

# World Journal of *Gastrointestinal Oncology*

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### REVIEW

- 942** Molecular determinants of response to 5-fluorouracil-based chemotherapy in colorectal cancer: The undisputable role of micro-ribonucleic acids  
*Sabeti Aghabozorgi A, Moradi Sarabi M, Jafarzadeh-Esfehani R, Koochakkhani S, Hassanzadeh M, Kavousipour S, Eftekhari E*
- 957** Notch signalling pathway in development of cholangiocarcinoma  
*Rauff B, Malik A, Bhatti YA, Chudhary SA, Qadri I, Rafiq S*

### ORIGINAL ARTICLE

#### Basic Study

- 975** Identification of a nine-gene prognostic signature for gastric carcinoma using integrated bioinformatics analyses  
*Wu KZ, Xu XH, Zhan CP, Li J, Jiang JL*

#### Retrospective Cohort Study

- 992** Prognostic significance of Borrmann type combined with vessel invasion status in advanced gastric cancer  
*Zhai Z, Zhu ZY, Zhang Y, Yin X, Han BL, Gao JL, Lou SH, Fang TY, Wang YM, Li CF, Yu XF, Ma Y, Xue YW*

#### Retrospective Study

- 1005** Efficacy of uncovered self-expandable metallic stent for colorectal obstruction by extracolonic malignancy  
*Ahn JS, Hong SN, Chang DK, Kim YH, Kim ER*
- 1014**  $\gamma$ -glutamyl transferase-to-platelet ratio based nomogram predicting overall survival of gallbladder carcinoma  
*Sun LJ, Guan A, Xu WY, Liu MX, Yin HH, Jin B, Xu G, Xie FH, Xu HF, Du SD, Xu YY, Zhao HT, Lu X, Sang XT, Yang HY, Mao YL*
- 1031** Clinical characteristics and outcome of primary hepatic neuroendocrine tumors after comprehensive therapy  
*Wang HH, Liu ZC, Zhang G, Li LH, Li L, Meng QB, Wang PJ, Shen DQ, Dang XW*
- 1044** Oncological outcomes and predictors of radiofrequency ablation of colorectal cancer liver metastases  
*Wang CZ, Yan GX, Xin H, Liu ZY*

#### Observational Study

- 1056** Methylation changes at the GNAS imprinted locus in pancreatic cystic neoplasms are important for the diagnosis of malignant cysts  
*Faia S, Duarte M, Pereira L, Chaves P, Cravo M, Dias Pereira A, Albuquerque C*

**CASE REPORT**

- 1065** Response of human epidermal growth factor receptor 2-positive colorectal cancer to lapatinib monotherapy: A case report

*Guan JL, Liu JH, Wang Q, Cong YW, Chen YX, Huang KF, Huang ML, Huang L*

- 1073** Colorectal cancer metastatic to the breast: A case report

*Taccogna S, Gozzi E, Rossi L, Caruso D, Conte D, Trenta P, Leoni V, Tomao S, Raimondi L, Angelini F*

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## Molecular determinants of response to 5-fluorouracil-based chemotherapy in colorectal cancer: The undisputable role of micro-ribonucleic acids

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### Abstract

5-fluorouracil (5-FU)-based chemotherapy is the main pharmacological therapy for advanced colorectal cancer (CRC). Despite significant progress in the treatment of CRC during the last decades, 5-FU drug resistance remains the most important cause of failure in CRC therapy. Resistance to 5-FU is a complex and multistep process. Different mechanisms including microsatellite instability, increased expression level of key enzyme thymidylate synthase and its polymorphism, increased level of 5-FU-activating enzymes and mutation of *TP53* are proposed as the main determinants of resistance to 5-FU in CRC cells. Recently, micro-ribonucleic acids (miRNA) and their alterations were found to have a crucial role in 5-FU resistance. In this regard, the miRNA-mediated mechanisms of 5-FU drug resistance reside among the new fields of pharmacogenetics of CRC drug response that has not been completely discovered. Identification of the biological markers that are related to response to 5-FU-based chemotherapy is an emerging field of precision medicine. This approach will have an important role in defining those patients who are most likely to benefit from 5-FU-based chemotherapy in the future. Thereby, the identification of 5-FU drug resistance mechanisms is an essential step to predict and eventually overcome resistance. In the present

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comprehensive review, we will summarize the latest knowledge regarding the molecular determinants of response to 5-FU-based chemotherapy in CRC by emphasizing the role of miRNAs.

**Key Words:** 5-fluorouracil; Colorectal cancer; Chemotherapy resistance, Thymidylate synthase; Microsatellite instability; Micro-ribonucleic acid; TP53

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**Core Tip:** Resistance to the main chemotherapy drug, 5-fluorouracil (5-FU), is an important cause of failure in clinical colorectal cancer therapy. Microsatellite instability, increased activity and expression level of thymidylate synthase and dihydropyridine dehydrogenase, mutation of *TP53* as well as micro-ribonucleic acids alterations are among the main molecular determinants of response to 5-FU-based chemotherapy in colorectal cancer. The identification of potential molecular determinants of response to 5-FU could be an important clinical tool for developing treatment strategies and selecting colorectal cancer patients who are most likely to benefit from 5-FU chemotherapy.

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## INTRODUCTION

Colorectal cancer (CRC) is the third most common malignancy and the second leading cause of cancer related-death globally<sup>[1,2]</sup>. Surgical procedures are the primary treatment choice for CRC, and other strategies such as chemotherapy are also used as complementary therapy to decrease the risk of local recurrences and to increase quality of life for patients afflicted with metastatic CRC (mCRC). 5-fluorouracil (5-FU), leucovorin, capecitabine, oxaliplatin and irinotecan chemotherapy drugs are the standard neoadjuvant and adjunctive therapeutic options<sup>[3]</sup>. 5-FU is the main component in most of the gastrointestinal malignancies chemotherapy regimens<sup>[4,5]</sup>. Although combined treatment approaches have contributed to the current improvements in response rates, drug resistance and tumor recurrence occur in most colon cancer patients<sup>[6,7]</sup>.

A great proportion of clinical data highlights the need for addressing the interindividual differences in 5-FU-based chemotherapy responses. Different mechanisms including increased expression of the target thymidylate synthase (TS) and a decreased level of 5-FU-activating enzymes are the cause for resistance of CRC cells to the cytotoxic effect of 5-FU<sup>[8,9]</sup>. On the other hand, micro RNAs (miRNAs) and their alterations play a crucial role in cancer initiation, progression and drug resistance<sup>[10,11]</sup>. The miRNA-mediated mechanisms of drug resistance reside among the new fields of pharmacogenetics of cancer, yet they have not been discovered thoroughly<sup>[10]</sup>. Therefore, investigating the involvement of miRNAs in anticancer drug resistance is important in overcoming the barriers in human cancer therapy applications. In this review, we summarized the latest knowledge regarding the molecular determinants of response to 5-FU-based chemotherapy in CRC with more emphasis on the role of miRNAs.

