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Review article

MicroRNAs and colorectal cancer chemoresistance: New solution for old problem

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ABSTRACT

Background: Colorectal cancer (CRC) is one of the most common gastrointestinal malignancies with a significant mortality rate. Despite the great advances in cancer treatment in the last few decades, effective treatment of CRC is still under challenge. One of the main problems associated with CRC treatment is the resistance of cancer cells to chemotherapy drugs.

Methods: Many studies have been carried out to identify CRC chemoresistance mechanisms, and shed light on the role of ATP-binding cassette transporters (ABC transporters), enzymes as thymidylate synthase, some signaling pathways, and cancer stem cells (CSC) in chemoresistance and failed CRC chemotherapies. Other studies have also been recently carried out to find solutions to overcome chemoresistance. Some of these studies have identified the role of miRNAs in chemoresistance of the CRC cells and the effective use of these micro-molecules to CRC treatment.

Results: Considering the results of these studies, more focus on miRNAs likely leads to a proper solution to overcome CRC chemoresistance.

Conclusion: The current study has reviewed the related literature while discussing the efficacy of miRNAs as potential clinical tools for overcoming CRC chemoresistance and reviewing the most important chemoresistance mechanisms in CRC cells.

1. Background

CRC is one of the most common types of cancer with a global incidence of 6.1% and a mortality rate of 9.2% in 2018. It is the third common cancer in both males and females in terms of its incidence and mortality rate [1]. Generally, CRC is divided into three families encompassing sporadic, inflammation-dependent, and familial CRC which is altered in molecular mechanisms of cancer development. For example, in familial CRC, hereditary mutation occurs in adenomatous polyposis coli (APC) suppressor tumor gene, and some other mutations gradually occur in the P53 suppressor tumor gene, while the hereditary factor has not been involved in sporadic CRC, and mutations occur with

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aging [2–4]. Chronic inflammation plays a major role in tumorigenic activity in the inflammation-dependent CRC that occurs in patients with inflammatory bowel disease (IBD) [5]. Among the three CRCs, sporadic type accounts for the highest prevalence (≈75%) [6]. As mentioned above, the risk of this type of CRC is increased with age, therefore, screening is recommended over 50 years old, because the early diagnosis has significantly increased the chance of successful treatment. However, screening is recommended at younger ages in people with a family history of CRC which is diagnosed with colonoscopy and histopathological examinations and medical imaging to detect metastasis [7]. Current CRC treatment approaches (traditional therapies) include surgery, chemotherapy, and radiotherapy simultaneously. The 5-year survival for CRC patients is about 60% and if it is detected at early stages, the 5-year survival rate could increase to 90%. However, only 39% of colorectal cancers are diagnosed at this stage due to a lack of effective screening programs in many countries [9]. Undoubtedly, one of the most important barriers to effective treatment of CRC is the problem of chemoresistance that leads to chemotherapy failure, cancer recurrence, metastasis, and ultimately patient's death. Many studies have been carried out to identify the mechanisms of chemoresistance and to find solutions to overcome this fundamental problem including promising results. For example, one recent study has shown that melatonin increases the sensitivity of CRC cells to chemotherapy through the down-regulation of thymidylate synthase [10]. The role of thymidylate synthase in chemoresistance of CRS cells is explained in the next sections. The main focuses of recent studies are on miRNA as small, non-coding RNA molecules that are about 20 to 22 nucleotides long, targeting mRNAs results in mRNA instability and prevents them from being translated [11]. Also, they have focused on the use of miRNAs to overcome CRC chemoresistance, say miR330 can significantly attenuate CRC chemoresistance of cells by inhibiting thymidylate synthase [12]. The current study has reviewed the effectiveness of miRNAs to overcome this problem, along with a brief overview of the mechanisms of chemoresistance in colorectal cancer.

2. Colorectal cancer treatment: a serious challenge

CRC treatment is difficult, thus the success of treatment has highly depended on early diagnosis. Surgery, chemotherapy, radiotherapy, and targeted therapy are common methods for treating CRC known as traditional therapies. Determining the therapeutic strategies also has highly depended on the stage of the disease, which is determined in CRC based on the TNM system. This system determines the stage of solid tumors based on tumor size, and its spreading degree to lymph node (metastasis) [13,14]. In general, CRC has five stages from 0 to IV, the first stage that polyps are created in colon tissue is called stage 0. Subsequently, the polyp can be removed during colonoscopy with forceps.

In stage I, these polyps become cancerous with the ability to invade the underlying mucus layers. Thus, the surgical removal of the tumor is beneficial, and the 5-year survival rate is about 90% [9,16]. In stage II, cancer is spread, however, it is still limited to the colon tissue without involving the lymph nodes. Therefore, surgery is also effective and the survival rate is relatively high. In some cases, adjuvant chemotherapy is also recommended at this stage [16,17]. In stage III, cancer affects the lymph nodes, but it is not metastasized. In addition to surgery, chemotherapy should also be performed and the 5-year survival rate is between 30%–60%. At stage IV, cancer cells spread to other tissues, especially to the liver to make secondary tumors. Accordingly, surgery, chemotherapy, and radiotherapy are performed; however, the 5-year survival rate is very low about 10% [9,16]. As stated earlier, if the disease is detected at the early stages, the chance of success would be higher. However, CRC is usually detected at end stages, so it is difficult to be treated. In addition to the traditional therapies, new therapies such as immunotherapy and cancer vaccines have also been proposed for colorectal cancer treatment, but with low success to effective treatment of cancer without being replaced with chemotherapy. Despite extensive advances in CRC treatment, chemotherapy drugs are still the most commonly used drugs for cancer treatment. 5-fluorouracil (5-FU) and Oxaliplatin are among the most commonly used chemotherapy drugs to treat CRC. 5-FU is one of the oldest chemotherapy drugs that is used intravenously and inhibits thymidylate synthase.

