR-522 significantly inhibited cell survival and doxorubicin (DOX) resistance in CRC cells by directly targeting ABCB5.[66]

Furthermore, multidrug resistance-associated protein (MRP1) is generally referred to ABCC1, playing a pivotal role in the development of MDR of CRC cells against various chemotherapeutic agents.[158] In L-OHP-resistant CRC cells, miR-506 upregulation accompanied with downregulated low MDR1/P-gp expression suppressed cell growth and elevated L-OHP-induced cell apoptosis. Mechanically, miR-506 overexpression reduced MDR1/P-gp expression in L-OHP-resistant CRC cells by inhibiting the Wnt/β-catenin signing pathway, enhancing the sensitivity of CRC cells to L-OHP.[67] Similarly, ectopic enforced miR-219-5p expression decreased the level of P-gp and MRP1 by directly regulating Sall4 expression, resulting in reduced resistance of CRC to 5-FU and L-OHP. And ectopic expression of miR-219-5p also suppressed cell proliferation, migration, invasion and G0/G1 cell cycle arrest by targeting Sall4 in CRC.[68] A recent study revealed that transfection of miR-297 mimics into L-OHP-resistant HCT116/L-OHP cells remarkably downregulated MDR-associated protein 2 (MRP2) expression, overexpression of which was related to platinum-drug resistance.[161] Ectopic expression of miR-297 sensitizes MDR CRC cells to some anti-cancer drugs by directly inhibiting MRP-2 expression at the post-transcriptional level.[69]

In addition to the previously mentioned miRNAs, miR-34a has also been proven to involve in MDR of CRC through regulating the activation of ABC transporters and anti-apoptosis pathways. miR-34a overexpression reversed the resistance of L-OHP-resistant colon cancer to L-OHP-resistant colon cancer *via* inhibition of P-gp, MRP2, BCRP, and Bcl-2 by positively targeting the 3′UTR of ornithine decarboxylase antizyme 2 (OAZ2). Augmentation of OAZ2 expression potentiated the chemosensitivity of CRC cells to L-OHP.[70]

MiRNAs and apoptosis regulating genes

BCL-2 family. Apoptosis refers to the autonomous and orderly death of cells controlled by genes in order to maintain the homeostasis of the internal environment, and resistance to apoptosis is commonly characterized as a hallmark of cancer and limits the effectiveness of anti-cancer drug treatment in CRC.[151] Drug resistance in CRC is significantly associated with dysregulation of apoptosis-related genes, of which the B-cell lymphoma-2 (BCL-2) family members, including the death antagonists (Bcl-2, Bcl-X_L, Bcl-w, Mcl-1, and A1/Bfl1), death agonists (Bax, Bak, Bad, Bcl-xS, Bid, Bik, and Hrk), and the BCL-2 homology 3 (BH3)-only (BH3-only) proteins,[162] which play important roles in inhibiting mitochondria-dependent intrinsic and extrinsic cell death pathways and in the development of drug resistance in CRC.[163] Investigations have stated that many miRNAs regulate drug resistance by targeting apoptosis-related genes, particularly those of BCL-2 family members.

