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REVIEW

MicroRNAs and drug resistance in colorectal cancer with special focus on 5-fluorouracil

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Abstract

Colorectal cancer is globally one of the most common cancers in all age groups. The current chemotherapy combinations for colorectal cancer treatment include 5-fluorouracil-based regimens; however, drug resistance remains one of the main reasons for chemotherapy failure and disease recurrence. Many studies have determined colorectal cancer chemoresistance mechanisms such as drug efflux, cell cycle arrest, DNA damage repair, apoptosis, autophagy, vital enzymes, epigenetic, epithelial-mesenchymal transition, stem cells, and immune system suppression. Several microRNAs affect drug resistance by regulating the drug resistance-related target genes in colorectal cancer. These drug resistance-related miRNAs may be used as promising biomarkers for predicting drug response or as potential therapeutic targets for treating patients with colorectal cancer. This work reviews and discuss the role of selected microRNAs in 5-fluorouracil resistance and their molecular mechanisms in colorectal cancer.

Keywords Colorectal cancer · MicroRNA · Drug resistance · 5-fluorouracil

Introduction

Colorectal cancer (CRC) is a highly heterogeneous disease, representing the third most prevalent malignancy and the second cause of cancer-related death worldwide [1]. The incidence rates range remarkably by region, with up to 25-fold variations worldwide [2]. Despite novel diagnostic and therapeutic approaches in CRC treatment have been implemented in day-to-day clinical practice, survival rates remain poor, especially in the later stages of the disease [3].

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Improvements over the last decades in the diagnosis of CRC have been achieved by employing early diagnostic methods and effective therapeutic strategies, such as surgery, radiotherapy, and targeted drug therapy. Backbone therapy in both neoadjuvant and adjuvant treatments still includes fluoropyrimidine-based chemotherapy regimens [4]. For example, 5-fluorouracil (5-FU) is applied in the treatment of CRC, which is converted to active metabolites needed to inhibit the growth of cancer cells after intravenous injection [5]. Yet, the life expectancy of CRC patients is only five years, which is a disappointing rate [6], and one of the main reasons is the development of drug resistance in patients after a treatment period. Drug resistance to 5-FU is defined in two ways. One is primary resistance that the patient has resisted the drug from the beginning, and another resistance that develops after a course of treatment is acquired resistance. 5-FU as an anti-metabolic drug by its active metabolites impairs the biosynthesis of DNA and RNA by inhibiting fundamental enzyme thymidylate synthase [7]. Chemoresistance, however, remains a major clinical issue that leads to treatment failure and tumor recurrence [8].

Researchers have shown that enzymes involved in 5-FU anabolism or catabolism pathways lose their primary function and become resistant to 5-FU [9]. Also, noncoding

RNAs (microRNAs (miRNAs)) have essential roles in 5-FU resistance [10–12]. The discovery of miRNA has provided a new perspective on cancer investigations [13]. miRNAs are short sequences of 19 to 22 nucleotides of RNA and are involved in cell differentiation, cell cycle progression, and apoptosis. It was recently demonstrated miRNAs have vital roles in tumorigenesis and may be beneficial to detect specific cancers and determine prognosis and response to various therapies [14]. Several studies have shown that miRNAs play a critical role in cancer progression by several mechanisms. miRNAs regulate molecular pathways in cancer by targeting different types of tumor suppressors and oncogenes [13]. Their regulatory function has also been reported in cancer-stem-cell biology, angiogenesis, epithelial-mesenchymal transition, metastasis, and drug resistance [15]. Various factors, in terms of drug resistance, are involved, such as reduced intracellular drug accumulation, increased DNA damage repair, reduced apoptosis, and dysregulation of oncogenes and tumor suppressors [16]. miRNAs are critically involved in the process of drug resistance [16]. Many miRNAs are dysregulated in CRC, and some are associated with responses to anti-cancer therapies by regulating drug metabolism, drug delivery, DNA damage response, and cell apoptosis [17].

The present work aims to review the main associations between representative miRNAs and 5-FU resistance in CRC patients.

Regulation of miRNA expression

miRNAs are small, non-coding single-stranded RNAs with about 22 nucleotides. A single miRNA can regulate the expression of many target genes, and many of them regulate a single gene expression [20]. The primary miRNA, termed pri miRNAs, are formed in the nucleus as multiple "hairpin structures" of 100 to 1000 nucleotides. This step is performed with the help of nuclear RNA polymerase II or III enzymes [18]. Principally, 70% of miRNAs are formed from introns or exons controlled through a gene promoter, while 30% of pri-miRNAs are transcribed by independent promoters in the intergenic region. Then, the RNase III Drosha enzyme cleaves pri-miRNAs to up to six miRNA precursors. These generated precursors (pre-miRNAs), which have 70 to 90 nucleotide sequences, are exported from the nucleus to the cytoplasm by Exportin 5, a RanGTPdependent double-stranded (ds) RNA-binding protein [19]. The hairpin loop, then, is cleaved in the cytoplasm by RNAase III DICER. It produces a double-stranded miRNA: miRNA * duplex. Of the two miRNA duplex strands, only the mature one is incorporated into the RNA-induced silencing complex (RISC) to interact with the target mRNA and suppress protein synthesis [20]. miRNAs are molecules that have essential roles in controlling mRNA transcription and protein translation [21, 22]. Their expressions are regulated by various processes such as specific translational regulation, methylation, histone deacetylation, changes in DNA copy structure and different gene mutations, as well as genetic polymorphisms on miRNA 3 -UTR (3′untranslated region) binding sites and gene expression of the tumor suppressor protein53 (p53) [23–25]. Because cancer is caused by the deregulation of biological processes [26], scientific evidence shows that abnormal expression of miRNA plays an important role in carcinogenesis [27]. Low- and over-expression of miRNAs involved in suppressor tumors and oncogenesis, respectively, are being investigated [28, 29]. These deregulated miRNAs are involved in tumor progression, invasion, metastasis, and drug resistance [30].