Thymidylate synthase converts deoxyuridine monophosphate (dUMP) into deoxythymidine monophosphate (dTMP) during the methylation process, so inhibition of such enzyme obliviously causes thymidine deficiency and attenuates DNA replication [18]. Some 5-FU metabolites such as 5-fluorouridine triphosphate 5-FUIP are also produced by a series of enzymatic reactions and stimulate cell death [19]. Oxaliplatin is also an effective chemotherapy drug used intravenously, inhibits DNA replication, and induces apoptosis by creating cross-links in DNA structure [20]. In addition, other drugs such as Capecitabine, Doxorubicin, and Irinotecan are common chemotherapy drugs used for colorectal cancer treatment. In spite of the significant anti-tumor properties of these drugs, chemotherapy fails in many cases and releasement occurs due to the resistance of cancer cells to chemotherapy. Chemotherapy drugs usually target rapidly dividing cells, so cancer stem cells (CSCs) which are quiescent in the G0 phase of cell cycle show significant resistance to chemotherapy and play a vital role in the recurrence of disease and metastases [21]. CSCs have other characteristics that led to chemoresistance. Chemoresistance poses a very serious challenge to CRC treatment in which an 8-year survival rate is 53% after surgery and chemotherapy in stage III CRC patients. Thus the amount of treatment failure is approximately half of the cases [22]. Following the recent studies, it is tried to transform CRC into a controllable disease by solving the problem of chemoresistance and increasing the chances of effective treatment, particularly to identify the mechanisms of chemoresistance, while another part focuses on finding solutions to attenuate these mechanisms and increase the sensitivity of CRC cells to chemotherapy. Using miRNAs is one of the solutions with promising results. After reviewing the main mechanisms of chemoresistance, the role of miRNAs in overcoming such a problem has been also discussed.

3. Chemoresistance: a major problem in colorectal cancer treatment

As mentioned in the previous sections, most CRC cases are detected in advanced stages where the survival rate is low because chemotherapy has failed and recurrence of disease is observed in many cases. Many studies have been carried out to find the reasons for CRC chemoresistance led to defining the dimensions of many chemoresistance mechanisms (Fig. 1). In the following, a brief overview of important mechanisms is explained.

3.1. ABC transporters, drug detoxification, and chemoresistance

ABC transporters are transporters presented in the plasma membrane of cells while performing various duties. Overall, these transporters play a vital role in the uptake of nutrients and some of the biosynthetic precursors required by cells as well as the export of certain compounds such as lipids and drugs. These transporters provide the energy needed to transport materials across the membrane through ATP hydrolysis [23]. ABC transporters are classified into seven families, ranging from A to G based on their amino acid sequence differences. Each of them consists of subgroups for example multidrug resistance protein 1 (MDR1) and ABCB1 which possess P-glycoprotein (Pgp) are subgroups of B family (ABCB). Multidrug resistance-associated protein 1 (MRP1) or ABCC1 and breast cancer resistance protein (BCRP) or ABCG2 belong to the C family (ABCC) and G family (ABCG), respectively. ABC transporters can remove toxic drug metabolites from the cell, important in physiological conditions, and prevents cytotoxicity. However, this property of ABC transporters reduces drug concentration

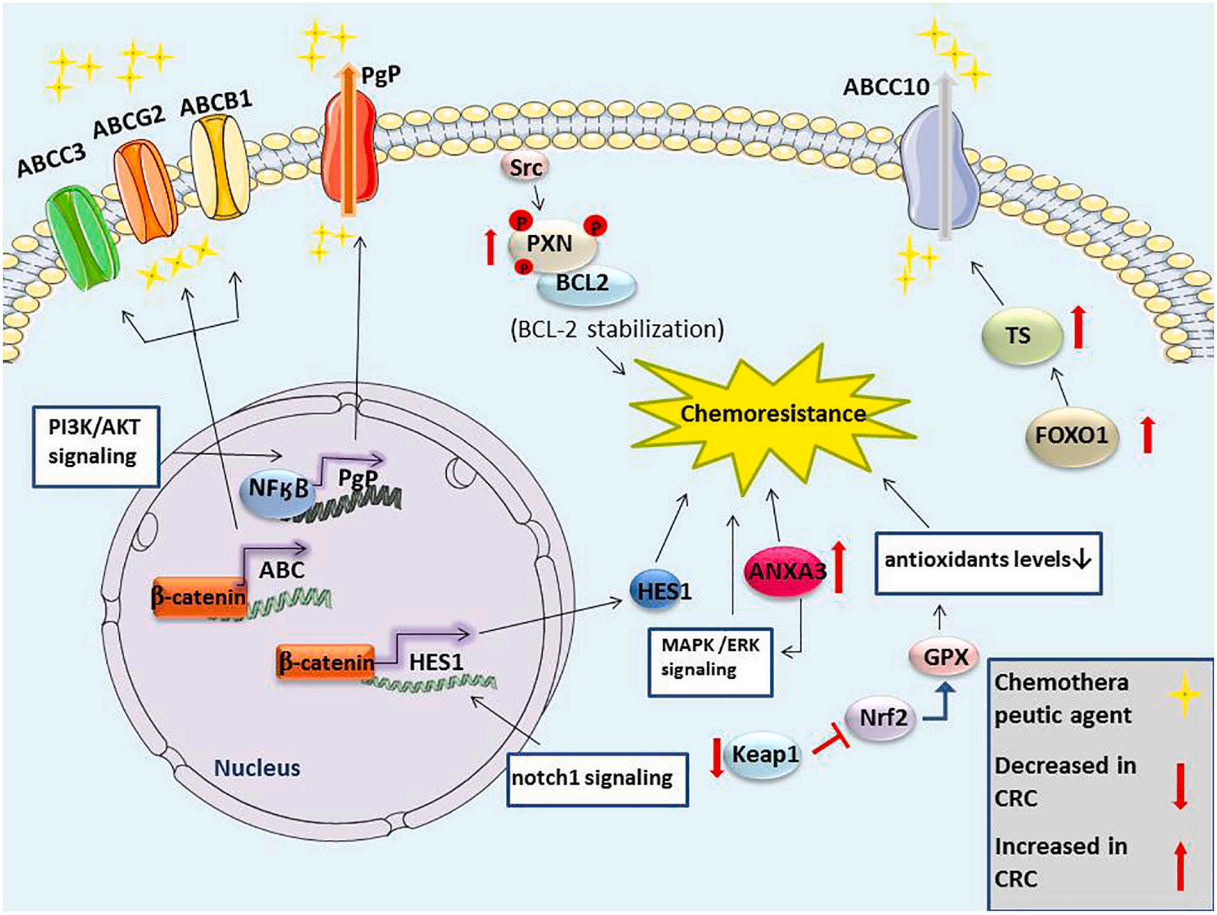

Fig. 1. Chemoresistance mechanisms in the colorectal cancer (CRC): Signaling pathways such as NFKB, Wnt/ β-catenin, and PI3K/AKT lead to ABC transporters overexpression which has a vital role in chemoresistance. Both notch1 and Wnt/β-catenin pathways increase chemoresistance by HES1 gene overexpression. Thymidylate synthase (TS) and FOXO1 are proteins which have overexpressed in CRC and cause to chemoresistance. The ANXA3 levels also increase in CRC, which rises chemoresistance directly as well as indirectly, by increasing the MAPK signaling pathway. Paxillin (PXN) also overexpress in CRC cells and phosphorylates by Src and implicates chemoresistance by BCL-2 stabilization.