Decreased expression of miR-1915 was detected in L-OHP-resistant HCT116 cells (HCT116/L-OHP), and HCT116/L-OHP overexpressed Bcl-2 mRNA and protein in comparison with their parental cells. miR-1915 directly reduced Bcl-2 expression at the posttranscriptional level through binding to its 3′-UTR. Modulation of miR-1915 expression sensitized CRC cells to L-OHP-induced apoptosis *via* targeting Bcl-2.[71] In addition, Bcl-2 is also a target of miR-139-5p, which exerted its inhibitory effects on CRC tumorigenesis, metastasis and drug sensitivity by the downregulation of its target Bcl-2. Of note, Bcl-2 overexpression reversed the inhibitory effects of miR-139-5p on progression and drug resistance in CRC cells.[72] Karaayvaz *et al.* reported that miR-129 is downregulated in CRC, and its forced expression inhibited cell proliferation, caused cell-cycle arrest, and promoted apoptosis. Importantly, up-regulated miR-129 could sensitize CRC cells to 5-FU both *in vitro* and *in vivo* through triggering the intrinsic apoptotic pathway *via* inhibiting Bcl-2. In addition to inducing apoptosis by targeting Bcl2, miR-129 can also activate the intrinsic apoptotic pathway by cleavage of caspase-9 and caspase-3.[73] Another study conducted by Meng *et al.* demonstrated that miR-206 can also target Bcl-2 to mediate 5-FU resistance, proliferation, and apoptosis in CRC.[74] In addition, inhibition of Bcl-2 has been reported to enhance CDDP-induced apoptosis *via* the mitochondrial pathway.[164] ASK1, a key mediator in the ROS-dependent cell death pathway, was identified as a target of miR-20a.[165] Knockdown of miR-20a promoted the CDDP-induced production of ROS, which subsequently augmented ASK1 activation and further increased the cellular level of phosphorylated JNK in CRC cells. Activation of JNK signaling in CRC cells promoted mitochondrial apoptosis by inhibiting the anti-apoptotic function of Bcl-2.[166] Taken together, knockdown of miR-20a reversed CDDP resistance in CRC cells through the ROS/ASK1/JNK pathway.[75]

miRNAs also regulate other members of BCL-2 family, contributing to drug resistance in CRC. In the case of miR-195, the authors demonstrated that blockage of miR-195 significantly enhanced DOX resistance in CRC cells through repression of BCL2L2 expression.[76] Huang *et al.* found that high level of miR-20a was associated with TRAIL resistance in CRC. miR-20a silencing sensitized the CRC cells to TRAIL-induced cell death, whereas miR-20a mimics attenuated the cytotoxic effect of TRAIL. Mechanically, knockdown of miR-20a reversed TRAIL resistance on account of the dysfunction of mitochondria triggered by upregulation of BID.[77] Another miRNA which confers resistance to 5-FU in CRC is oncogenic miR-10b. High level of miR-10b expression is correlated significantly with high incidence of lymphatic invasion and poor prognosis in CRC patients. BIM, a member of BH3-only proteins, was identified as a direct target of miR-10b. miR-10b modulates 5-FU resistance in CRC cells *via* directly inhibiting proapoptotic BIM.[78]

X-linked inhibitor of apoptosis protein pathway. X-linked inhibitor of apoptosis protein (XIAP), an important member of the IAP family proteins, has been found to inhibit the activities of caspase-3, -7 and -9, leading to inhibition of apoptosis.[167] Accumulating evidence suggests that XIAP is upregulated and functions as an oncogene in multiple cancers, including CRC.[168] Previous studies have shown that overexpression of XIAP promoted cell proliferation and inhibited apoptosis, as well as conferred resistance to chemotherapeutic agents in cancer cells.[169] Evidence has shown that some miRNAs were involved in the formation of CRC MDR by regulating XIAP expression.

For instance, miR-874 functions as a tumor suppressor, is downregulated in CRC tissues and cell lines, and its expression is negatively correlated with TNM stage and lymph node metastasis. Ectopic expression of miR-874 inhibited cell proliferation and colony formation, enhanced cell apoptosis and sensitized CRC cells to 5-FU *in vitro*, as well as repressed tumor growth *in vivo* through inhibition of XIAP.[79] Another study conducted by Hua *et al.* showed that miR-122 was downregulated in L-OHP-resistant CRC cells, and restoration of miR-122 can reverse L-OHP resistance in CRC by targeting XIAP.[80] Furthermore, forced expression of miR-96 accelerated cell proliferation and sensitized CRC cells to 5-FU through indirect negative regulation of expression of XIAP in a three-dimensional (3D) tumor spheroid model of CRC.[81]

The insulin-like growth factor 1 receptor pathway. The insulin-like growth factor 1 receptor (IGF1R), a transmembrane protein, plays a pivotal role in activating certain downstream signaling pathways including PI3K/AKT pathway for regulating angiogenesis and tumorigenesis.[170] Activation of IGF-1R-dependent pathways has

also been considered as a critical step that confers chemotherapeutic agents resistance to CRC.[171] In addition, miRNAs were recently reported to participate in IGF1R-mediated drug resistance in CRC.