Involvement of miRNAs in chemotherapy resistance

Despite advances in the treatment of CRC before and after surgery with the help of chemotherapy drugs, success in treating patients has not been effective. Drug resistance has been identified as one of the main barriers to the treatment of cancer patients; therefore, understanding the basis of the molecular mechanisms involved in drug resistance can be beneficial in finding treatment strategies. In recent years, much attention has been paid to the function of miRNAs as biomarkers in CRC.

5-FU is one of the basic therapies in CRC; its mechanism of action in the body is to inhibit DNA replication. This function leads to the thymidine replacement by fluorinated nucleotides into the DNA, and cell death occurs [31]. Thus, miRNA expression profiles in tumor cells are changed. Two molecular mechanisms describe how miRNA acts. miRNA binds to the 3'-UTR mRNA of the target gene to sensitize cancer cells to 5-FU in the CRC. When mRNA and miRNA pairing is complete, the target is cleaved, and the protein is not expressed. But in defective base pairs, the target protein is silenced, or the expression level is reduced. miRNA can also be at the origin of translational reprogramming, creating steric blockade on the mRNA target or dysregulating transcription/translation effectiveness. Exposure of CRC cells to 5-FU has shown that some miRNAs increase and some decrease compared to healthy cells. In CRC tumor cells, the increased miRNAs are oncogenic, and the decreasing ones are tumor suppressors, leading to the induction of drug resistance to 5-FU [9, 32]. Also, the studies have shown that miRNAs modulate metabolic enzymes, adenosine triphosphate-binding cassette (ABC) transporter proteins, cell cycle, apoptosis, and epithelial-mesenchymal transition (EMT) to induce drug resistance of 5-FU [21, 33–35]. The

following offers a brief overview of some mechanisms of miRNAs in drug resistance to 5-FU.

Mechanisms of drug resistance in CRC

One of the main problems with CRC treatment is the lack of early diagnosis. Most often, the disease is diagnosed after the spread of cancer cells. Yet, chemotherapy after a while cannot prevent the progression of the disease. The cause is found in the drug resistance of tumor cells [31].

Drug resistance is a well-described phenomenon that is associated with treatment failure. This concept was initially observed when certain bacteria became resistant to some antibiotics. Similarly, chemoresistance in cancer develops against chemotherapy drugs [36]. Currently, several mechanisms have been reported including, reduced intracellular drug concentrations via drug efflux transporters such as P-glycoprotein (P-GP), impaired cell cycle arrest, apoptosis, DNA damage repair mechanisms, and abnormal DNA methylation, and histone modification [37] (Fig. 1).

5-FU has been one of the most common CRC therapies since 1950 [38, 39]. Besides this drug, other chemotherapeutic drugs, such as oxaliplatin, irinotecan, and capecitabine, were developed. However, in patients with advanced CRC cancer, the use of a single drug is not responsible for inhibiting the disease, and a combination of 5-FU and leucovorin with oxaliplatin or irinotecan is used [40]. The discovery of monoclonal antibodies such as Bevacizumab and Cetuximab has added them to the list of CRC treatments. The use of monoclonal antibodies in combination with chemotherapy drugs has increased the five-year survival rate for metastatic CRC by just over 12% [41]. Therefore, the mechanisms involved in the development of drug resistance should be well known to design an appropriate treatment.