in cells and acts as a barrier to the effectiveness of chemotherapy drugs in cancers, regarding its role in destroying cancer cells. Studies have shown the elevated Pgp and MRP1 expression in CRC [24,25]. More interestingly, following the use of chemotherapy drugs, the expression of these transporters is increased in cancer cells and the treatment process consequently became more difficult [26–28]. In addition to playing a role in chemoresistance, some of these transporters enhance some characteristics of cancer cells including their invasiveness. For example, ABCB5 besides its role in 5-FU resistance could increase the invasiveness of CRC cells [29]. Many studies have shown a relationship between the expression of ABC transporters, especially Pgp and some of the signaling pathways. For example, there is a relationship between Pgp and NFKB signaling pathway, and it seems that inhibiting this signaling pathway leads to Pgp downregulation [30]. Studies have also shown a relationship between the AKT/PI3K signaling pathway and Pgp upregulation and CRC chemoresistance [31]. These signaling pathways are regulated by control mechanisms under physiological conditions. For example, PTEN controls AKT/PI3K signaling pathway by inhibiting PI3K; however, this signaling pathway is activated uncontrollably in cancer cells due to the activation of mutations in various components of this pathway, as well as mutations in inhibitors such as PTEN while enhancing chemoresistance [31,32]. In the following sections, further details on the relationship between the signaling pathway and chemoresistance are provided. Conjugation of chemotherapy drugs with some compounds makes these drugs better substrates for ABC transporters. Glutathione is one of the most important compounds. Glutathione and glutathione S transferase (GST) play an important role in detoxification of chemotherapy drugs and can facilitate the function of ABC transporters in the efflux of these drugs. Glutathione is a tripeptide composed of glutamate, cysteine, and glycine, whose reduced form (GSH) is highly important against oxidative stress and detoxification of drugs [33]. Glutathione expression seems to be increased in CRC cells. According to [34], glutathione-producing enzymes have a higher expression rate in colon tumor tissue than normal tissues by using immunohistochemistry analysis [34]. [35] has shown a significant relationship between glutathione upregulation in colon tumor tissue and poor survival in CRC patients [35]. Another study also has shown a relationship between intracellular glutathione and the resistance of cancer cells to Cisplatin. Also, cancer cells can respond to increasing glutathione expression following exposure to Cisplatin, and even the response rate is suggested as a predictor of resistance to Cisplatin chemotherapy [36]. In addition to playing a role in facilitating the function of ABC transporters, especially MRP2, the antioxidant properties of GSH are also important in chemoresistance development because some chemotherapy drugs induce apoptosis in cancerous cells through oxidative stress, and glutathione can make the treatment difficult by neutralizing the oxidative stress [37,38]. Overall, the elevated levels of antioxidants are one of the major barriers to the effectiveness of chemotherapy (discussed later). The role of GST in chemoresistance has not seemed to be limited to the catalysis of the conjugation of chemotherapy drugs with glutathione and detoxification of these drugs. Moreover, it seems that GST can attenuate apoptosis through its non-

enzymatic function. Some chemotherapy drugs trigger apoptosis through the P38-MAPK signaling pathway, and GST attenuates this signaling pathway and induces chemoresistance by targeting JNK as one of the key components of this signaling pathway [37,39]. Immunohistochemistry methods are used by [40] and the results have shown elevated glutathione S-transferase P1 (GSTP1) gene expression in colon tumor tissue in comparison with normal tissue [40]. GST1 targeting seems to be able to overcome the chemoresistance of cancers which is confirmed by the related studies. [41] These studies have shown that the knock-downing GST1 gene has significantly increased the sensitivity of cancer cells to Cisplatin and Carboplatin [41]. Some of the extensive recent studies illustrate many aspects of chemoresistance causes in CRC cells and have referred to the process of detoxification and the efflux of chemotherapy drugs as one of the most important factors in this regard.

3.2. Thymidylate synthase and chemoresistance

As previously mentioned, targeting of thymidylate synthase is one of the most common strategies for CRC chemotherapy and also the attenuation of thymidine synthesis led to the attenuated proliferation of cancer cells. 5-fu is the most commonly used chemotherapy drug that exerts its anti-tumor effects by targeting thymidylate synthase, but one of the major problems that make cancer cells resistant to 5-FU is the overexpression of thymidylate synthase in cancer cells, which in turn attenuates the effects of 5-FU and compensation for thymidine deficiency. It seems that the overexpression of thymidylate synthase in CRC cells is associated with poor overall survival [42], while the down-regulation of this enzyme as well as dihydropyrimidine dehydrogenase which catabolizes 5-FU, are associated with increased sensitivity to 5-FU treatment in CRC [43,44]. It has been recently shown that the overexpression of thymidine phosphorylase, which converts thymidine into thymine, is associated with a recurrence of cancer in stage II/III CRC patients undergoing surgery and chemotherapy [45]. Long-term 5-FU exposure seems to increase the expression of thymidylate synthase and reinforce chemoresistance via an HSP90/src-dependent mechanism in CRC cells [46]. FOXM1 is a proto-oncogene and its expression is increased in colorectal cancer, which can make CRC cells resistant to 5-FU by increasing the expression of thymidylate synthase and ABCC10 transporter [47–49]. Considering the findings of a direct correlation between FOXM1 and thymidylate synthase in colon tumor tissue, and the positive effects of FOXM1 inhibition on increasing the sensitivity of CRC cells to 5-FU, it is hoped to achieve a significant advancement in solving the problem of chemoresistance by targeting FOXM1 [48]. The use of miRNAs has yielded promising results in this regard, which will be discussed in later sections.