IGF-1R is identified as a direct target of miR-302a, which was significantly downregulated in CRC cells. In addition to IGF-1R, miR-302a could target Akt and inhibit Akt signaling. Ectopic expression of miR-302a enhancing 5-FU-induced cell death and viability inhibition by downregulating IGF-1R expression and inactivating Akt signaling in CRC.[82] Similarly, miR-143 was significantly downregulated both in CRC patients' blood samples and tumor specimens, and its expression level was inversely correlated with IGF-1R expression. Importantly, miR-143 expression was remarkably associated with clinical stages and lymph node metastasis in CRC, upregulation of miR-143 inhibited cell proliferation, migration, tumor growth and angiogenesis and sensitized CRC cells to L-OHP treatment through inhibiting IGF-1R expression.[83]

Other apoptosis-related pathways. Apart from the apoptotic pathways mentioned previously, other networks also contribute to drug resistance in CRC *via* regulating apoptosis. For instance, the cytosolic protein apoptosis-activating factor-1 (APAF-1), also known as the human homolog of the *Caenorhabditis elegans* cell death protein CED-4, is required for mitochondrial-mediated apoptosis.[172] Apaf-1 oligomerizes into the apoptosome upon binding to deoxyadenosine triphosphate and cytochrome *c*, subsequently recruiting and activating cell-killing caspases.[173] Apaf-1 was found to be a target of microRNA-27a in CSCs that exhibited high level of miR-27a expression. miR-27a overexpression was strongly correlated with the resistance to TRAIL in CSCs. Knockdown of miRNA-27a rescued the expression level of Apaf-1, thus promoting the formation of the Apaf-1-caspase-9 complex and subsequently enhancing TRAIL-induced apoptosis in CSCs. In summary, miR-27a silencing has the potential to reverse the chemoresistance to TRAIL by promoting the formation of an Apaf-1-caspase-9 complex in CSCs.[84] In addition, miR-23a can also bind directly to the 3′UTR of Apaf-1 and downregulate its expression. Knockdown of miR-23a re-sensitized CRC cells to 5-FU-induced apoptosis through the Apaf-1/caspase-9 apoptotic pathway.[85] Furthermore, ectopic expression of miR-128 can also sensitize CRC cells to TRAIL-induced cytotoxicity by regulating apoptosis. Mechanistically, miR-128 can directly target sirtuin 1 (SIRT1) and suppress SIRT1 expression, which accelerated the production of reactive oxygen species (ROS) in CRC cells following TRAIL treatment. Elevated ROS expression subsequently increased death receptor 5 (DR5) expression, and thus enhanced TRAIL-induced apoptosis in CRC cells. Altogether, these results indicated that miR-128 sensitized CRC cells to TRAIL-induced apoptosis *via* targeting the SIRT1/ROS/DR5 pathway.[86]

Another apoptosis-related gene programmed cell death protein 10 (PDCD10) was identified as a direct target of miR-425-5p, which was upregulated in chemo-resistant CRC cells as compared with isogenic parental cells. Knockdown of miR-425-5p sensitized CRC cells to 5-FU and L-OHP both *in vitro* and *in vivo* through inducing apoptotic cell death by modulating PDCD10 expression level.[87]