## FLUOROURACIL-BASED CHEMOTHERAPY AND CRC

Cytotoxic chemotherapy has long been used as the backbone of treatment for CRC patients and evolved significantly over the last decades. 5-FU-based chemotherapy is a primary chemotherapeutic option for advanced CRC. Although the response rate to 5-FU as a single antitumor medicine is typically below 20%, there are interindividual

differences regarding the clinical effectiveness of 5-FU-based chemotherapy<sup>[12,13]</sup>. 5-FU is a synthetic pyrimidine antagonist (uracil analog) and belongs to the group of anticancer medicine known as antimetabolites<sup>[14,15]</sup>.

Adequate 5-FU transformation to 5-fluorouridine-5'-monophosphate fluorouridine monophosphate is necessary for its function<sup>[16]</sup>. Nevertheless, 5-FU is converted intracellularly to several other active metabolites. Each of them has a distinctive role in cytotoxic effects. These metabolites include (1) 5-fluorodeoxyuridine-5'-monophosphate fluorodeoxyuridine monophosphate, which interferes with TS, a key enzyme in the creation of the DNA nucleotide deoxythymidine-5 monophosphate deoxythymidine monophosphate, in the ternary complex; (2) 5-fluorodeoxyuridine-5'-triphosphate fluorodeoxyuridine triphosphate, which acts as a substrate for DNA polymerases and is incorporated into DNA in place of deoxythymidine-5 triphosphate deoxythymidine triphosphate and inhibits DNA elongation thus leading to DNA fragmentation; and (3) 5-fluorouridine-5 triphosphate fluorouridine triphosphate, an eligible substrate for RNA polymerases, which is integrated into RNA instead of uridine triphosphate. These active metabolites disrupt RNA synthesis, making single and double-strand DNA breaks and inhibit TS action, resulting in cellular apoptosis (Figures 1-3)<sup>[16-19]</sup>.

## RESISTANCE TO 5-FU

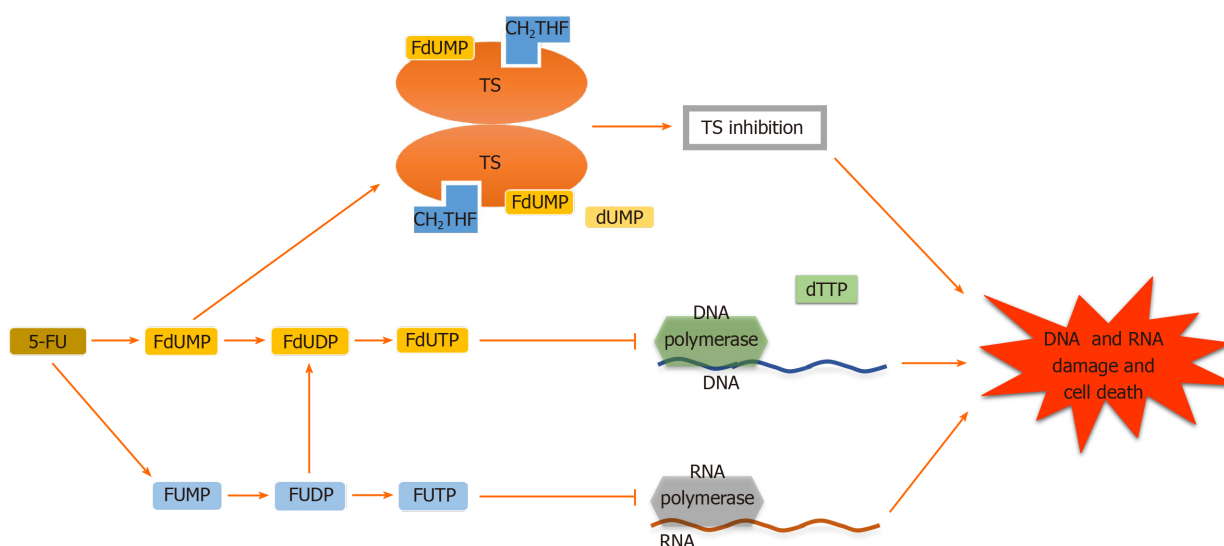
Malignant tumors may show either intrinsic or acquired resistance that requires special lines of treatment. Innate resistance is generally attributed to the capacity of tumoral cells to escape from drug effects spontaneously during the early phase of drug administration<sup>[23]</sup>. Acquired resistance has different mechanisms dedicated to specific cytotoxic and targeted therapy. However, different mechanisms of drug resistance interact with each other, and acquired resistance to one drug may result in resistance to other drugs. This phenomenon is known as multidrug resistance<sup>[23,24]</sup>. Different molecular mechanisms are involved in drug resistance. Decreased drug delivery rates to the cancerous cells through excessive efflux, reduced influx, the increment of drug inactivation, mutation of the drug target genes, defective drug transportation and overexpression of p170 (protein of multidrug resistance) are the main mechanisms for drug resistance. Moreover, alterations in the enzyme activity involved in the metabolism of drugs are considered the other main pathways of drug resistance during cancer management<sup>[23,24]</sup>.

One of the greatest challenges for CRC management is drug resistance to 5-FU that can be intrinsic or acquired during treatment and is believed to occur in nearly half of patients with metastatic cancer<sup>[25]</sup>. Identification of the biological rules that are related to 5-FU-based chemotherapy response is an emerging field of precision medicine. This approach will have an important role in defining those patients who are most likely to benefit from 5-FU-based chemotherapy in the future. Thereby, comprehending the mechanisms by which tumors become resistant to 5-FU is a prerequisite for predicting or overcoming resistance.

## MIRNAS FUNCTION IN CANCER PROGRESSION AND 5-FU DRUG RESISTANCE IN CRC

miRNAs are short RNA molecules with various regulatory effects. These small RNA molecules are transcribed from DNA sequences within exons or introns. miRNA genes transcribed by RNA polymerase undergo a maturation process by different enzymes before gaining their ability to perform their action<sup>[25,26]</sup>.