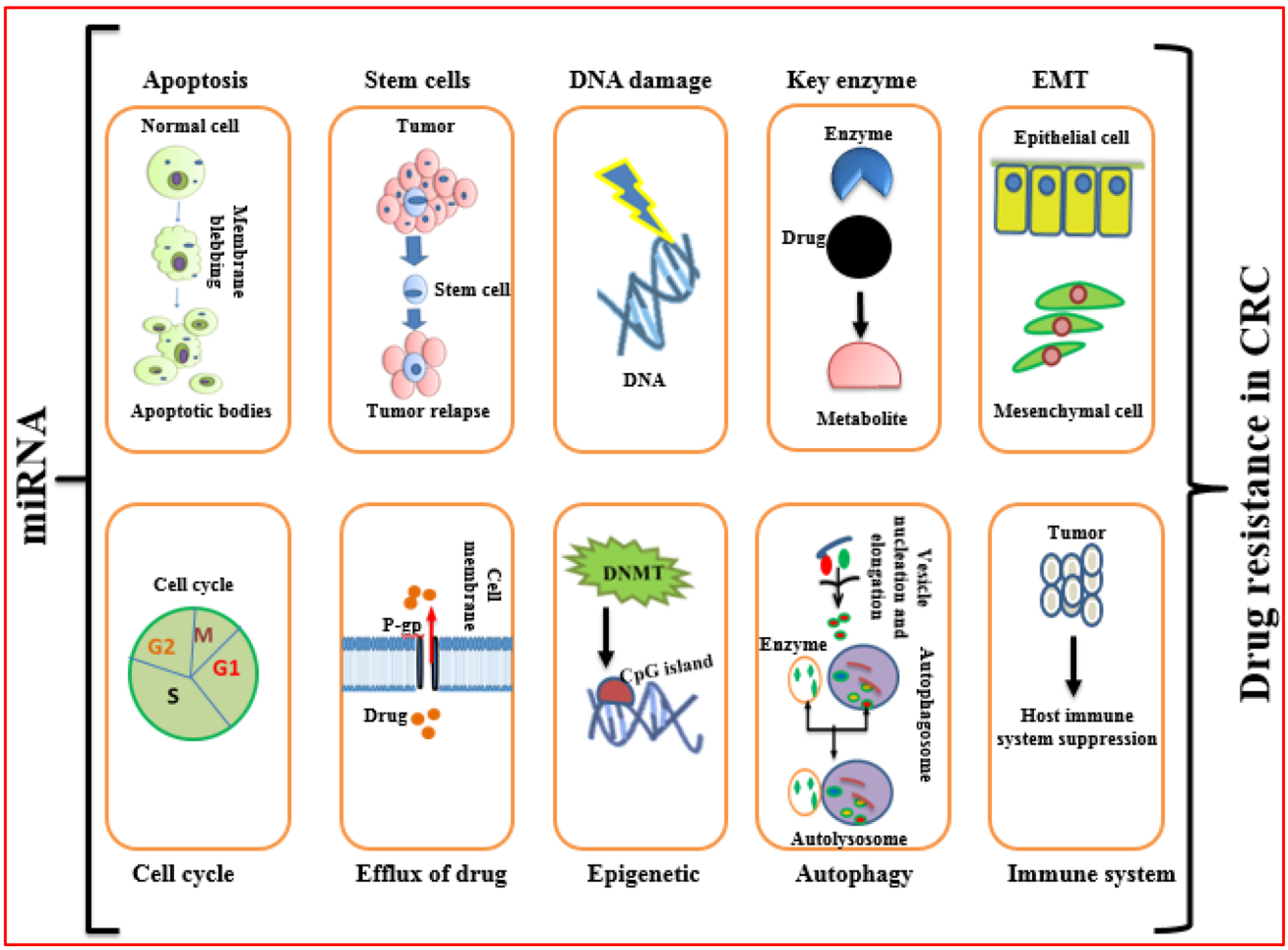

Fig. 1 Molecular mechanisms of miRNAs in drug resistance in CRC. *P-gp* P-glycoprotein, *EMT* epithelial-mesenchymal transition, *Autophagosome* spherical structure with the intracellular degradation system, *Lysosome* organelle that contains digestive enzymes, *Autolysosome* the fusion of an autophagosome and a lysosome, *DNMT* DNA methyltransferase

Mechanisms of 5-FU drug resistance by miRNAs in CRC

miRNAs in CRC can act as tumor suppressors or oncogenes. When irregularity occurs in their production, drug resistance occurs by various mechanisms. 5-FU is the first-line chemotherapy drug in CRC, and this article reviews miRNAs developing drug resistance to 5-FU and several common chemotherapeutic drugs by the mechanisms listed above.

The role of selected miRNAs in increased drug efflux

Overexpression of drug transporters and drug-metabolizing enzymes are important defensive cellular mechanisms and have crucial roles in regulating cellular absorption, distribution, and excretion of chemotherapeutic agents and their metabolites [42, 43]. Recently, many studies of miRNAs have indicated a subset of target genes involved in drug efflux and metabolism [44–47]. A major reason for chemotherapy failure is an increase in energy-dependent drug efflux mediated by ATP-binding cassette (ABC) drug transporters. An important representative of this family is P-gp which encodes the multidrug resistance gene 1 (MDR1) [48]. One of the cellular functions of ABC drug transporters is to remove drug metabolites from the cell and prevent them from causing cytotoxicity. According to this function, the cellular concentration of the drug decreases, and the effectiveness of drugs such as CRC chemotherapy drugs decreases with increasing expression of P-gp and multidrug resistance-associated protein 1 (MRP1) [49]. P-gp overexpression is related to cellular resistance in anticancer agents, such as anthracyclines, plant alkaloids, taxanes, and platinum-based drugs [50, 51]. Wang et al. [52] showed overexpression of the miR-26b tumor suppressor in CRC is associated with sensitization cells to 5-FU treatment and P-gp low-expression. On the other hand, expression of stemness-related miRNAs (miR-302, miR-369, miR-200c) via the suppression of the MRP8 or ATP-binding cassette transporter sub-family C member 11 (ABCC11) may increase the sensitivity of CRC cells to 5-FU [53–55]. Moreover, overexpression of ATP-binding cassette transporter sub-family G2 member (ABCG2) promotes resistance to 5-FU and irinotecan. More specifically, there is evidence that miR-519c suppresses ABCG2 expression through binding to its 3′-UTR and mRNA binding protein HuR (human antigen R). In CRC cells, chemoresistance to 5-FU is caused by miR-519c suppression through regulating the miR-519c-HuR-ABCG2 pathway [56]. Also, in SW1116 CRC cell lines, decreased miR-142-3p expression is associated with increased ABCG2 expression and drug resistance to 5-FU [57]. Li et al. [58] reported that miR-23a enhances 5-FU resistance by targeting ATP-binding cassette transporter sub-family F1 member (ABCF1) in microsatellite instability (MSI) CRC cells. These results provide novel tools for more effective therapeutic approaches to control 5-FU resistance in MSI CRC. Studies have also shown that restoration of the miR-451 expression reduces ATP-binding cassette drug transporter B1 (ABCB1) expression and increases drug sensitivity to irinotecan in CRC stem cells (CRC-SCs) [59]. Also, the ABCB1 level has an inverse correlation with the miR-302c-5p level in CRC cells. Low-expression of miR-302c-5p is identified in oxaliplatin-resistant CRC cells. Overexpression of miR-302c-5p induces the sensitivity of CRC cells to oxaliplatin through regulating ABCB1 expression [60]. In the case of miR-522 in CRC cells, miR-522 represses cell survival and doxorubicin resistance by directly targeting ABCB5 [61]. (Table 1). Therefore, stimulating the expression of tumor suppressor miRNAs and inhibiting the expression of oncogenic miRNAs involved in reducing and increasing the expression of ABCs, respectively, can significantly help reduce the drug resistance induced by ABCs in the CRC.