The forkhead transcription factor Forkhead box O3a (FOXO3a) plays a critical role in initiating apoptotic programs *via* upregulating proapoptotic genes such as Bim and PUMA.[174] FOXO3a was identified as a target of miR-153. miR-153 overexpression reduced FOXO3a expression at transcriptional and protein level, inhibiting the apoptotic response to CDDP. Restoration of FOXO3a can reverse L-OHP resistance induced by miR-153 in CRC.[88] Moreover, the proapoptotic gene PUMA is also a posttranscriptional repression target of miR-503-5p. Knockdown of miR-503-5p expression could reverse L-OHP resistance of CRC by modulating PUMA expression.[89]

MiRNAs and autophagy

Autophagy promotes the survival of tumor cells under therapeutic and metabolic stress,[175] contributing to the development of acquired drug resistance.[176] Mounting evidence revealed that miRNAs could mediated drug resistance *via* regulating autophagy by targeting autophagy-related molecules.[177]

Previously, researchers found that miR-218 was downregulated in CRC cells and regulated 5-FU resistance of CRC cells by modulation of apoptosis *via* targeting BIRC5.[52] A recent study suggested that this miRNA could modulate L-OHP resistance of CRC cells *via* inhibiting

cytoprotective autophagy by directly downregulating YEATS4 expression.[90] miR-22 was another autophagy-related modulator that was downregulated in CRC. miR-22 overexpression was found to reverse 5-FU-induced chemoresistance through suppressing autophagy, as evidenced by enhancement of p62 (an autophagy marker, also known as SQSTM1) and reduced LC3-II (a hallmark protein for increased autophagy) expression. B-cell translocation gene 1 (BTG1) is identified as a direct target of miR-22 in regulating autophagy. Re-expression of BTG1 in miR-22-overexpressing CRC cells potentiated the formation of LC3-II and abrogated the effects of miR-22.[91] Augmentation of 5-FU-induced cleavage of LC3- Ⅰ into LC3-II was observed in the miR-125b mimics-transfected CRC cells, which exhibited poor response to 5-FU. In addition, xenograft tumor model with miR-125b overexpression also exhibited enhancement of cleaved LC3-II and autophagic proteins beclin-1 as well as elevated formation of autophagosomes following 5-FU treatment, indicating that miR-125b confers CRC cells to 5-FU resistance through inducing cell autophagy.[92]

The mammalian homologue of yeast autophagy-related gene 6,also known as Beclin-1, contributes to the formation of autophagosome.[178] Beclin-1 was found to be a direct target of miR-409-3p, which was significantly downregulated in CRC cells. Importantly, the miR-409-3p expression levels were negatively associated with resistance to L-OHP in CRC. miR-409-3p overexpression sensitized CRC cells to L-OHP by suppressing Beclin-1-mediated autophagy.[93]

Another autophagy marker, the mammalian target of rapamycin (mTOR) has been reported to negatively regulate autophagy and correlates with 5-FU-induced apoptosis.[179] miR-338-3p can bind to the 3′UTR of mTOR, inhibiting its expression and further activating autophagy in 5-FU-treated CRC cells. miR-338-3p-mTOR-autophagy attenuated 5-FU induced apoptosis and promoted 5-FU resistance.[94]

Of note, *Fusobacterium nucleatum* confers CRC resistance to L-OHP and 5-FU by activating the autophagy pathway, and the autophagy elements ULK1 and ATG7 participate in the *F. nucleatum*-mediated chemoresistance in CRC cells. miR-18a* and miR-4802, which were significantly downregulated in the CRC patients administrating a high amount of *F. nucleatum*, could reverse *F. nucleatum*-mediated chemoresistance by blocking *F. nucleatum*-induced autophagy activation *via* regulating the expression of autophagy elements ULK1 and ATG7 respectively.[95]