3.3. Apoptosis, autophagy, and chemoresistance

Apoptosis and autophagy are two major types of programmed cell death that are significantly different from each other. When a DNA cell is damaged, DNA double-strand breaks (DSBs) (a protein called MRN) binds the site of damage and enhances the activation of ATM and ATR which have kinase activity. These kinases can phosphorylate and activate P53, and P53 can in turn inhibit cell cycle by increasing the expression of P21 [50,51]. This inhibition provides the opportunity for repair mechanisms to resolve the damage before cell division. If these mechanisms have not resolved the damage, the cell destroys itself via apoptosis. In fact, apoptosis is one of the most important barriers to tumorigenesis. P53 plays a key role in apoptosis and can increase the expression of proapoptotic proteins such as BAX [52]. BAX and BAK dimerization in the mitochondrial membrane are resulted in a split in the mitochondrial membrane, the release of cytochrome C, activation of caspase cascade, digestion of proteins, and DNA, and ultimately an apoptotic wrinkled cell remains. The problem of most cancers including CRC is that P53 function is impaired due to mutations resulted in the resistance of cancer cells to apoptosis. One of the most important goals of chemotherapy drugs is the induction of apoptosis. Unlike apoptosis, autophagy plays a double role in cancer cells.

When the cells undergo various stresses such as hypoxia and nutrient deprivation, autophagy signaling begins. Some cell organelles are degraded during the autophagy process to provide the nutrients needed to generate energy and ensure cell survival. Though excessive levels of autophagy can lead to cell death, it can be contributed to cell surveillance under hypoxia or nutrient deprivation conditions in cancerous cells [53]. Cancer treatment has also focused on the strategies for inducing apoptosis, while autophagy induction is not much of interest. One of the most important reasons for cancer development and chemotherapy failure is the resistance of cancer cells to apoptosis. Regarding the overexpression of anti-apoptotic proteins, p53 mutations as well as mutations in pro-apoptotic proteins such as BAX are the most important reasons for the resistance of cancer cells to apoptosis [54,55]. The results of a study on CRC have shown that the expression of BCL-XL (an anti-apoptotic protein) has been increased in colon tumor tissue compared to normal tissue, and such increase is associated with poor post-treatment overall survival [56]. Additionally, Bcl-xL inhibitor, ABT-737 as a molecular drug increases the apoptosis of CRC cells [57]. The results of another study on CRC cells have shown that down-regulation of BAX and upregulation of BCL-XL and BCL2 (another anti-apoptotic protein) are associated with greater resistance to 5-FU [58]. BCL2 performs in CRC chemoresistance via a src-dependent mechanism which is a proto-oncogene and leads to BCL-2 stabilization and the resistance of CRC cells to 5- FU by activating paxillin which is an adaptor protein [59]. Considering the importance of P53 in apoptosis and its effects on the increased expression of pro-apoptotic proteins, P53 mutation is observed in 55–60% of CRC cases and reaches about 80% in metastatic cases [60], also P53 dysfunction is associated with poor prognosis in CRC patients [61]. In addition, it seems that CRC cells with mutated p53 exhibit very strong resistance to 5-FU-based treatment, and apoptosis of these cells is also significantly lower, following the treatment with 5-FU or Oxaliplatin [62,63]. So far, many solutions have been proposed to overcome the problem of resistance to CRC cell apoptosis and the use of BH3 mimics, especially ABT-737 is one of these most promising solutions. Autophagy plays a dual role in cancer cells and though it is sometimes in favor of cancer cell surveillance, autophagy induction can be useful as a therapeutic approach in some circumstances [64]. For example, one study has shown that 5-FU causes cell death in BAX-free CRC cells by inducing autophagy. More interestingly, it seems that Rapamycin induced autophagy promotes the apoptotic and anti-proliferative effects of 5-FU in CRC cells [65]. However, the results of a study on CRC cells have shown that autophagy inhibition has increased the sensitivity to 5-FU in cells that lacking P53, or those having mutated P53 [66]. Considering these controversial findings, it is essential to carry out further studies on the role of autophagy in chemoresistance as well as the interplay between autophagy and apoptosis.

3.4. Signaling and chemoresistance

Undoubtedly, chemoresistance is also related to the signaling pathways similar to many other cell events. So far, many studies have shown the relationship between different signaling pathways with chemoresistance of CRC cells. RAS-MAPK, AKT/PI3K, mTOR, WNT/B-catenin, NFKB, and Notch1 signaling pathways seem to be the most important signaling pathways involved in chemoresistance of CRC cells [67–69]. Many studies have focused on targeting these signaling pathways to overcome CRC chemoresistance, thus some of the results are promising. Accordingly, [70] has reported that the silencing of the WNT/B-catenin signaling pathway reduces the expression of ABCB1 and ABCG2 transporters in chemo-resistant CRC cells and increases the sensitivity of these cells to chemotherapy drugs [70]. It seems there is an interesting relationship between the activity of this signaling

pathway and expression of ABCC3 in CRC cells, thus the elevated ABCC3 expression by this signaling pathway is probably another reason for CRC chemoresistance [71]. The role of the NFKB signaling pathway in increasing the expression of P-gp and chemoresistance is discussed in previous sections. Therefore, biglycan (a leucine-rich proto-glycan) is involved in CRC chemoresistance by enhancing NFKB signaling pathway [72]. ZBTB7 (an important proto-oncogene) seems to increase the resistance of CRC cells to 5-FU by enhancing NFKB signaling pathway [73]. Another study has shown the relationship between the Notch1 signaling pathway and the chemoresistance of CRC cells. As a result, the Notch signaling pathway exerts its effect on chemoresistance probably through the interaction with the WNT/ B-catenin signaling pathway [74]. ANXA3 (a growth-regulating protein) and MAPK /ERK signaling pathway seem to be related to the chemoresistance of CRC cells [75,76]. In this study, the relationship between the AKT/PI3K signaling pathway and P-gp overexpression has been explained. Respectively, [77] has shown that the inhibition of PRDX2 by attenuating the AKT/PI3K signaling pathway increases the sensitivity of CRC cells to 5-FU [77]. Adding that PRDX2 is a protein involved in free radical scavenging and neutralization of oxidative stress-related to AKT/PI3K and NFKB signaling pathways [78], but with many unknown aspects of this relationship. The role of PDRX2 in chemoresistance may be related to its antioxidant properties. However, it seems that further studies are needed in this regard. On the whole, oxidative stress plays a dual role in cancers. Oxidative stress is a phenomenon in which free radical production exceeds the scavenging capacity of the antioxidant response system. These free radicals can cause lipid peroxidation, DNA damage, and cell death, besides harmful effects. Although oxidative stress is involved in the pathogenesis of many human diseases such as diabetes, IBD, and even cancers or causes of tumorigenesis, some chemotherapy drugs utilize oxidative stress in cell death to help cancer treatment by inducing oxidative stress. Therefore, it is obvious that decreasing the antioxidants levels is another mechanism used by cancer cells to resist such drugs [79–82]. This mechanism is also observed particularly in CRC. In this regard, in a study by [83] on CRC cells, the results have shown that concurrent use of 5-FU and antioxidants reduces apoptosis and leads to chemoresistance in CRC cells [83]. Nrf2-Keap1 signaling pathway plays a very important role in regulating antioxidant defense of cells and chemoresistance of colorectal cancer. Keap1 (an adaptor protein) by binding Nrf2 as a transcription factor enhances the ubiquitination and decomposition of Nrf2 under normal circumstances, however, changes occur in cysteine residues in Keap1 under oxidative stress conditions, which weakens the binding of Keap1 to Nrf2 and the stability of Nrf2 [84]. Nrf2 enhances antioxidant defense by increasing the expression of antioxidant enzymes such as glutathione peroxidase, as well as enzymes responsible for the synthesis of glutathione, thereby counteracting the oxidative stress induced by some chemotherapy drugs and causing chemoresistance. In addition, Nrf2 also enhances the expression of some ABC and GST transporters [85,86]. Therefore, in addition to enhancing the neutralization of the apoptotic effects of some chemotherapy drugs, Nrf2 enhances the efflux of such drugs by enhancing antioxidant defense. Results of previous studies on colorectal tumor tissue have shown that Nrf2 expression is increased in colorectal tumor tissue in comparison with normal tissue and there is a direct correlation between the expression of Nrf2 and P-gp in colorectal tumor tissue [87,88]. Real-time quantitative MS-PCR is used in another study by [89], resulting that Nrf2 promoter CpG islands are significantly hypo-methylated in 5-FU-resistant colorectal cancer cells [89]. All evidence has suggested the effective role of Nrf2 in CRC chemoresistance. Therefore, it may be possible to overcome CRC chemoresistance by inhibiting the Nrf2-Keap1 signaling pathway.