The role of selected miRNAs in impaired cell cycle arrest

Cell cycle arrest is a regulatory process that stops cell cycle progression at specific points of the typical phases (G1, S, G2, and M). Cell cycle arrest is caused by DNA damage and tumor protein p53. The mechanism of action of p53 is stopping cyclin-dependent kinases (CDKs) activity. However, loss of p53 function correlates with reduced sensitivity to DNA damage and drug resistance [37]. A recent study revealed that HCT-116_lenti-miR-195 cells are drug-resistant after 5-FU treatment compared to control cells (HCT-116_lenti-control). More specifically, down-regulation of miR-195 decreases miR-195-target proteins, including checkpoint kinase 1 (CHK1) and G2 checkpoint kinase WEE1 (Ser/Thr family of protein kinases), thus resulting in cell growth inhibition and resensitization of the cancer cells to 5-FU [62]. It has been suggested that a higher level of miR-17-5p is associated with later CRC clinical stages. Moreover, among the studied population, the patients who had previously received chemotherapy displayed worse survival rates. Then, investigators suggested that phosphatase and tensin homolog (PTEN) is the miR-17-5p target in CRC cells [63]. PTEN is a tumor suppressor that controls the PTEN/protein kinase B (AKT)/phosphoinositide 3-kinases (PI3K) pathway; loss of PTEN function and AKT activation have been detected in several types of cancer, such as hepatocellular, prostate adenocarcinoma, and CRC [64]. According to the proposed mechanism above, chemotherapy

Table 1 miRNAs and 5-FU drug resistance targets in CRC

Drug resistance mechanisms	miRNAs	Alteration	Target	References
Efflux of drug	miR-23a	Up	ABCF1	[58]
	miR-26b	Down	P-gp	[52]
	(miR-302, miR-369, miR-200c)	Down	ABCC11	[53]
	miR-519c	Down	ABCG2	[56]
	(miR-451 in irinotecan)	Down	ABCB1	[59]
	miR-142-3p	Down	ABCG2	[57]
	(miR-302c-5p in oxaliplatin)	Down	ABCB1	[60]
Cell cycle arrest	miR-195	Up	(CHK1, WEE1)	[62]
	miR-17-5p	Up	PTEN	[63]
	miR-329	Down	E2F1	[65]
	miR-200c	Down	(E-cadherin, PTEN)	[66]
	miR-520 g	Up	p21	[67]
DNA damage	(miR-203 in oxaliplatin)	Up	ATM	[71]
	miR-21	Up	(hMsh2, RAD18)	[72]
	miR-145	Down	RAD18	[73]
	miR-1290	Up	hMsh2	[74]
Apoptosis	(miR-20a in oxaplatin)	Up	BNIP2	[77]
	(miR-20a in cicplatin)	Up	ASK1	[91]
	miR-425	Up	PDCD10	[78]
	miR-206	Down	BCL2	[79]
	miR-143	Down	(3,8, and 9 caspases)	[82]
	miR-520 g	Up	(p53, p21)	[67]
	miR-587	Up	PPP2R1B	[83]
	(miR-153 in oxaliplatin and cisplatin)	Up	(MMP-9, FOXO3a)	[84]
	(miR-503-5p in oxaliplatin)	Up	PUMA	[85]
	(miR-1915 in oxaliplatin)	Down	Bcl-2	[86]
	miR-129	Down	(Bcl-2, 3 and 9 caspases)	[87]
	miR-218	Down	Survivin	[88]
	(miR-195 in doxorubicin)	Down	BCL2L2	[92]
	miR-10b	Up	BIM	[4]
	miR-874	Down	XIAP	[93]
Autophagy	miR-125b	Up	CXCL12/ CXCR4, Beclin-1	[96]
	(miR-409-3p in oxaliplatin)	Down	Beclin-1	[97]
	miR-22	Down	(p62, LC3-II, BTG1)	[95]
Alterations in key enzymes	miR-494	Down	DPYD	[98]
	miR-21	Down	(TP, DPD)	[100]
	(miR-375-3p, miR-197, miR-203)	Down	TYMS	[101–103]
Epigenetic deregulation	(miR-181a, miR-135a, miR-302c)	Down	PLAG1 / IGF2	[112]
	miR-26b	Down	P-gp	[52]
	miR-140	Up	HDAC4	[115]
Epithelial-mesenchymal	miR-139-5p	Down	BCL2	[116]
Transition	(miR-514b-3p in cisplatin-and irinotecan)	Down	(E-cadherin, claudin 1, fibronectin-1, vimentin)	[117]
	(miR-223 in doxorubicin)	Up	FBXW7	[118]
	(miR-200c, miR-141 in oxaliplatin)	Down	ZEB1	[120]
Stem cells	miR-141	Down	Cyclin D2	[126]
	miR-196b-5p	Up	Stem cell-like phenotype	[127]
	(miR-451 in irinotecan)	Down	COX-2	[59]
Immune suppression	miR-146a	Up	Treg, TGF-β, IL-10	[135]

Table 1 (continued)

MicroRNA, miRNA P-gp, P-glycoprotein; *ABCC11* ATP-binding cassette transporter sub-family C member 11; *ABCG2* ATP-binding cassette transporter sub-family G2 member; *ABCB1* ATP-binding cassette drug transporter B1; *ABCF1* ATP-binding cassette transporter sub-family F1 member; *CHK1* Checkpoint kinase 1; *WEE1* Ser/Thr family of protein kinases; *PTEN* Phosphatase and tensin homolog; *CAC1* CDK2 associated cullin domain 1; *E2F1* E2F transcription factor 1; *ATM* Ataxia telangiectasia mutated; *hMsh2* (Human mutS protein homolog 2); *RAD18* E3 ubiquitin ligase; *BNIP2* BCL2/adenovirus E1B protein-interacting protein 2; *PDCD10* Programmed cell death 10; *P53* Protein53; *P21* Protein 21; *PPP2R1B* Serine/threonine-protein phosphatase 2A regulatory subunit A beta isoform; *MMP-9* Matrix metalloprotease enzyme 9; *FOXO3a* Forkhead box O3a; *PUMA* P53 up-regulated modulator of apoptosis; *CXCL12* C-X-C motif chemokine 12; *CXCR4* C-X-C chemokine receptor type 4; *MSH2* MutS protein homolog 2; *TP* Thymidine phosphorylase; *DPYD* Dihydropyrimidine dehydrogenase; *PLAG1/IGF2* Pleiomorphic adenoma gene 1/ insulin-like growth factor 2; *FBXW7* F-box and WD repeat domain-containing 7; *COX-2* Cyclooxygenase-2; *Treg* Regulatory T cells; *TGF-β* Transforming growth factor-β, (TGF-β); *IL-10* Interleukin-10