Furthermore, macroautophagy is a critical regulator of L-OHP resistance in CRC.[180] CRC patients treated with L-OHP-based combination chemotherapy exhibited downregulation of miR-34a and upregulation of TGF-β/Smad4, whereas miR-34a mimics reduced expression of LC3-II, beclin-1, SMAD4 and TGF-β. The miR-34a can target SMAD4 and suppress macroautophagy, mediating resistance to L-OHP in CRC patients following L-OHP treatment.[44]

MiRNAs and CSCs

CRC cancer stem cells (CSCs) are characterized by their ability to self-renew, proliferate indefinitely and differentiate into cancer cells, and have been reported to mediate the development of chemoresistance.[181] Studies have shown that miRNAs could modulate drug resistance by regulating the properties of CSCs.[182]

miR-141 expression was decreased in CSCs as compared with differentiated CRC cells. Cyclin D2, a member of the D-type cyclin protein family that regulates cell cycle progression, was identified as a novel target gene of miR-141 and an important regulator of self-renewal of human embryonic stem cells.[183] miR-141 affects the maintenance of stemness in CSCs *via* targeting cyclin D2, thereby enhancing 5-FU and L-OHP susceptibility in CRC.[96]

High expression of miR-196b-5p was detected in CRC patients with poor response to 5-FU treatment. Silencing miR-196b-5p represses the stem-cell-like phenotype and re-sensitizes CRC cells to 5-FU *in vitro* and *in vivo*. Mechanically, miR-196b-5p enhances stemness and chemoresistance of CRC cells to 5-FU *via* activating signal transducer and activator of transcription 3 (STAT3) signaling pathway by negatively regulating the expression of cytokine signaling 1 (SOCS1) and SOCS3.[97] Conversely, miR-450b-5p overexpression inhibited stemness and re-sensitizes CRC cells to 5-FU by targeting the transcription factor SOX2, which is essential for maintaining CSCs properties.[98]

Dual-specificity phosphatases 2 (DUSP2) suppressed CRC cell stemness and its downregulation was significantly associated with chemoresistance.[184] Dual luciferase assay revealed that DUSP2 was a direct target of miR-106a.The levels of miR-106a and DUSP2 were inversely correlated in CRC tissues. miR-106a can enhance cell stemness and resistance of CRC cells to 5-FU by negatively regulating DUSP2 expression.[99]

Furthermore, aldehyde dehydrogenase (ALDH1) A3 and Mcl1(a member of the prosurvival BCL2 family) played key roles in promoting survival of CSCs and were identified as targets of miR-125a/b, downregulation of which was responsible for chemoresistance to PTX in colon cancer cells.[185,186] miR-125a/b upregulation overcame chemoresistance in PTX-resistant colon cancer cells *in vitro* and *in vivo* by downregulating ALDH1A3 and Mcl1 expression, subsequently enhancing cell apoptosis and inhibiting cell survival and tumor growth.[100]

Epithelial-mesenchymal transition

The epithelial-mesenchymal transition (EMT) plays a critical role in cancer invasion and metastasis, and has been proved to contribute to the development of chemoresistance.[187] Ding *et al.* proposed that upregulation of miR-223 promotes the DOX resistance of CRC cells *via* regulating EMT by targeting a tumor suppressor F-box and WD repeat domain containing 7 (FBXW7), as evidenced by downregulation of the epithelial marker E-cadherin and upregulation of the mesenchymal marker Vimentin.[101] Conversely, overexpression of miR-514b-3p suppressed EMT process by upregulation of the epithelial marker(E-cadherin and CLDN-1) and downregulation of the mesenchymal marker (fibronectin-1 and vimentin) in both mRNA and protein levels, further accelerating cell death in CRC cells treated with CDDP or Irinotecan.[102]

In addition, zinc finger E-box-binding homeobox 1 (ZEB1),a transcription factor that can bind to the E-box elements of CDH1 (encoding E-cadherin), can cause EMT by downregulating the expression of E-cadherin.[188] ZEB1 was found to be a direct target of miR-200c, which was significantly downregulated in L-OHP-resistant CRC cells. miR-200c plays a role in mediating selective resistance to L-OHP in CRC cells through regulation of EMT.[103]