During cancer, miRNAs may become dysregulated<sup>[25-27]</sup>. In some cancers including leukemia, some DNA chromosomal regions become deleted, and therefore specific miRNAs in these locations may be lost. A decrease or complete loss of specific miRNA expression in cancers may upregulate the expression of oncogenes<sup>[25]</sup>. Also, the upregulation of specific transcription factors may result in the upregulation of oncogenic miRNAs and therefore dysregulate further cellular pathways<sup>[25]</sup>. Despite the role of miRNAs in the development and progression of cancers, these small RNA molecules are also important in the development of chemotherapy resistance. Each chemotherapy drug performs its action from a specific cellular pathway. For example, 5-FU induces apoptosis and cell cycle arrest as the main antitumor action<sup>[28]</sup>. However, overexpressing miR-21 can induce 5-FU chemoresistance through inhibition of



**Figure 1 Different mechanisms of 5-fluorouracil action.** 5-Fluorouracil (5-FU) and its derivative active metabolites exert their antitumor function at the levels of enzyme thymidylate synthase, DNA and RNA, leading to DNA and RNA damage and cell death. TS: Thymidylate synthase; FdUMP: Fluorodeoxyuridine' monophosphate; FdUDP: Fluorodeoxyuridine diphosphate; FdUTP: Fluorodeoxyuridine triphosphate; FUMP: Fluorouridine monophosphate; FUDP: Fluorouridine diphosphate; FUTP: Fluorouridine triphosphate; CH<sub>2</sub>THF: 5,10-methylenetetrahydrofolate; dTTP: Deoxythymidine triphosphate; dUMP: Deoxyuridine monophosphate.

apoptosis and cell cycle arrest in CRC cells<sup>[28,29]</sup>. miR-10b can also induce 5-FU resistance by downregulating proapoptotic proteins<sup>[28-30]</sup>.

Various studies evaluated the expression of different miRNAs in CRC tissue and discussed their effect on 5-FU response. Each of these miRNAs summarized in [Table 1](#) has their unique targets that affect specific cellular functions in CRC cells including apoptosis, proliferation, colony formation or metastasis as well as resistance to 5-FU<sup>[31-35]</sup>.

In the following sections, we reviewed the latest and most important molecular mechanisms in 5-FU resistance including microsatellite instability (MSI), altered expression of TS and dihydropyrimidine dehydrogenase (DPD) enzymes and loss of p53, along with the roles of related miRNAs.

## MICROSATELLITE INSTABILITY AND RESISTANCE TO 5-FU

MSI is an inherent mechanism of resistance to 5-FU. Microsatellites or simple sequence repeats are tracts of 15-30 repeated DNA units composed of 1-6 nucleotides distributed among all DNA regions (coding and noncoding). Instability of microsatellites result from sporadic or germline mutations in DNA mismatch repair (MMR) machinery genes including *PMS1*, *PMS6*, *MSH2*, *MSH6*, *MGMT* and *MLH1*, which are responsible for correcting errors occurring during DNA replication<sup>[36-38]</sup>.

About 10%-15% of all CRCs and more than 90% of cases of hereditary nonpolyposis colon cancer show levels of DNA MMR deficiencies (dMMR). MMR mutant genes are responsible for aberrant scanning and recognizing errors during DNA replication that lead to aberrant insertion or deletion of repeated units in microsatellites<sup>[24]</sup>. Loss of detection of mismatched and unpaired bases in cancerous cells make DNA damage and apoptosis caused by 5-FU tolerable, leading to 5-FU resistance<sup>[23]</sup>. Meyers *et al.*<sup>[39]</sup> demonstrated that restoring MMR efficiency through inserting a corrected clone of the *hMLH1* gene in MMR deficient cell lines, gave rise to an increased response to 5-FU treatment, suggesting that MMR-deficient cells are more resistant to 5-FU. Nonetheless, some conflicting results indicated that the MSI phenotype correlated with considerable survival of patients who benefit from adjuvant 5-FU-based chemotherapy. The finding can be explained by the fact that MSI-positive tumors may have intrinsic biological characteristics such as wild-type tumor suppressor p53, which aids 5-FU-mediated cytotoxicity in contrast to MSI-negative tumors. When wild-type p53 in MSI-positive tumors is compared to MSI-negative (TP53-mutant) tumors, it highlights the MSI phenotype influence<sup>[20]</sup>.

The role of different miRNAs targeting the MMR system is summarized in [Table 1](#).



**Table 1 Summary of studies evaluating the association of different micro-ribonucleic acids with 5-fluorouracil sensitivity or resistance in colorectal cancer**