3.5. Cancer stem cells and chemoresistance

Chemotherapy drugs can eliminate a significant number of differentiated cancer cells, but without a significant effect on cancer stem cells (CSCs). These cells often survive and subsequently cause recurrence of the disease [90]. In fact, CSCs are the most resistant cancer cells to chemotherapy. In general, being quiescent in the G0 phase of the cell cycle, lack of proliferation, high DNA repair ability, high expression of ABC transporters, and some of the anti-apoptotic proteins are the most important reasons for chemoresistance of CSCs [91]. Some of the cancerous epithelial cells can also take on the characteristics of CSCs under the influence of various signaling pathways, which is called the epithelial-mesenchymal transition (EMT) phenomenon, and excessive invasion capabilities, thus the chemoresistance of these cancer cells is due to this stemness [91,92]. Many studies have focused on targeting CSCs and finding solutions to increase the chemosensitivity of these cells. The use of natural compounds has been one of the most interesting of these solutions, as the combination of some of these compounds, such as Curcumin and thymoquinone with 5-FU has yelled promising results in the elimination of CSCs [93,94]. Curcumin seems to undermine EMT and increase the chemosensitivity of CRC cells through down-regulating some important factors in self-renewal such as Bmi-1 and up-regulating some EMT-suppressive miRNAs [95]. [96] has shown that Huaier aqueous extract is a Chinese medicine that could eradicate colorectal cancer stem cells through weakening the Wnt/b-catenin signaling pathway [96]. Subsequent studies have shown that the period circadian regulator 3 (PER3), which plays a role in the circadian clock, also weakens the chemoresistance and self-renewal ability of the colorectal carcinoma through weakening Wnt/b-catenin and Notch1 signaling pathways, and hence the PER3 expression is reduced in colorectal CSCs and chemotherapy-resistant colorectal CSCs. It is essential to carry out further studies on the role of this gene in chemoresistance [97]. Considering the aforementioned findings, there is a hope that a number of chemotherapy failure cases will be significantly reduced in the future by overcoming the problem of CSCs. It seems that an appropriate approach to achieve such a goal is to focus on miRNAs, which will be discussed later in this study.

4. Micro RNAs and colorectal cancer chemoresistance: from basic science to clinical application

Using miRNAs is one of the most promising solutions to overcome CRC chemoresistance. miRNAs can be used as therapeutic tools, therapeutic goals, and prognostic markers of response to chemotherapy. It is hoped that miRNAs could be used as new clinical tools in the near future to overcome the chronic problem of CRC chemoresistance. This section attempts to provide a comprehensive overview of the most interesting findings of recent years in this field.

4.1. MicroRNAs as therapeutic targets and therapeutic agents for overcoming chemoresistance in colorectal cancer

The most important mechanisms used by CRC cells to resist chemotherapy and some of the approaches suggested to overcome these problems are provided in this section. The use of miRNAs seems to be one of the most promising solutions to overcome CRC chemoresistance. These small molecules are related to all the mechanisms mentioned in previous sections, and targeting or using these molecules have promising results in solving the problem of CRC chemoresistance. Considering the key role of ABC transporters in CRC chemoresistance, a group of studies has examined the relationship between miRNAs with these transporters. [98] has shown that miR522 is down-regulated in Doxorubicin-resistant CRC cells, and using miR522 mimic and overexpressing these miRNAs reduce the expression of ABCB5 and increase the doxorubicin-sensitivity of CRC cells [98]. [99] has shown that miR506 is down-regulated in chemoresistant CRC tissue, which is associated with low 5-year survival. The study has shown that the overexpression of miRNAs increases the Oxaliplatin-sensitivity of CRC cells by attenuating the Wnt/b-catenin signaling pathway and inhibiting the expression of P-gp gene [99]. Therefore, the use of miR506 mimics can

Table 1
Micro RNAs role in colorectal cancer cells chemosensitivity.