resistance is associated with miR-17-5p overexpression and PTEN downregulation resulting in 5-FU treatment [63]. A positive correlation between miR-329 overexpression and 5-FU sensitivity in CRC has been proposed by Yin et al., via the reduced expression of E2F transcription factor 1 (E2F1) [65]. The miR-200c inhibition is related to the resistance of HCT-116 cells to 5-FU with E-cadherin and PTEN low-expression. Therefore, inducing miR-200c can be a therapeutic agent against resistance chemotherapy [66]. The p53/miR-520 g/p21 signaling axis plays an essential role in the response of CRC cells to 5-FU and oxaliplatin. P53 is an inhibitor of miR-520 g expression, and deletion of p53 expression is associated with increased miR-520 g expression. miR-520 g reduces 5-FU-induced apoptosis and increases drug resistance by decreasing p21 expression [67] (Table 1). Therefore, over-and lower-expression of some miRNAs causes the deregulation of proteins involved in the cell cycle arrest. Defects in cell cycle arrest in CRC cancer cells cause tumor cell proliferation and drug resistance.

The role of selected miRNAs in impaired DNA damage repair mechanisms

DNA damage can result from physical, chemical, or biological agents, and DNA repair pathways are activated to sustain the stability of the genome [68, 69]. Increased expression of DNA repair mechanisms is vital to maintain DNA structure in normal cells. For instance, the nucleotide excision repair (NER) system protects cells from DNA damage caused by chemotherapy drugs [70]. DNA damage occurs via several endogenous (such as ROS-reactive oxygen species) and exogenous factors (such as radiation and genotoxic components). Zhou et al. [71] investigated oxaliplatin resistance in three different CRC cell lines (HT29, HCT116, and RKO). The authors showed miR-203 expression induces drug resistance by suppression ataxia telangiectasia mutated (ATM) as a potential miR-203 target. ATM activation occurs in response to DNA damage, and the low-expression of ATM leads to oxaliplatin resistance in CRC cells. Moreover, DNA mismatch repair protein mutS protein homolog 2 (Msh2), recognized as mutator S (MutS), is involved in DNA damage repair. It has been documented up-regulation of miR-21 decreases human Msh2 (hMsh2) and induces chemoresistance to 5-FU in a CRC xenograft model. In cancer cells, DNA damage activates E3 ubiquitin ligase (RAD18), which is significant in DNA damage repair [72]. Furthermore, RAD18 is up-regulated following 5-FU treatment in 5-FU-resistant cancer cells and may serve as a target for overcoming drug resistance. The authors also observed that tumor suppressor miR-145 is associated with RAD18 down-regulation in CRC patients, and they also suggested that miR-145 may promote DNA damage by inhibiting RAD18 in CRC cells. These results indicate that miR-145 can act as an inhibitor of RAD18 and may reverse drug resistance after chemotherapy [73]. Of the targets of miR-1290 is the hMSH2 protein. Inhibition of hMSH2 expression by this miRNA induces resistance of CRC cells to 5-FU [74] (Table 1). The mechanism of DNA repair is a factor that reduces DNA damage. Any change in the gene expression of this system is involved in increased DNA damage. Irregularities in the miRNAs expression of DNA damage repair, by targeting the expression of the system's proteins, and they are effective in developing drug resistance by increasing DNA damage.

The role of selected miRNAs in impaired apoptosis

Programmed cell death (apoptosis) is a complex cell death process. It is caused by several biochemical events to eliminate unwanted cells in tissue homeostasis. Apoptosis occurs in cells through extrinsic and/or intrinsic apoptotic pathways in cells [75]. Cancer cells have the deficiency of apoptosis [76], and Chai et al. [77] reported that the up-regulation of miR-20a is associated with oxaliplatin resistance by targeting B-cell lymphoma 2 (BCL2)/adenovirus E1B protein-interacting protein 2 (BNIP2) as an apoptotic protector. In HCT-116 cell lines, it has been asserted that miR-425 overexpression has a role by programmed cell death 10 (PDCD10) down-regulation that may lead to 5-FU and oxaliplatin resistance [78]. Many miRNAs play a significant role in drug resistance by inducing the expression of apoptosis-related genes, especially BCL-2 family genes. In drug resistance to 5-FU in CRC, the low-expression of miR-206 relates to overexpression of BCL2 as an inhibiting