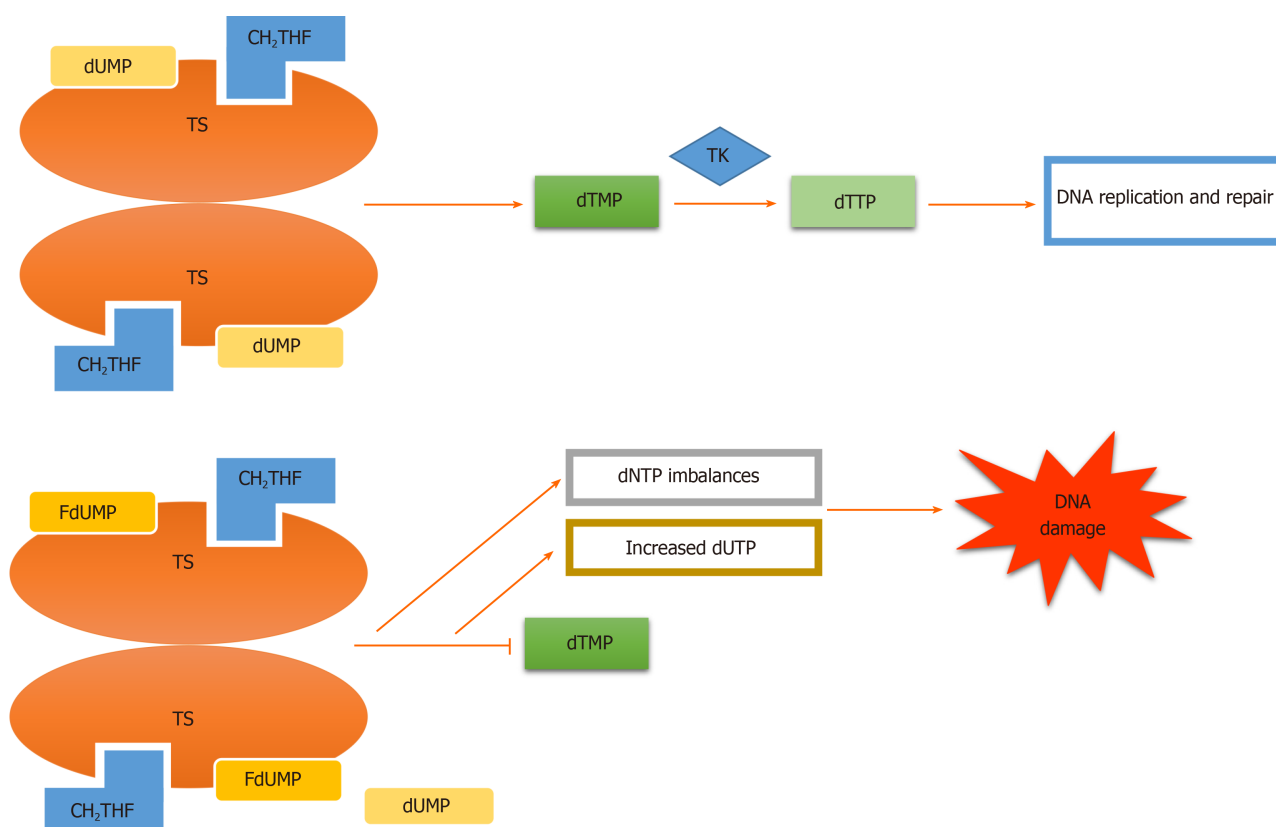
Ref.	miRNA	CRC source	miRNA target	miRNA effect on 5-FU treatment	miRNA-related pathways (KEGG Identifier) <sup>[89]</sup>	Other findings
Zhang <i>et al</i> <sup>[82]</sup>	miR-24	HCT116, RKO, SW480, and SW48 cell lines	Downregulation of RNA binding protein DND1 expression	Overexpression enhanced the chemosensitivity of SW48 cell lines	Fatty acid biosynthesis (00061). Proteoglycans in cancer (05205). Cell cycle (04110). Glycosaminoglycan biosynthesis-keratan sulfate (00533). Pancreatic cancer (05212)	miR-24 acted as a tumor suppressor
Zhang <i>et al</i> <sup>[83]</sup>	miR-361	HCT116 and HT29	Forkhead box M1 (FOXO1)	Overexpression increased chemosensitivity <i>via</i> modulation of FOXO1-ABCC5/10	Adherens junction (04520). Proteoglycans in cancer (05205). Protein processing in the endoplasmic reticulum (04141). miRNAs in cancer (05206). ECM-receptor interaction (04512)	ATP binding cassette subfamily C members 5 and 10 (ABCC5/10) were the downstream effectors of miR-361
Xu <i>et al</i> <sup>[84]</sup>	miR-375-3p	Tissue and cells	YAP1 and SP1	Overexpression enhanced the chemosensitivity	Hippo signaling pathway (04390). Lysine degradation (00310). Protein processing in the endoplasmic reticulum (04141). Proteoglycans in cancer (05205). Viral carcinogenesis (05203)	Low miR-375 expression was strongly correlated with poor overall survival in CRC patients
Lv <i>et al</i> <sup>[85]</sup>	miR-133b	Tissue and cells	H3K79me2	Overexpression enhanced the chemosensitivity and reduced CRC stemness	Sulfur relay system (04122). ECM-receptor interaction (04512)	miR-133b overexpression suppressed DOT1L-mediated H3K79me2 modification of stem cell genes
Zhao <i>et al</i> <sup>[41]</sup>	miR-552	5-FU-resistant tissues and cells	SMAD2 cascade	Overexpression decreased chemoresistance and miR-552 inhibition led to increased chemoresistance	Fatty acid degradation (00071). Fatty acid metabolism (01212). Fatty acid elongation (00062). Biosynthesis of unsaturated fatty acids (01040). TGF-beta signaling pathway (04350)	Expression of miR-552 downregulated in 5-FU-resistant tissues and cells that were regulated by dMMR
Liu <i>et al</i> <sup>[88]</sup>	miR-543	HCT8/FU	Phosphatase and tensin homolog/ PI3K/ protein kinase B (PTEN/PI3K/ AKT)	Downregulation enhanced chemosensitivity	TGF-beta signaling pathway (04350). Signaling pathways regulating pluripotency of stem cells (04550). FoxO signaling pathway (04068). Transcriptional misregulation in cancer (05202). Hippo signaling pathway (04390)	miR-543 enhanced chemoresistance by downregulating expression of PTEN, which negatively regulated AKT activation
Zhao <i>et al</i> <sup>[89]</sup>	miR-1260b	HCT116	Cell death 4 was a direct target of miR-1260b inhibitor	Inhibition of miR-1260b enhanced chemosensitivity	Wnt signaling pathway (04310). Hippo signaling pathway (04390). Central carbon metabolism in cancer (05230). Adherens junction (04520).Lysine degradation (00310)	miR-1260b inhibitor reduced proliferation and increased apoptosis while downregulating cell death 4, phosphorylated-Akt, and phosphorylated-extracellular-signal-regulated kinase (p-ERK) expression
Guo <i>et al</i> <sup>[90]</sup>	miR-191	Beta-elemene on colorectal carcinoma HCT116 and HT29	Expression of kinases, including Wnt3a and $\beta$ -catenin	Downregulation of miR-191 improved chemoresistance	Colorectal cancer (05210). Lysine degradation (00310). Steroid biosynthesis (00100). Hippo signaling pathway (04390). Transcriptional misregulation in cancer (05202)	Beta-elemene downregulated miR-191 and thereby inhibited the Wnt/ $\beta$ -catenin pathway
Cao <i>et al</i> <sup>[31]</sup>	miR-761	HT29	FOXO1	Overexpression increased chemosensitivity	Glycosphingolipid biosynthesis. Lacto and neolacto series (00601). Mucin Type O-Glycan biosynthesis (00512). Biosynthesis of unsaturated fatty acids (01040)	MiR-761 expression negatively associated with FOXO1 expression and elevated FOXO1 expression suppressed cell proliferation, colony formation and invasion
Kong <i>et al</i> <sup>[91]</sup>	miR-195	5-FU-resistant HCT116 and SW480	PI3K/ AKT and NF- $\kappa$ B pathways	Overexpression enhanced chemosensitivity	Viral carcinogenesis (05203). Hippo signaling pathway (04390). Proteoglycans in cancer (05205). Adherens junction (04520). Pathways in cancer (05200). Fatty acid degradation (00071)	Schizandrin A (SchA) sensitized 5-FU-resistant cells by upregulating miR-195, which inhibited PI3K/ AKT and NF- $\kappa$ B pathways