Regulations on cell cycle and checkpoint

CRC MDR is attributed partly to altering cell cycle and checkpoint.[189] miRNAs mediating chemoresistance in CRC by impacting cell cycle and checkpoint were also identified. miR-195 regulates chemoresistance by alleviating G2/M phase arrest induced by 5-FU partially through inhibiting the expression of check point kinase 1 (CHK1) and G2 check point kinase WEE1 in CRC. CHK1 and WEE1, known to play critical roles in cell cycle regulation, were identified as direct targets of miR-195. miR-195 silencing sensitized CRC cells to 5-FU by downregulating CHK1 and WEE1.[104] In addition, a novel p53/miR-520g/p21 signaling axis identified by Zhang *et al.* played a critical role in the response of CRC cells to chemotherapy chemotherapeutic agents including 5-FU and L-OHP. P53 inhibited miR-520g expression, whereas deletion of p53 up-regulated miR-520g expression. MiR-520g mediated drug resistance through downregulating p21 expression, a major cycle regulator that is required for 5-FU-induced apoptosis.[105] Restoration of p21 enhanced 5-FU-induced apoptosis in miR-520g-expressing CRC cells.

Other chemoresistance-related miRNAs

Besides the examples mentioned previously, a great number of miRNAs as well as their associated molecular targets have been identified (Table 2), whereas detailed mechanisms and intracellular pathways of these miRNAs in regulation of chemosensitivity in CRC remain largely unclear. Further prospective studies are warranted to explore the concrete mechanisms and related pathways by which miRNAs modulate the MDR of CRC.

Drug resistance-related miRNAs as biomarkers in CRC

Although great progress has been made in the treatment of CRC in the past decades, including colorectal resection, perioperative management, adjuvant chemotherapy, neoadjuvant chemotherapy, and radiotherapy, CRC patients still present with a poor prognosis on account of there being no effective approach for early detection and prognostic evaluation in current clinical practice. Therefore, it is imperative to identify novel biological markers for CRC patients (especially those who exhibit poor response to chemotherapy) to improve the early diagnosis rate and

develop individual therapies. Several studies have indicated that miRNAs are involved in modulating MDR and might serve as promising diagnostic or prognostic biomarkers of CRC.

For example, a variety of miRNAs that are released into the bloodstream, such as miR-182 and miR-143,[33,83] had high sensitivity and specificity for detecting CRC patients amongst cancer-free controls. In addition, Kaplan–Meier survival curves and univariate and multivariate survival analysis, as well as Cox proportional hazards risk analysis, showed that elevated expression of miR-182 was associated with poor OS in patients with CRC, indicating that miR-182 could serve as an independent and adverse prognostic biomarker for CRC patients.[33] Moreover, the plasma miR-1914* and -1915 also play a role in the diagnosis of CRC.[120]

Notably, recent studies demonstrated that exosome-derived miRNAs were identified as highly stable and noninvasive biomarkers, exhibiting great potential to detect CRC. For instance, miR-196b-5p is dramatically upregulated in the serum exosomes in CRC patients and positively correlated with T stage and M-category, indicating exosomal 196b-5p may serve as a valuable serum biomarker for the diagnosis of CRC.[97]

Kaplan–Meier analysis showed that a group of drug resistance-related miRNAs, including miR-17-5p, miR-199a/b, miR-10b, miR-21, miR-1290, miR-19b-3p, and miR-338-3p were upregulated in CRC and associated with poor prognosis,[23,41,43,78,94,119,121] while CRC patients with the low expression of miR-7, miR-218, miR-204-5p, miR-506 or miR-128 had worse outcomes.[26,30,52,67,113] In addition, multivariate analysis indicated that miR-204-5p, miR-7, miR-19b-3p and miR-10b were independent prognostic factors for CRC survival (Table 3).[26,30,43,78] Of note, miR-224 overexpression not only promotes cell proliferation, migration and invasion, but also correlates with a high risk of relapse in CRC.[190]