factor of apoptosis [79]. Furthermore, the overexpression of miR-148a, miR-125a-5p, and miR-143 decrease BCL2 expression [80, 81], and miR-143 induces the expression of 3,8, and 9 caspases and enhance the apoptosis in CRC cells [82]. In colon cancer cells, miR-520 g overexpression promotes chemoresistance to 5-FU or oxaliplatin by inhibiting apoptosis in vitro and in vivo. miR-520 g targets p53 and (p21), both of which play essential roles in CRC response to chemotherapy. Thus, inhibition of miR-520 g or restoration of p21 expression may have therapeutic potential in eliminating drug resistance in patients with CRC (especially in p53 mutation carriers) [67]. A study has shown that miR-587 suppresses 5-FU-induced apoptosis in vitro and reduces the ability of 5-FU for inhibiting tumor growth in a mouse xenograft model in vivo. miR-587 moderates the serine/threonine-protein phosphatase 2A regulatory subunit A beta isoform (PPP2R1B) expression, a regulatory subunit of protein phosphatase 2 (PP2A) complex, which inhibits its AKT activation. Subsequently, suppressed expression of PPP2R1B induces AKT phosphorylation and leads to overexpression of the X-linked inhibitor of apoptosis protein (XIAP) and drug resistance to 5-FU. It has also demonstrated that MK2206, a candidate drug for cancer treatment and effective AKT inhibitor, acts through suppressing miR-587 and decreasing 5-FU resistance. Examination on CRC specimens has shown that expression of miR-587 and PPP2R1B positively and inversely associate with drug resistance, respectively [83]. Over-expression of miR-153 promotes CRC invasion and resistance to oxaliplatin and cisplatin in vitro and in vivo. Also, miR-153 indirectly induces matrix metalloprotease enzyme 9 (MMP-9) and directly mediates forkhead box O3a (FOXO3a) suppression that leads to invasiveness and drug resistance, respectively [84]. The miRNA expression profiles investigation in two CRC cell lines (HCT116 and HT29) shows that excessive expression of miR-503-5p induces resistance to oxaliplatin-induced apoptosis by reducing p53 up-regulated modulator of apoptosis (PUMA) expression in vitro and in vivo. This study has reported PUMA expression leads to miR-503-5p inhibition and increased sensitivity of CRC cells to oxaliplatin. More importantly, analysis of CRC patient samples has shown that miR-503-5p expression is associated with PUMA low-expression [85]. Studies have shown that decreased expression of miR-1915 in HCT116 cells increases the expression of Bcl-2 protein in cancer cells, and it leads to drug resistance to oxaliplatin. Upregulation of miR-1915 is associated with the sensitization of cancer cells to oxaliplatin [86]. One of the regulators of the apoptotic pathway is miR-129. This miRNA inhibits cell proliferation and cell cycle and promotes apoptosis. Up-regulated miR-129 also sensitizes CRC cells to 5-FU by inhibiting Bcl-2 and cleavage of caspase-9 and caspase-3 [87]. Survivin (baculoviral inhibitor of apoptosis repeat-containing5 or BIRC5) is one of the proteins in the apoptosis inhibitor family (IAP). Survivin protein acts as a caspase inhibitor. The researchers have found that miR-218 is one of the regulators of survivin expression. In CRC cells, decreased miR-218 expression leads to forced expression of survivin and increases cellular resistance to the cytotoxic effect of 5-FU [88]. One of the major mediators in the ROS-dependent cell death pathway is apoptosis signal-regulating kinase 1 (ASK1). This protein activates c-Jun N-terminal kinase (JNK) and p38 mitogen-activated protein kinases under cellular stress [89, 90]. ASK1 is one of the targets of miR-20a. Studies in CRC cells have shown that miR-20a suppression in cancer cells increases ROS production in cisplatin-treated cells. As ROS increases, ASK1 expression levels and JNK signaling increase. As a result, inhibited Bcl-2 activity induces apoptosis in CRC cells [91]. miRNAs are involved in regulating other members of the BCL-2 family called Bcl-2-like protein 2 (BCL2L2). Expression of this gene is associated with decreased apoptosis in cells under cytotoxic conditions. Expression of miR-195 in CRT cells treated with doxorubicin is associated with decreased drug resistance through reduced BCL2L2 levels [92]. miR-10b is associated with a high incidence of lymphatic invasion in CRC patients. miR-10b is associated with a higher incidence of lymphatic invasion in CRC patients. The Bcl-2 interacting mediator of cell death (BIM) is one of the direct targets of miR-10b. Forced expression of miR-10b in CRC cells induces 5-FU resistance through direct inhibition of BIM [4]. miR-874 is a tumor suppressor in CRC tissues and cell lines. As the disease progresses to malignancy, its expression decreases, leading to cell proliferation and XIAP activation. CRC cells also become resistant to 5-FU in vitro [93] (Table 1). Apoptosis is one of the most important cellular mechanisms that is activated by the formation of unwanted cells in the cell. Any change in the gene expression of this system is involved in the proliferation of unwanted cells such as CRC cancer cells. Regulating miRNAs apoptosis is involved in inhibiting the expression of unwanted cells by targeting the expression of proteins in this system. Drug resistance is occurred by decreased apoptosis due to the irregular expression of these miRNAs.

The role of selective miRNAs in impaired autophagy

Autophagy is a lysosomal degradation procedure that cytoplasmic materials are transported and degraded by lysosomes. But, the goal of autophagy is not to remove materials; instead, it refers to a dynamic recycling process that generates new building blocks and energy for cellular renewal and homeostasis [94]. Recently, considerable attention has been devoted to the role of autophagy in chemotherapy resistance. The studies have shown that autophagy enhances the survival of tumor cells under metabolic and therapeutic stress. Cancer cells maintain their survival by

collecting organelles and cytoplasmic proteins in autophagosomes by transferring them to the lysosomes for energy production. Also, they induce autophagy-related miRNAs [95]. Yu et al. [96] showed that miR-125b plays a role in drug resistance to 5-FU by inducing the C-X-C motif chemokine 12 (CXCL12)/C-X-C chemokine receptor type 4 (CXCR4) axis. CXCL12/CXCR4 axis activation in human CRC cells leads to EMT and overexpression of miR-125b. miR-125b and CXCR4 downregulate the adenomatous polyposis coli (APC) gene. In CRC, miR-125b promotes 5-FU resistance by enhancing autophagy both in vitro and in vivo, thus it plays a prominent role in 5-FU resistance and invasion. miR-125b is involved in the invasion and the expression of EMT and ultimately the increased expression of CXCR4 in cancer. miR-125b is also involved in 5-FU resistance development in CRC by upregulation of an autophagy protein called beclin-1 that contributes to the formation of autophagosomes [96]. Beclin-1 is a direct target of miR-409-3p, expressed in CRC cells. miR-409-3p expression is inversely related to oxaliplatin resistance in CRC. The overexpression of miR-409-3p sensitizes cancer cells to oxaliplatin by suppressing autophagy mediated by beclin-1 [97]. In tumor samples of CRC, decreased miR-409-3p expression is associated with autophagy activity by beclin-1 overexpression in oxaliplatin-resistant compared to oxaliplatin-sensitive CRC cells. High expression of miR-409-3p prevents beclin-1 expression and autophagy activity and increases the sensitivity of CRC cells to oxaliplatin [97]. Among the autophagy proteins involved in CRC are ubiquitin-binding protein p62 (p62 known as SQSTM1), microtubule-associated proteins 1A/1B light chain 3B (LC3-II), and B-cell translocation gene 1 (BTG1). P62 acts as an autophagosome cargo protein; LC3-II is involved in autophagosome biogenesis, and BTG1 acts as a regulator autophagy protein. These proteins are targets of miR-22. Increased expression of miR-22 is involved in the sensitization of CRC cells to 5-FU through inhibition of autophagy. These proteins are targets of miR-22. Increased expression of miR-22 is involved in the sensitization of CRC cells to 5-FU through inhibition of autophagy. Inhibition of autophagy occurs by p62 overexpression, down-regulation of LC3-II, and BTG1 [95] (Table 1). Increased autophagy in CRC cancer cells accelerates the progression of cancer by creating drug resistance. Increased expression of autophagic proteins occurs when their regulatory miRNAs become uncontrolled.