Que <i>et al</i> <sup>[92]</sup>	miR-874-3p	Tissue and cells	Transcriptional co-activators YAP and TAZ of the Hippo signaling pathway	Overexpression enhanced chemosensitivity		miR-874-3p indirectly inactivated TEAD transcription
Liu <i>et al</i> <sup>[79]</sup>	miR-135b and miR-182	5-FU resistant Cell lines	ST6GALNAC2 <i>via</i> PI3K/AKT pathway	Overexpression of these two miRNAs increased drug resistance	miR-135b: Hippo signaling pathway (04390). Thyroid hormone signaling pathway (04919). Steroid hormone biosynthesis (00140). Signaling pathways regulating pluripotency of stem cells (04550) cGMP-PKG signaling pathway (04022) miR-182. Fatty acid biosynthesis (00061). Viral carcinogenesis (05203). Adherens junction (04520). Cell cycle (04110). Pancreatic cancer (05212)	miR-135b and miR-182 overexpression were seen in 5-FU resistance cell lines
Zhao <i>et al</i> <sup>[32]</sup>	miR-15b-5p	Tissue and cells	NF-κB pathway and XIAP	Overexpression decreased chemoresistance	Fatty acid biosynthesis (00061). Fatty acid metabolism (01212). Viral carcinogenesis (05203). Hippo signaling pathway (04390). Adherens junction (04520)	miR-15b mediated apoptosis regulation by negative regulation of NF-κB1 and kinase complexes IKK-α and also targeting anti-apoptosis protein XIAP
Ye <i>et al</i> <sup>[40]</sup>	miR-1290	Tissue and cells	hMSH2	Inhibition decreased chemoresistance	Proteoglycans in cancer (05205). Fatty acid degradation (00071). ErbB signaling pathway (04012). Signaling pathways regulating pluripotency of stem cells (04550). Estrogen signaling pathway (04915)	miR-1290 was positively correlated with dMMR status and predicted poor prognosis in stage II and III colon cancer patients who received 5-FU
Ren <i>et al</i> <sup>[34]</sup>	miR-196b-5p	Tissue and cells	SOCS1 and SOCS3 of STAT3 signaling pathway	Downregulation increased chemosensitivity and ectopic expression yielded the opposite effect	Adherens junction (04520). TGF-beta signaling pathway (04350). Proteoglycans in cancer (05205). Hippo signaling pathway (04390). Glycosaminoglycan biosynthesis. Keratan sulfate (00533)	Silencing miR-196b-5p suppressed spheroids formation ability and expression of stem cell factors and enhanced the apoptosis induced by 5-FU. Overexpression of this microRNA correlated with poor survival
Xu <i>et al</i> <sup>[60]</sup>	miR-330	Tissues and cell	TYMS	Ectopic expression decreased cell proliferation and enhanced chemosensitivity	Adherens junction (hsa04520). ECM-receptor interaction (04512). Thyroid hormone signaling pathway (04919). Proteoglycans in cancer (05205). Hippo signaling pathway (04390)	miR-330 affected thymidylate synthase (TYMS) in the cell apoptosis pathway
Yu <i>et al</i> <sup>[34]</sup>	miR-125b	Tissues and cell	CXCL12/CXCR4 and Wnt/β-catenin signaling	Expression interfered with chemoresistance	Fatty acid biosynthesis (00061). Fatty acid metabolism (01212). Hippo signaling pathway (04390). Other types of O-glycan biosynthesis (00514). Lysine degradation (00310)	Overexpression of miR-125b triggered epidermal mesenchymal transition and invasion
Jiang <i>et al</i> <sup>[93]</sup>	miR-577	5-FU resistant SW480 cells	Heat shock protein 27 (HSP27)	Ectopic expression enhanced chemosensitivity	Lysine degradation (00310). Mucin Type O-Glycan biosynthesis (00512). Viral carcinogenesis (05203). p53 signaling pathway (04115). Colorectal cancer (05210)	Restoration of miR-577 suppressed proliferation and induced a G0/G1 cell cycle arrest
Fu <i>et al</i> <sup>[94]</sup>	miR-20b	5-FU-sensitive (HCT116) and -resistant (HCT116-R)	ADAM9/EGFR	Expression reduced chemoresistance and induced apoptosis	Prolactin signaling pathway (04917). TGF-beta signaling pathway (04350). FoxO signaling pathway (04068). Pancreatic cancer (05212). Bladder cancer (05219)	miR-20b expressed at lower levels in the 5-FU resistant tissues
Liu <i>et al</i> <sup>[95]</sup>	miR302a	HCT116 and HT29	Insulin-like growth factor1 receptor (IGF1R)	Expression induced chemosensitivity	Lysine degradation (00310). Wnt signaling pathway (04310). Proteoglycans in cancer (05205). Signaling pathways regulating pluripotency of stem cells (04550). Transcriptional misregulation in cancer (05202)	miR302a enhanced 5FUinduced cell death
Dong <i>et al</i> <sup>[96]</sup>	miR-429	Tissues and cells	-	Decreased expression correlated with better response	Fatty acid elongation (00062). Fatty acid degradation (00071). Adherens junction (04520). Fatty acid metabolism (01212). Ras signaling pathway (04014)	An increase in miR-429 level was associated with tumor size, metastasis, lymph node invasion and TNM stage
Liu <i>et al</i> <sup>[35]</sup>	miR-149	5-FU-resistant CRC cells (HCT-	FOXMI	Re-expression enhanced chemosensitivity	RNA transport (03013). Spliceosome (03040). Gap junction (04540). Sulfur relay system (04122). Thyroid hormone synthesis (04918)	miR-149 enhanced 5-FU sensitivity by increasing apoptosis