Since miRNAs are not prone to degradation and could be easily isolated and detected in paraffin-embedded CRC tissue using quantitative real-time PCR or *in situ* hybridization, certain drug resistance-related miRNAs are identified as promising predictors of chemotherapy response in CRC. For instance, aberrant expression of miR-17-5p,[23] miR-497,[49] miR-197,[53] miR-21,[57] miR-203,[58] miR-519c,[62] miR-218,[90] miR-22,[91] miR-450b-5p,[98] miR-143,[191] miR-519b-3p were demonstrated to be potential biomarkers to predict drug efficacy in CRC.[107] Some of them, like miR-17-5p,[23] miR-203,[58] miR-519c,[62] and miR-218[90], were proven to have potential to mediate MDR in CRC.

A growing body of studies on miRNAs shed new light on the concrete mechanisms underlying drug resistance in CRC and provide an experimental basis for the clinical development of novel and advantageous targets for reversing CRC MDR. The previously mentioned studies on the role of miRNAs in drug resistance of CRC demonstrated that some miRNAs can simultaneously regulate various MDR-related genes, such as miR-21,[126] miR-200c,[25] and miR-125b,[42] etc., could be candidates for therapeutic biomarkers of CRC patients with MDR. In addition, different miRNAs could target the same MDR-related gene, suggesting that combining a panel of miRNAs may present a promising alternative tool for overcoming MDR.

Conclusion

miRNAs have been established as a means of inducing CRC sensitivity or resistance to anticancer drugs. Identification of MDR-related miRNAs and their targets is the key to understanding the molecular mechanisms of CRC chemoresistance and to designing novel effective therapeutic targets. In addition, combining miRNAs with existing chemotherapeutic agents may be a promising therapeutic approach to maximize therapeutic effect and improve clinical outcomes in CRC patients. Moreover, it is plausible that targeting multiple MDR-associated pathways to reverse miRNAs-mediated CRC chemoresistance in future clinical practice on account of the complicated interactions among these miRNAs and target molecules.

The combination of immunotherapy and traditional therapies has shown great potential in the treatment of tumors.[192] Interestingly, miRNAs play a pivotal role in immune cell development, differentiation and regulation, as well as in innate and adaptive immune response.[193,194] Of note, a recent study reported that the miRNA-200/ZEB1 axis could not only modulate tumor cell PD-L1 expression and intratumoral immunosuppression,[195] but was also implicated in regulating drug resistance of CRC *via* induction of EMT,[103] highlighting the roles of miRNAs in modulating the

sensitivity of immunotherapy and in reversing MDR in tumors. Taken together, an miRNA-based strategy combined with traditional chemotherapy and immunotherapy has a bright prospect in prolonging the survival of CRC patients. Further prospective studies are warranted to explore this field.

However, there have been no studies on the safety and efficacy of miRNA-based treatment for CRC to date. Furthermore, several obstacles, such as variability in patient characteristics and lack of standardized methods for miRNA detection, hinder the translation of promising findings into clinical application. Further investigations are anticipated to engage in large clinical trials to explore the underlying mechanisms in CRC and to validate the therapeutic value, as well as prognostic and predictive potential, of these MDR-related miRNAs.

Conflict of interest statement

The authors declare that there is no conflict of interest.

Funding

The authors disclosed receipt of the following financial support for the research, authorship, and/or publication of this article: This study was supported in part by grant from the Scientific Foundation of Shaanxi Province (Grant number 2019ZDLSF01-02-01, 2018SF-240), grant from the State Key Laboratory of Cancer Biology (Grant number CBSKL2014Z13) and grant from the National Clinical Research Center for Digestive Diseases (Grant number 2015BAI13B07). It was not supported by any private or public company or organization.

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