The role of selected miRNAs in key enzymes alteration

Dihydropyrimidine dehydrogenase (DPD) is the rate-limiting enzyme in the pathway of uracil and thymine catabolism. DPD is also the principal enzyme involved in the degradation of 5-FU. The overexpression of the DPD correlates with a short half-life of 5-FU and chemoresistance cancer cells because of the fast elimination of 5-FU. Studies have shown that the miR-494 expression decreases in 5-FU-resistant SW480 cells as compared to parental cells. Also, ectopic expression of miR-494 increases sensitivity to 5-FU in chemoresistant CRC cells and xenografts by DPD coding gene (DPYD) down-regulation [98]. Decreased activity of DPD in patients due to long-term exposure to 5-FU increases the risk of 5-FU toxicity [99]. Other miRNAs that affect 5-FU metabolic enzymes include miR-21 which increases the sensitivity of the 5-FU in CRC HT-29 cells by indirectly reducing the expression of thymidine phosphorylase (TP) and DPD (by targeting MSH2) [100]. Another enzyme involved in 5-FU metabolism is thymidylate synthase (TYMS). This enzyme is involved in the biosynthesis of thymidylate, a nucleotide involved in the structure of DNA. One study showed that the expression of miR-375-3p in CRC cells inhibited TYMS and sensitized cancer cells to 5-FU [101]. miR-197 [102] and miR-203 as the tumor suppressor by binding to TYMS reduced its expression. Thus, upregulation of these miRNAs increases the sensitivity of CRC cells to the cytotoxic effect of 5-FU [103] (Table 1). As enzymes involved in drug metabolism are important in both activating and converting them to inactive metabolites, in abnormal conditions such as cancer, they become unusually active, and it leads to drug resistance. One of the factors involved in this irregularity is miRNAs. In cancer, the miRNAs that play the role of tumors suppressor decrease, and instead, the miRNAs that have low expression increase abnormally, and lead to overexpression of drug metabolic enzymes.

The role of selected miRNAs in epigenetic deregulation

Epigenetics is the study of changes in gene functions that can be inherited mitotically or meiotically, excluding alterations in DNA sequence [104]. The epigenetic mechanism regulates the miRNAs expression, and miRNAs affect enzymes and pathway-related genes involved in epigenetic changes [105].

DNA methylation and histone deacetylation are involved in the epigenetic regulation of gene expression. DNA methylation occurs in cytosine-guanine-rich regions (CpG islets), usually in the promoter region of the target gene. This reaction is mediated by DNA methyltransferases and S-adenosyl methionine (SAM) as the methyl donor [106]. Cancer cells display an unusual DNA methylation pattern [76]. DNA hypo and hypermethylation may result in alterations in cell signaling, proliferation, and apoptosis, all of which act in favor of cancer cells [76, 107]. Three DNA methyltransferases (DNMTs) are involved in tumorigenesis: DNMT1 (which is a maintenance DNMT), DNMT3A, and

DNMT3B (de novo DNMTs) [108, 109]. Histone deacetylases (HDACs) or methyltransferases represent two classes of enzymes that remove acetyl-groups from or transfer methyl-groups to amino acid residues of histones, respectively [110]. Epigenetic modulation alerts the chromatin structure towards transcription or replication. In CRC, promoter regions of CpG island hypermethylation are associated with transcriptional inactivation of miRNA genes [111]. Shi et al. [112] demonstrated that DNA methylation led to miR-181a, miR-135a, and miR-302c down-regulation in CRC patients with MSI, inflicting 5-FU resistance. Therefore, reduced expression of miR-181a, miR-135a, and miR-302c via targeting the pleiomorphic adenoma gene 1/insulin-like growth factor 2 (PLAG1/IGF2) signaling pathway, have an essential role in the development of drug resistance to 5-FU. Therefore, reduced expression of miR-181a, miR-135a, and miR-302c via targeting the pleiomorphic adenoma gene 1/insulin-like growth factor 2 (PLAG1/IGF2) signaling pathway is essential in the development of drug resistance to 5-FU. In addition, hypermethylation in the CpG islands of the miR-26b promoter region induces 5-FU resistance in CRC cell lines (HT-29/LOVO Also, miR-26b expression and P-gp in colorectal tumor samples have shown an inverse correlation with each other [52]. Histone deacetylases involve in controlling nucleosome conformation, gene expression [113], cell cycle regulation, and cell differentiation. Any change in the expression of HDACs is associated with cancer [114]. Histone deacetylases 4 (HDAC4), one of the subtypes of HDACs, is regulated by miR-140. The authors have claimed that miR-140 induces chemoresistance to methotrexate and 5-FU in osteosarcoma and colon cancer cells by suppressing HDAC4 [115] (Table 1). Phenotypic changes caused by epigenetic mechanisms are important in gene function. Therefore, for any reason, such as CRC, the expression of some miRNAs involved in the expression of methyltransferase and deacetylase enzymes change cell proliferation and replication continue, and the cytotoxic effect of the drug reduces.