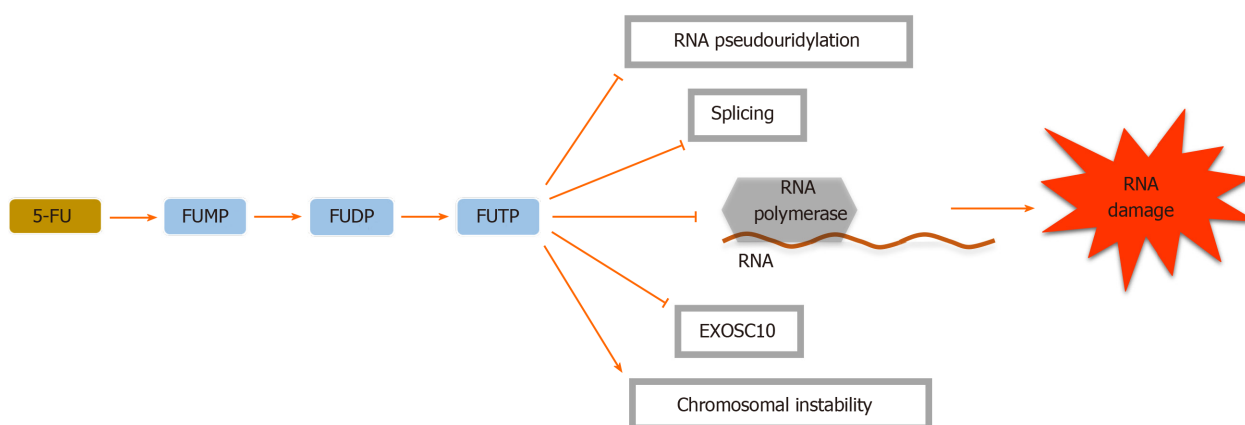
		8/5-FU and LoVo/5-FU)				
Han <i>et al</i> <sup>[97]</sup>	miR-874	Tissues and cell line	XIAP	Re-expression enhanced chemosensitivity, inhibited proliferation and enhanced apoptosis	Tyrosine metabolism (00350). Thyroid hormone signaling pathway (04919). Glycosphingolipid biosynthesis. Globo series (00603). Thyroid cancer (05216). Glycosphingolipid biosynthesis. ganglio series (00604)	miR-874 expression negatively correlated with TNM stage and lymph node metastasis
Liu <i>et al</i> <sup>[98]</sup>	miR-139-5p	HCT-8/5-FU and HCT-116/5-FU	NOTCH-1 and MDR-associated genes	Ectopic expression enhanced chemosensitivity and induced apoptosis	Hippo signaling pathway (04390). Neurotrophin signaling pathway (04722). Glioma (05214). Prostate cancer (05215). Estrogen signaling pathway (04915)	Upregulation of NOTCH-1 repealed miR-139-5p-mediated sensitization to 5-FU
Wu <i>et al</i> <sup>[99]</sup>	miR-204	HCT116 and SW480	High mobility group protein A2	Overexpression decreased chemoresistance	Steroid biosynthesis (00100). Estrogen signaling pathway (04915). ECM-receptor interaction (04512). Metabolism of xenobiotics by cytochrome P450 (00980). Apoptosis (04210)	miR-204 took action by activation of high mobility group protein A2 and the PI3K/AKT pathway
Li <i>et al</i> <sup>[61]</sup>	miR-218	HCT116 and HT29 cells	Thymidylate synthase (TS)	Overexpression increased chemosensitivity	Fatty acid biosynthesis (00061). Proteoglycans in cancer (05205). Viral carcinogenesis (05203). Pathways in cancer (05200). p53 signaling pathway (04115)	miR-218 suppressed BIRC5 and TS and promoted apoptosis
Zhang <i>et al</i> <sup>[81]</sup>	miR-587	Tissues and cell	PPP2R1B	Inhibition decreased chemoresistance	GABAergic synapse (04727). Valine, leucine and isoleucine degradation (00280). TGF-beta signaling pathway (04350). Lysine degradation (00310). Signaling pathways regulating pluripotency of stem cells (04550)	miR-587 inhibited AKT activation
Amankwatia <i>et al</i> <sup>[80]</sup>	miR-224	isogenic KRAS WT and mutant HCT116 cells	ERK and AKT	Decreased expression increased chemosensitivity	Lysine degradation (hsa00310). Fatty acid metabolism (01212). Glioma (05214). Biosynthesis of unsaturated fatty acids (01040). Fatty acid elongation (00062)	miR-224 target genes altered cell proliferation and invasion as well as epithelial-mesenchymal transition
Zhang <i>et al</i> <sup>[75]</sup>	miR-520g-3p	Tissues and cell	p21	Inhibition of miR-520g in p53 negative cells increased chemosensitivity.	TGF-beta signaling pathway (04350). Folate biosynthesis (00790). Transcriptional misregulation in cancer (05202). Signaling pathways regulating pluripotency of stem cells (04550)	p53 suppressed the miR-520g expression
Kim <i>et al</i> <sup>[74]</sup>	miR-96	Tissues and cell	XIAP and UBE2N	Expression modulated chemosensitivity and promoted apoptosis	Adherens junction (04520). ECM-receptor interaction (04512). Prostate cancer (05215). Viral carcinogenesis (05203). Protein processing in the endoplasmic reticulum (04141)	Following 5-FU exposure, the expression of the antiapoptotic regulator (XIAP) and p53 stability regulator (UBE2N) decreased
Li <i>et al</i> <sup>[59]</sup>	miR-203	5-FU-resistant cell line LoVo/5-Fu	Thymidylate synthase (TYMS)	Inhibition of expression increased chemoresistance and the overexpression increased chemosensitivity	Sulfur metabolism (00920). MAPK signaling pathway (04010). Thyroid hormone signaling pathway (04919)	miR-203 increased the inhibitory effect of 5-FU on tumor growth and suppressed TYMS protein levels
Boni <i>et al</i> <sup>[58]</sup>	miR-192 and miR-215	Tissue and cells	TYMS	The expression did not affect chemoresistance but overexpression reduced cell proliferation	miR-192: Folate biosynthesis (00790). Wnt signaling pathway (04310). Steroid biosynthesis (00100). Lysine degradation (00310). Signaling pathways regulating pluripotency of stem cells (04550). miR-215: Folate biosynthesis (00790). Estrogen signaling pathway (04915). One carbon pool by folate (00670)	Ectopic expression of these miRNAs was a strong predictor of 5-FU response. The expression did not affect chemoresistance but overexpression reduced cell proliferation

miRNA: Micro-ribonucleic acid; 5-FU: 5-fluorouracil; CRC: Colorectal cancer; TS: Thymidylate synthase; TK: Thymidylate kinase; MMR: Mismatch repair; MDR: Multidrug resistance; DOT1L: Disruptor of telomeric silencing 1-like; ECM: Extracellular matrix; KEGG: Kyoto Encyclopedia of Genes and Genomes; TNM: Tumor, node, metastasis.

Ye *et al*<sup>[40]</sup> evaluated the effect of miR-1290 on CRC cells, which targets HSMH2. They reported that this miRNA is positively correlated with dMMR status. Moreover, the



**Figure 2 Thymidylate synthase inhibition.** Fluorodeoxyuridine monophosphate (FdUMP) incorporation into thymidylate synthase in place of deoxyuridine monophosphate (dUMP) results in suppression of thymidylate synthase (TS). Consequently, the synthesis of thymidine monophosphate required for DNA replication and repair is diminished, which leads to deoxyuridine triphosphate (dUTP) imbalances, increased dUTP, DNA damage and finally apoptosis of actively dividing cancerous cells<sup>[20]</sup>. TK: Thymidylate kinase; CH<sub>2</sub>THF: 5,10-methylene tetrahydrofolate; dTMP: Deoxythymidine monophosphate; dTTP: Deoxythymidine triphosphate; dNTP: Deoxynucleotide triphosphate.



**Figure 3 5-Fluorouracil inhibits ribonucleic acid pseudouridylation including the conversion of uridine to pseudouridine and formation of stable ribonucleoprotein complexes.** These actions will interrupt cellular tRNA, pre-mRNA and rRNA production and also post-transcriptional modification, leading to RNA biosynthesis cessation. Moreover, 5-fluorouracil (5-FU) disrupts the assembly and activity of snRNA and protein complexes through its effect on the pseudouridylation of U2 snRNA, thereby inhibiting the splicing of pre-mRNA<sup>[21]</sup>. Because of the similarity between the 5-FU metabolite fluorouridine triphosphate (FUTP) with uridine triphosphate, FUTP can be identified by RNA polymerases and incorporated into both nuclear and cytoplasmic RNA molecules, interrupting normal RNA processing and function<sup>[22]</sup>. RNA-based 5-FU toxicity decreases the cellular levels of the nuclear exosome Rrp6 or exosome component 10, a breakdown complex for RNA, banning the effectual turn-over of aberrant RNA transcripts<sup>[21]</sup>. FUMP: Fluorouridine monophosphate; FUTP: Fluorouridine triphosphate.

expression of miR-1290 was associated with poor prognosis in stage II and III CRC patients who received 5-FU. They also demonstrated that inhibition of miR-1290 decreased 5-FU chemoresistance<sup>[40]</sup>. miR-552 is another miRNA that targets the SMAD2 cascade. Zhao *et al.*<sup>[41]</sup> evaluated the effect of different expression levels of miR-522 on 5-FU chemoresistance. They demonstrated that expression of miR-552 that was



downregulated in 5-FU-resistant tissues and cells was regulated by dMMR. Moreover, the expression of this miRNA was associated with poor post-chemotherapy prognosis. In terms of 5-FU resistance, overexpression of miR-552 reduced chemoresistance, and its inhibition may lead to increased 5-FU chemoresistance (Table 1)<sup>[41]</sup>.