miRNAs name	Cellular target	Chemotherapeutic agent that cells are resistant to	Main findings	Ref
miR522	ABC-transporters	Doxorubicin	miR522 ↑ ABCB5↓ chemosensitivity ↑	98
miR506	Wnt/b-catenin signaling pathway	Oxaliplatin	miR506 ↑ expression of P-gp gene ↓ Wnt/b-catenin ↓ chemosensitivity ↑	99
MiR200C	JNK2/c-Jun	5-FU	MiR200C ↑ downstream factors of the JNK signaling pathway ↓ chemosensitivity ↑	101
MiR23a	ABCF1	5-FU	MiR23a ↑ ABCF1 ↓ chemosensitivity ↑	102
MicroRNA-23a	Apoptotic APAF1-Caspas9 pathway	5-FU	MicroRNA-23a ↓ APAF1-Caspas9 ↑ Apoptosis ↑ chemosensitivity ↑	103
MiR297	MRP-2 protein	Platinum	MiR297 ↑ MRP2 expression ↓ chemosensitivity ↑	104
miR133b	miR133b	5-FU	miR133b ↑ miR133b ↓ chemosensitivity ↑	105
MiR519c and miR203	ABCG2	5-FU	MiR519c and miR203 ↑ ABCG2↓ chemosensitivity ↑	106–107
miR142-3P	ABCG2	5-FU	miR142-3P ↑ ABCG2↓ chemosensitivity ↑	108
miR199a/b	Wnt/b-catenin	Cisplatin	miR199a/b↑ ABCG2↑ Wnt/b-catenin↑ chemosensitivity ↑	109
miR3664-5P miR-302c-5p	GSTP1 ABCB1	Oxaliplatin	miR3664-5P ↓ miR-302c-5p↓ GSTP1↓ ABCB1↑ Chemosensitivity ↓	111
miR-203 miR197	Thymidylate synthase	5-FU	miR-203 or miR197 ↑ thymidylate synthase ↓ chemosensitivity ↑	112, 113
miR1307-3P	Thymidylate synthase	Capecitabine	miR1307-3P ↓ thymidylate synthase ↑ chemosensitivity ↓	114
miR192 and miR215	Thymidylate synthase	5-FU	Thymidylate synthase ↓ chemosensitivity not affected	115
miR494	Dihydropyrimidine dehydrogenase	5-FU	miR494 ↓ dihydropyrimidine dehydrogenase ↑ chemosensitivity ↓	116
miR206, MiR148a, and miR125a-5p	BCL2	5-FU	miR206 ↑ BCL2 ↓ Apoptosis ↑ chemosensitivity ↑	117, 118, 119

5-fluorouracil (5-FU)/ATP-binding cassette (ABC)/Glutathione S-transferase P (GSTP).

be a solution to overcome chemoresistance and increase the overall survival in colorectal cancer. MiR200C and miR145 seem to reduce P-gp levels in CRC cells and can increase the chemosensitivity of CRC [100,101]. MiR23a overexpression has also shown that it increases the sensitivity of CRC cells by reducing ABCF1 through microsatellite instability [102]. However, it seems that miRNA attenuates the apoptotic APAF1-Caspas9 pathway, and its antisense has interesting effects on the augmenting apoptotic effects of 5-FU in CRC cells [103]. MiR297 is another miRNA that can be used to overcome CRC chemoresistance. Another study has shown a reverse correlation between the expression of this miRNA and MRP2 expression in colorectal tumor tissue, representing that ectopic expression of this miRNA reduces MRP2 expression levels in chemo-resistant CRC cells and increases the chemosensitivity of these cells [104]. It seems that miR133b can also increase CRC chemoresistance by targeting ABBCC1 and the use of AgomiR133b in combination with chemotherapy drugs has promising results and enhanced the effects of chemotherapy drugs on chemo-resistant CRC cells [105]. Some miRNAs also increase the chemoresistance of CRC cells by targeting ABCG2. MiR519 and miR203 are among these miRNAs [106,107]. It seems that the expression of miR142-3P is also reduced in colorectal tumor tissue, which is associated with an increase in the expression of ABCG2. More interestingly, miR142-3P mimics increase the sensitivity of CRC cells to 5-FU probably by applying inhibitory effects on ABCG2 [108]. Also, miR199a/b can be considered as one of the therapeutic goals to overcome the chemoresistance of CRC cells. miR199a/b increases the expression of ABCG2 by enhancing Wnt/b-catenin signaling pathway and induces resistance to Cisplatin in some CRC cancer stem cells [109]. The role of GST in facilitating the function

of ABC transporters and their importance in chemoresistance is discussed in previous sections. Although there are few studies on the relationship between miRNAs with GST in CRC, previous studies on other cancers have yielded very interesting results. On the other hand, miR133b increases the sensitivity of Cisplatin-resistant lung cancer cells to Cisplatin by targeting GST1 [110]. [111] has reported a reverse correlation between the level of GSTP1 and miR3664-5P in Oxaliplatin-resistant CRC cells [111]. Therefore, miRNA can be considered for further studies.

Overexpression of thymidylate synthase is another mechanism used by CRC cells to resist chemotherapy. A group of studies has also examined the association of miRNAs with this enzyme. Therefore, [112] has shown that miR203 increases the chemosensitivity of CRC cells by targeting thymidylate synthase, thus miR-203- mimic induced miR203 overexpression can be a useful solution to increase the sensitivity of CRC cells to 5-FU [112]. Another study revealed an inverse correlation between the decreased expressions of miR197 and increased expression of thymidylate synthase in the colorectal tumor tissue obtained from CRC stage IV patients. Also, overexpressing of miRNA with miR197 mimics can increase the sensitivity of CRC cells to 5-FU by targeting the thymidylate synthase [113]. MiR330 and miR1307-3P seem to be among other miRNAs that can increase the chemosensitivity of CRC cells by targeting thymidylate synthase [12,114]. Another study showed that miR192 and miR215 could target thymidylate synthase, however, down-regulation of thymidylate synthase with these miRNAs has not significantly affected the increase in sensitivity of CRC cells to 5-FU [115]. In addition to thymidylate synthase, targeting of dihydropyrimidine dehydrogenase with miRNAs can also be a useful solution to increase the chemosensitivity of CRC cells (not studied frequently). However, miR494 has significantly enhanced the sensitivity of CRC cells to 5-FU by targeting this enzyme [116]. Induction of apoptosis is one of the most important mechanisms by which chemotherapy drugs eliminate cancer cells and resistance of cancer cells to chemotherapy drugs. Induced apoptosis is one of the most important problems in treating cancers such as colorectal cancer. Thus, this resistance is caused by mechanisms such as increasing the expression of anti-apoptotic proteins as well as their antioxidant defense capacity. Some studies have focused on the use of miRNAs to overcome the problem of apoptosis resistance in CRC cells provided promising results. Accordingly, miR206 expression is decreased in 5-FU-resistant CRC cells and the overexpression of this miRNA with miR206 mimics reduces the expression of BCL2 expression as an anti-apoptotic protein while increasing the chemosensitivity of CRC cells [117]. MiR148a and miR125a-5p can also target BCL2, and the overexpression of these miRNAs can also be considered as a solution to enhance the apoptosis of CRC cells [118,119]. The information on the role of miRNAs in CRC chemosensitivity summarized in Table 1.