The role of selected miRNAs in epithelial-mesenchymal transition abnormal

EMT is a dynamic process during which epithelial cells lose certain characteristics (cellular polarity and cell-to-cell adhesion) and convert to mesenchymal stem cells that can subsequently transdifferentiate into cell types. EMT is involved in many different processes, including the formation of mesoderm and neural tube, wound healing, and the onset of metastasis in most cancers. Also, EM develops chemoresistance by transient epigenetic modifications in genes that are overexpressed in chemo-resistant cells undergoing EMT. miR-139-5p significantly suppresses the EMT and increases chemosensitivity in CRC to 5-FU by lowering the anti-apoptosis protein BCL2 expression [116]. Furthermore, miR-514b-3p accelerates apoptosis in cisplatin-and irinotecan-treated CRC cells by inhibiting EMT through up-and downregulation of epithelial regulation (E-cadherin and claudin 1) and mesenchymal markers (fibronectin-1 and vimentin), respectively [117]. It is well-known that doxorubicin is associated with drug resistance in CRC. miR-223 overexpression reduces sensitivity to doxorubicin. In particular, it has been suggested that miR-223 is involved in drug resistance through EMT induction by reducing F-box and WD repeat domain-containing 7 (FBXW7). Overexpression of FBXW7 as a tumor suppressor and one of the most commonly deregulated ubiquitin–proteasome system proteins in human cancer increases doxorubicin sensitivity in CRC cells [118]. Studies have shown that a transcription factor called zinc finger E-box-binding homeobox1 (ZEB1) may be involved in inducing the overexpression of EMT. This process occurs by binding ZEB1 to the E-box elements of CDH1 (encoding E-cadherin) and reducing E-cadherin expression [119]. ZEB1 is a direct target of miR-200c detected. Increased expression of ZEB1 was observed in oxaliplatin-resistant CRC cells through downregulating miR-200c and miR-141 [120]. As downregulation of miR-200c and miR-141 are associated with EMT upregulation (Table 1); thus, increased expression of EMT by miRNAs tends CRC cells to metastasize and become drug-resistant.

The role of selected miRNAs in CSCs abnormal

Stem cells can differentiate into other cells or divide in a self-renewal manner to produce more stem cells. According to tumor heterogeneity theory, there are cells in a tumor that can act as tumor-initiating cells and non-tumor-initiating cells. Tumor-initiating cells, which have the property of self-renewal and proliferation, are known as cancer stem cells (CSCs) [121]. Despite that both adult stem (undifferentiated cells) and differentiated/cancer cells have been proposed as possible cells of origin of CSCs, the exact "ancestor" cells remain still obscure [122].

Studies are ongoing, and a particular focus has been on inhibiting the proliferation of these cells in cancer. Many anti-tumor therapies target rapid cell division. However, CSCs exhibit several defense mechanisms that allow them to escape chemotherapy, thus promoting chemoresistance and tumor relapse [59]. CRC-SCs have a significant effect on the development of chemoresistance by maintaining the characteristic properties of CSCs [123]. miRNAs can also induce drug resistance by regulating the properties of CSCs [124]. The expression of miR-141 in CRC cells differentiates stem cells and inhibits cell proliferation. Cyclin type D protein is one of the proteins affected by miR-141 [125]. Cyclin D2 is a major regulator of the cell cycle and self-renewal of human embryonic stem cells; therefore, miR-141 reduces the

expression of cyclin D2 and makes CRC cells sensitive to the cytotoxic effects of 5-FU and oxaliplatin [126]. In patients treated with 5-FU, high expression of miR-196b-5p causes disease progression due to drug resistance. When miR 196b-5p expression is knocked out, the stem cell-like phenotype is suppressed, and drug sensitivity is increased [127]. According to Bitarte et al. [59], miR-451overexppression decreases self-renewal, cell proliferation and increases chemosensitivity to irinotecan in CRC-SCs. The authors also found that miR-451 down-regulation increased the expression of cyclooxygenase-2 (COX-2), which promoted CSC growth, via Wnt signaling activation (Table 1). Therefore, CSCs are one of the main factors in the progression and recurrence of cancer. When their growth is stimulated by irregulation of miRNAs, the effectiveness of the drug decreases, and drug resistance increases the severity of the disease.

The role of selected miRNAs in immune suppression

Immunosuppression refers to reduced activation or performance of the immune response. Numerous studies have revealed that cancer cells have a main function in the recurrence and progression of tumors, exhibiting suppressive effects on the host immune system [128, 129]. T cells, or T lymphocytes, are essential components of the immune system, and there are three types of these cells in the immune system. Cytotoxic T cells (Tc) that kill infected host cells in the setting of infection, cancer, and helper T cells (Th) stimulate the activity of other immune cells; [130, 131] and regulatory T cells (Tregs) regulate immune responses [132]. Some miRNAs are associated with Treg homeostasis, T lymphocyte proliferation, and cytokine production in normal and cancer tissues [133, 134]. Khorrami et al. [135] co-cultured colon cancer HT-29 cells with peripheral blood mononuclear cells from healthy subjects to investigate possible associations between miRNAs and tumor development through the promotion of immunosuppression. According to their results, miR-146a overexpression: (i) induces immune suppression [by increasing transforming growth factor-β (TGF-β), interleukin-10 (IL-10), and Treg expression], and (ii) may associate with resistance to 5-FU and irinotecan (Table 1). Thus, cancer cells reduce the effectiveness of chemotherapy drugs and increase drug resistance by inhibiting the immune system by specific miRNAs.

Conclusion

CRC is among the most common malignancies with increasing incidence rates over the last decades. Toxicity and drug resistance to 5-FU and other chemotherapeutic drugs are major problems in CRC treatment. Also, numerous studies have demonstrated the importance of miRNAs in the development of drug resistance in CRC through disruption of various cellular mechanisms such as drug efflux, cell cycle arrest, DNA damage repair mechanisms, apoptosis, autophagy, key enzymes, epigenetic, EMT, stem cells, and immune system. Nowadays, delivery systems have been designed that can be effective in treating cancer by specific miRNAs carrier to specific target [136]. These technologies are supposed to be used for the benefit of cancer patients.

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