## THYMIDYLATE SYNTHASE AND RESISTANCE TO 5-FU

Abundant research regarding 5-FU resistance in mCRC have highlighted that various genes were involved in 5-FU pharmacokinetic and pharmacodynamic metabolic pathways. One of the major key enzymes in 5-FU metabolism is TS. TS expression is the main determinant of 5-FU sensitivity. Disturbed methylenetetrahydrofolate or one of its polyglutamate pools that results in an unstable ternary complex of fluorodeoxyuridine' monophosphate and TS (which leads to poor inhibition of TS) along with a high level of TS enzyme before treatment are two main factors of intrinsic resistance to 5-FU<sup>[42]</sup>. 5-FU chemotherapy nonrespondents have higher TS enzyme activity in comparison to 5-FU respondents. TS has a negative autoregulatory role in the translational level by binding to its own TS mRNA, thereby it inhibits the production of functional TS enzyme. However, the inhibition becomes interrupted by TS enzyme interaction with 5-FU metabolite. As a result, the 5-FU treatment causes acquired resistance by affecting TS stability. Besides, acquired resistance to chemotherapy that is emanating from the gene amplification of TS with consequent increases in TS mRNA and protein is observed in 5-FU and 5-fluorouridine deoxyribose (5-FUDR) treated cell lines<sup>[43-46]</sup>. Moreover, TS overexpression may result in oncogenic phenotypes by decreasing the translational efficiency of the TP53 transcript<sup>[47]</sup>. Manifold clinical and preclinical investigations showed that colorectal tumors are more sensitive to 5-FU-based therapy in patients with low tumoral TS expression<sup>[48-50]</sup>. In line with these findings, Abdallah *et al*<sup>[51]</sup> reported that analyzing TS expression in circulating tumor cells of mCRC patients would be a promising tool as a 5-FU resistance predictor biomarker.

Genotyping of the *TYMS* promoter shows interindividual differences among patients with variable sensitivity to 5-FU treatment and divides CRC patients into those who receive a survival benefit from 5-FU chemotherapy and those who do not<sup>[52,53]</sup>. The 5'-region of the *TYMS* gene promoter has a variable number of tandem repeats, and this is composed of usually either two (TSER\*2 or 2R) or three (TSER\*3 or 3R) 28-base-pair tandem-repeat sequences<sup>[54]</sup>. Preliminary studies indicated that TSER\*3/TSER\*3 homozygous patients are less likely to respond to 5-FU-based chemotherapy than TSER\*2/TSER\*2 homozygous or TSER\*2/TSER\*3 heterozygous patients<sup>[55,56]</sup>. *In vitro* studies showed that *TYMS* promoter variants observed in tissue tumors with the TSER\*3 alleles produce nearly four times higher mRNA in comparison to patients with mCRC who carry TSER\*2 alleles ( $P < 0.004$ )<sup>[57]</sup>. Homozygous TSER\*2/TSER\*2 alleles have a significantly higher percentage of a favorable response to 5-FU treatment compared to those who were homozygous for TSER\*3/TSER\*3 (50% *vs* 9%,  $P = 0.04$ )<sup>[20]</sup>.

*TYMS* is the target of miRNAs, and it is demonstrated in Table 1. Boni *et al*<sup>[58]</sup> demonstrated that ectopic expression of miR-192 and miR-215 are stronger predictors of 5-FU response than *TYMS* inhibition. In their study, miR-192 and miR-215 expression do not affect chemoresistance, although their overexpression reduced cell proliferation. Li *et al*<sup>[59]</sup> reported that miR-203 increased the inhibitory effect of 5-FU on tumor growth and suppressed *TYMS* protein levels. Inhibition of miR-203 expression increased chemoresistance, and the miR-203 overexpression increased chemosensitivity<sup>[59]</sup>. Another miRNA affecting 5-FU response is miR-330. Ectopic expression of miR-330 reduced cell proliferation and enhanced chemosensitivity<sup>[60]</sup>. In HCT116 and HT29 cell lines, miR-218 expression suppressed BIRC5 and TS, promoting apoptosis. Overexpression of this miRNA showed an increase in 5-FU chemosensitivity<sup>[61]</sup> (Table 1).

## DIHYDROPYRIMIDINE DEHYDROGENASE AND RESISTANCE TO 5-FU

Patients with decreased 5-FU catabolize capacity due to partial or complete DPD deficiency are prone to severe systemic toxicity in response to 5-FU<sup>[12]</sup>. Increased drug concentration and longer half-life due to the decreased drug catabolism may be the possible explanation for this finding. The assessment of more than 60 human cancer cell lines illustrated a highly significant inverse relationship between the 5-FU

response and both *DPD* mRNA expression and *DPD* activity. Low *DPD* mRNA levels and *DPD* activity in human tumor xenografts are in strong correlation with better response to 5-FU in comparison with tumors expressing a higher level of *DPD* mRNA<sup>[12]</sup>. Furthermore, *in vitro* studies have also shown that high levels of *DPD* mRNA expression in colorectal tumors and the corresponding catabolism of 5-FU correlate with resistance to 5-FU<sup>[62]</sup>. Importantly, previous studies showed that *DPD*, *TS* and thymidine phosphorylase are independent prognostic markers of 5-FU response, and measurement of all three markers significantly enhanced the ability to predict tumor response to 5-FU-based chemotherapy<sup>[63-65]</sup>.

As alterations in *DPD* is correlated with 5-FU chemoresistance, miRNAs regulating its expression can interfere with chemotherapy resistance. When miR-494 is bound to the 3'UTR of *DPD*'s gene, it can decrease its expression<sup>[66]</sup>. Similarly, miR-27a and miR-27b decrease 5-FU resistance by targeting *DPD*<sup>[67]</sup>.

## P53 AND RESISTANCE TO 5-FU

Some *in vitro* and *in vivo* studies reported that loss of p53 function (due to mutant or inactive *TP53*) reduced cellular sensitivity to cytotoxic agents including 5-FU, which is accompanied by poor prognosis and poor survival rates<sup>[68-70]</sup>. One of the main outcomes of 5-FU treatment is the induction of apoptosis in normal and tumoral intestinal cells. Thereby, any alterations in genes involved in apoptotic pathways may have extensive impacts on chemotherapy and can take part in the induction of 5-FU resistance by cancerous cells<sup>[71]</sup>. Disrupting both alleles of *TP53* in a colon cancer cell line made the cells strikingly resistant to apoptosis induced by 5-FU compared with the parental line<sup>[69]</sup>. Remarkably, several clinical studies reported that p53 overexpression correlates with resistance to 5-FU<sup>[72,73]</sup>.