Recently, it has been shown that miR1271 mimics have decreased the expression of BCL2, increased the expression of BAX, and has also significant effects on augmentation of apoptosis and increased sensitivity of CRC cells to Cisplatin [120]. MiR143 also enhances apoptosis by down-regulating BCL2 and increasing the activity of 3,8, and 9 caspases and increases the sensitivity of colorectal cancer cells to 5-FU [121].

As explained before, BCL-XL is also an important anti-apoptotic protein targeted by miR49. miRNA can induce apoptosis in CRC cells by targeting BCL-XL [122]. Studies have shown that miR133a, miR195-5P, and miR874 also have significant effects in enhancing apoptosis and increasing the chemosensitivity of CRC cells [123–125]. MiR34a is another miRNA downregulated in CRC cells, which is relatively contributed to chemoresistance [126]. Also, long non-coding RNA Kcnq1ot1 has a significant effect on the attenuation of apoptosis and chemoresistance of CRC cells, likely applied by targeting miR34a and attenuation of its function [127]. It seems that the above lncRNAs can also downregulate miR760, thereby increasing the chemoresistance in CRC cells [128]. Considering the studies, RNAmimics-induced inhibition of KCNQ1OT1lncRNA and overexpression of miR34a and miR760 can be further explored as new approaches to overcome CRC chemoresistance. Adding that lncRNAs are also non-coding RNA molecules with a length of about 200 nucleotides, therefore, identifying their role in health and disease is among the newest fields of research in medicine and biology [129]. MiR129 is another miRNA that enhances apoptosis by targeting BCL2 and increases the sensitivity of CRC cells to 5-FU [130]. Therefore, the combination of 5-FU with miR129mimic is produced under the name of mimic-1 with 5-FU integration into miR129. It seems that mimic-1 can be delivered to CRC cells without using transfection reagents, moreover, its use has significant effects on the increase of chemosensitivity of cancer stem cells in colorectal cancer [131].

Carrying out further relevant studies in the future can enable the clinical use of miRNAs to overcome the chemoresistance. Another miRNA that can be used to overcome CRC chemoresistance is miR215. It seems that the overexpression of miR215-3p significantly enhances the apoptotic effects of 5-FU on CRC cells. [132]. MiR215 is also associated with CRC-induced liver metastases, and UCLM lncRNAs are likely to exert its stimulatory effects on liver metastases in CRC by attenuating the function of this miRNA [133]. Therefore, it is likely that the use of miR215mimic is an interesting solution for increasing chemosensitivity and attenuating liver metastasis in colorectal cancer.

The effects of miR215 systemic administration on CRC cells in vivo has been conducted to deliver miR215mimic to the tumor site by using liposomes, however, this delivery method is not successful in delivering miR215mimic to the tumor site [134]. In fact, difficult delivery is one of the barriers in the clinical use of miRNA and could be eliminated in further studies.

miR 203a-3p and miR204 seem to play a role in increasing the chemosensitivity of CRC cells targeted by lncRNAs HOTATR and CAT6 lncRNA. These lncRNAs play a role in CRC chemoresistance [135,136]. Therefore, targeting some of the lncRNAs or overexpressing miRNAs targeted by them can be an interesting solution to overcome the chemoresistance in CRC cells. According to [137], Propofol (an anesthetic agent) enhances the apoptosis in CRC cells by attenuating the inhibitory effects of lncRNA HOXAII-AS on miRNA let-7i [137]. However, the action of lncRNAs in CRC chemoresistance needs further explanations for understanding the nature of this effect. As mentioned before, some chemotherapy drugs induce apoptosis in cancer cells by increasing the level of free radicals and causing oxidative stress. One of the mechanisms used by cancer cells to resist apoptosis is the increased antioxidant defense capacity, thus Nrf2 plays a key role in this regard. It is also suggested that targeting the Nrf2-Keap1 signaling pathway is an effective approach to overcome CRC chemoresistance. There are still few studies on the relationship between miRNAs with this pathway in CRC, however, some studies on some other types of cancers have reported very interesting results, say a study on hepatocellular cancer cells shows that the ectopic expression of miR-144 increases the sensitivity of hepatocellular cancers to 5-FU by attenuating Nrf2 [138].

Also, another study on CRC cells has reported an interesting relationship between miR-181c and Nrf2. subsequently, NFE2L2 / NRF2 silencing significantly increases the expression of miR181c, and this overexpression also leads to the attenuated mitochondrial respiratory chain, reduced ATP levels, increased AMPK activity, attenuated fatty acid biosynthesis, and ultimately better responding to AMPK inhibitor treatment [139]. Considering the important role of Nrf2 in resistance to apoptosis and chemoresistance of CRC cells, it is essential to carry out further studies on miR181. Thereafter, the overexpression of this miRNA can be effective in attenuating the chemoresistance of CRC cells. Another study has reported that miR210 can induce apoptosis in CRC cells by increasing the level of free radicals and causing oxidative stress. Therefore, the overexpression of this miRNA is likely to enhance the apoptotic effects of chemotherapy drugs and increase chemo-sensitivity. In addition, miRNAs can be considered as potential therapeutic tools to enhance apoptosis in colorectal cancer cells regarded as

potential therapeutic targets.

Moreover, some miRNAs are contributed to the resistance to apoptosis and CRC chemoresistance like miR338-3P. This miRNA seems to attenuate apoptosis in CRC cells with mutated p53 and cause chemoresistance [141]. MiR520g also attenuates the apoptotic effects of 5-FU and Oxaliplatin on CRC cells. The expression of this miRNA is regulated by P53 which its deletion causes the upregulation of this miRNA. More interestingly, the inhibition of this miRNA in P53-lacking cells has significantly increased their sensitivity to 5-FU [142]. Considering these interpretations and regarding P53 mutation in many CRC cases, this miRNA can be one of the most interesting potential targets to overcome chemoresistance.