Some studies evaluated the effect of the expression of different miRNAs targeting p53. Kim *et al*<sup>[74]</sup> studied the p53 stability regulator (*UBE2N*) in CRC tissue. miR-96 targets *UBE2N*. Kim *et al*<sup>[74]</sup> demonstrated that exposing CRC cells to 5-FU decreased the expression of an antiapoptotic regulator (*XIAP*) and *UBE2N*<sup>[74]</sup>. Also, in another study, the miR-96 expression was reported to be a modulator of 5-FU chemosensitivity and promoted apoptosis of CRC cells<sup>[74]</sup>. Zhang *et al*<sup>[75]</sup> investigated the miR-520g expression and its target, p21, in CRC cells. p53 suppressed miR-520g expression, and inhibition of miR-520g in p53 negative cells increased chemosensitivity to 5-FU<sup>[75]</sup> (Table 1).

## CIRCULAR RNAs AND RESISTANCE TO 5-FU

One of the new research fields of transcriptome studies performed on drug resistance in CRC is circular RNAs (circRNAs). Recently, these noncoding closely looped RNAs were found to be involved in 5-FU-based chemotherapy resistance in CRC mainly because of their ability to act as a miRNA sponge. Using microarray analysis, Xiong *et al*<sup>[76]</sup> for the first time revealed that circRNAs were expressed differently in 5-FU chemoradiation resistant CRC cells than parental control cells, suggesting the new potential role of these biomolecules in 5-FU drug resistance. This study introduced hsa circ 0007031 as the most upregulated circRNA (116 fold) in 5-FU chemoradiation resistant CRC cells<sup>[76]</sup>. In line with the work of Xiong *et al*<sup>[76]</sup>, Abu *et al*<sup>[77]</sup> compared the expression profile of circRNAs between chemosensitive and chemoresistant FOLFOX (5-FU + oxaliplatin) HCT-116 colon cancer cells. They concluded that up to 773 and 732 circRNAs were upregulated and downregulated in these two cell lines, respectively. Among the investigated circRNAs, hsa circ 32883 that encodes for the *EML5* gene was believed to be a potential molecular target demanding further research<sup>[77]</sup>.

## MIRNAS PROMOTE 5-FU DRUG RESISTANCE IN CRC

Among miRNAs presented in Table 1, some miRNAs can induce 5-FU resistance. Upregulation of *ST6GALNAC2* (which further activates the PI3K/AKT pathway) is one of the main mechanisms resulting in chemoresistance caused by miR-182 and miR-135b<sup>[78]</sup>. Based on the DIANA-miRPath database, these two miRNAs play a role in signaling pathways regulating the pluripotency of stem cells, adherent junctions and cell cycle<sup>[79]</sup>. In a study by Amankwatia *et al*<sup>[80]</sup>, it has been shown that miR-224

knockdown significantly increased sensitivity of HCT116 KRAS wild-type cells to 5-FU but did not affect sensitivity to oxaliplatin or irinotecan. Additionally, they demonstrated that miR-224 silencing markedly enhanced KRAS activity and ERK and AKT phosphorylation, suggesting a direct effect of miR-224 on pro-survival RAS/AKT/PI3K pathway<sup>[80]</sup>. miR-587 is another miRNA that can downregulate activation of the AKT/XIAP axis and induce 5-FU resistance<sup>[81]</sup>. miR-587 inhibited AKT activation; when this miRNA was inhibited, it decreased chemoresistance to 5-FU<sup>[81]</sup>. Regardless of the cancer cells, expression of some specific miRNAs including miR-196b-5p in cancer stem cells is also related to 5-FU resistance, and it activates JAK/STAT3 signaling<sup>[33]</sup>.

## MIRNAS REVERSE 5-FU DRUG RESISTANCE IN CRC

In contrast to the previous section, other miRNAs are involved in reducing 5-FU chemoresistance in CRC patients. miR-24 is a tumor suppressor and increases the chemosensitivity of SW48 cells to 5-FU, probably due to targeting and downregulating *DND1*, which is upregulated in CRC cell lines up to 5.3-fold<sup>[82]</sup>. Moreover, according to the DIANA-miRPath database, miR-24-3p is involved in proteoglycans in cancer, cell cycle and pancreatic cancer pathways. Likewise, miR-361 overexpression increased cell apoptosis in 5-FU-resistant HCT116 and HT29 cells through targeting and modulation of *FOXO1* and *ABCC5/10*, respectively<sup>[83]</sup>. miR-361 is also involved in adherent junction as well as extracellular matrix receptor interaction cellular pathways (DIANA-miRPath database). miR-375-3p targets *YAP1* and *SP1*. Inhibition of *YAP1* downstream genes including survivin, *CTGF*, and cyclin D1 promoted CRC cell sensitivity to 5-FU<sup>[84]</sup>. miR-133b also increased the sensitivity of cancer stem cells within colorectal spheroids to 5-FU by targeting disruptor of telomeric silencing 1-like, which is responsible for H3K79 methylation<sup>[85]</sup>. Similar to miRNAs promoting 5-FU drug resistance, some miRNAs reverse 5-FU drug resistance in CRC and are listed in Table 1 along with detailed explanations.

## CONCLUSION

The latest and most important molecular mechanisms of 5-FU resistance including MSI, altered expression of TS and DPD enzymes and loss of p53 were introduced in detail. As discussed above, MSI induced by sporadic or germline mutations in DNA mismatch repair machinery genes increased the tolerance of CRC cells to DNA damage and apoptosis caused by 5-FU, leading to 5-FU resistance. High expression levels of TS and DPD before treatment are two important factors for intrinsic resistance to 5-FU in CRC. Polymorphism of the 5'-region of the *TS* gene promoter and loss of p53 function due to mutation or TP53 overexpression are other molecular determinants of response to 5-FU. miRNAs and their alterations are other important factors in 5-FU drug resistance in CRC. New emerging evidence indicated that the consideration of miRNAs not only confer great assurance for the diagnosis, prognosis and clinical follow-up of CRC patients but also can be considered as a potential tool for anticancer therapies. Moreover, miRNAs can be utilized as predictive markers for CRC patients<sup>[86,87]</sup>. As it is shown in Table 1, some miRNAs promote 5-FU drug resistance in CRC, while some reverse it. The identification of new potential molecular determinants of response to 5-FU could be an important clinical tool to develop treatment strategies and select CRC patients who would most likely benefit from 5-FU-based chemotherapy.

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