MiR 587, miR135b, and miR21 are other miRNAs that attenuate the apoptosis and cause chemoresistance in CRC cells through various mechanisms considered as therapeutic targets to overcome chemoresistance [143–145]. The dual role of autophagy in CRC chemoresistance is explained in previous sections. Therefore, some miRNAs are also associated with autophagy while enhancing the chemosensitivity by attenuating the autophagy process. MiR22 is one of these miRNAs that increases the sensitivity of CRC cells to 5-FU by attenuating the autophagy process, enhancing the apoptosis process [146]. MiR409-3P also increases the sensitivity of CRC cells to Oxaliplatin by attenuating the autophagy process. For example, one study has shown that this miRNA inhibits autophagy by targeting Beclin 1(a key gene in autophagy) and the overexpression of this miRNA with miR409-3Pmimic can significantly increase the sensitivity of CRC cells to Oxaliplatin [147]. It seems that hsa-miR-140-5p can also attenuate the autophagy process. Respectively, this miRNA attenuates the growth, proliferation, and invasion ability of colorectal cancer stem cells by targeting SMAD2, which is a stemness stimulus factor as well as the attenuation of autophagy. The expression of this miRNA is mightily associated with better survival in stage III and IV CRC patients [148]. It seems necessary to carry out further studies on this miRNA, especially accurately examining the effects of its overexpression on chemoresistance. Some miRNAs also play a role in CRC chemoresistance by enhancing autophagy considered as potential therapeutic targets like miR125b. In addition to enhancing autophagy and resistance to 5-FU, this miRNA also has significant stimulatory effects on EMT, and the invasive ability of CRC cells [149] make this miRNA be one of the most interesting therapeutic targets to overcome chemoresistance and effectively CRC treatment. As mentioned before, autophagy is not always in favor of the surveillance of cancer cells, thus the induction of autophagy can have a remarkable effect on the elimination of cancer cells, and miRNAs play a role to enhance these effects. For example, [150] has studied esophageal cancer, showing that miR193b enhances chemotoxicity, and cancer cell death by enhancing autophagy [150]. The results of CRC have presented that miR183 attenuates both apoptosis and autophagy processes, and the inhibition of this miRNA would enhance both of these processes [151]. There are still many unclear aspects of the role of the autography process in chemoresistance of CRC and the relationship between miRNAs and this process needed to be investigated.

Also, some of the signaling pathways are associated with CRC chemoresistance. Alternatively, few studies have shown a significant number of miRNAs that are related to these signaling pathways. NFKB signaling pathway is one of the most important of these pathways while playing an important role in chemoresistance. It seems that miR15 decreases the expression of BCL2 and BCL-XL by attenuating NFKB signaling pathway, and the overexpression of this miRNA has promised results in increasing the sensitivity of CRC cells to 5-FU [152]. MiR 143 that its effects on decreasing the expression of anti-apoptotic proteins and increasing CRC chemoresistance are discussed previously can reduce the expression of NFKB in CRC cells [121,153]. There is also a very interesting relationship between HOTAIR lncRNA, miR218, NFKB signaling pathway, and 5FU resistance in CRC cells. MiR218 seems to increases the sensitivity of CRC cells to 5-FU by attenuating the NFKB signaling pathway, and HOTAIR lncRNA plays a role in CRC chemoresistance by targeting miR218 [154]. MiR221 and miR222 are also among miRNAs that exert stimulatory effects on the NFKB signaling pathway and the inhibition of these miRNAs seems to attenuate the growth of colon tumors in mice [155].

The Notch signaling pathway also plays an important role in chemoresistance and stemness. miR-139-5p and miR-195-5p seem to attenuate the chemoresistance in CRC cells by targeting Notch1 and Notch2, respectively [156,157]. Further studies are required because these miRNAs are also likely to contribute to the attenuation of EMT in CRC cells. Also, their overexpression by using RNA mimics can be considered as a potential therapeutic approach to overcome CRC chemoresistance [158,159]. Wnt/b-catenin signaling pathway can also be targeted by some miRNAs. One of these miRNAs is miR320, which seems to increase the chemoresistance in cancer cells by targeting FOXM1. It is an oncogene as well as attenuating Wnt/b-catenin signaling pathway [160]. The importance of the AKT/PI3K signaling pathway in resistance to apoptosis and chemoresistance is discussed in previous sections. The relationship between a number of miRNAs with this signaling pathway is explained. One of these miRNAs is miR203, which is to increase the chemosensitivity of p53-mutated colon cancer cells by inhibiting AKT2, reducing the expression of BCL-XL, and increasing the expression of BAX [161]. It seems that miR22 also increases the chemosensitivity in p53-mutated colon cancer cells by increasing PTEN expression and attenuating the AKT/PI3K signaling pathway [162]. In contrast, miR17-5P and miR543 enhance the activity of the AKT/PI3K signaling pathway by targeting PTEN and enhances chemoresistance and metastasis in CRC cells [163,164]. On the other hand, the relationship between miRNAs with signaling pathways have been investigated (partly explained here). As a result, a greater focus on the relationship between signaling and miRNAs and CRC chemoresistance can lead to effective solutions in overcoming the chemoresistance. As mentioned earlier, one of the most important barriers to the effectiveness of CRC chemotherapy is the presence of CSCs and EMT. In this case, CSCs can be considered as the most resistant cancer cells to chemotherapy and the main cause of the relapse of disease after chemotherapy. The major goal of studies is to increase chemosensitivity and to eliminate CSCs achieved by focusing on miRNAs and signaling pathways. For example, antagomiR-induced the overexpression of miR145 and inhibiting the expression of miR21 known as an oncogenic miRNA to reduce the proliferation of CSCs and to enhance their differentiation by reducing the expression of CD44, β-catenin, and sox-2 as important factors in stemness [165]. It seems that miR-450b-5p also attenuates stemness by targeting Sox-2 and increases chemosensitivity in CRC cells [166]. MiR-30-5p can also attenuate the expression of CD133 and Sox2, Wnt/b-catenin signaling pathway, and increase chemosensitivity in CRC cells [167]. MiR200 seems to increase the expression of E-cadherin and attenuates EMT in CRC cells. It should be noted that the expression of E-cadherin is decreased in cancer cells during the EMT process, and such a reduced expression is known as the main marker of EMT [168]. As previously mentioned, miR-139-5p and miR-195 -5p attenuate EMT in CRC cells [158,159]. Some miRNAs also exert stimulatory effects on EMT and CRC chemoresistance which is considered as therapeutic targets. MiR21 is one of the important miRNAs seemed to enhance stemness in CRC cells by attenuating the expression of PDCD4, which is contributed to the induction of apoptosis, as well as TGFβR2 while enhancing the expression of CD44 β-catenin and Sox-2 [165,169]. MiR20a-5p also enhances EMT in CRC by targeting SMAD4 [170]. As mentioned earlier, CSCs can be highly resistant to chemotherapy because of its characteristics such as the overexpression of ABC transporters and high DNA repairability. Thus, there is a hope to overcome the CSCs problem and increase the efficacy of chemotherapy in CRC by the overexpression of miRNAs that attenuates stemness and EMT while targeting miRNAs that enhances stemness and EMT by using RNA mimics and antagomiR.

4.2. Micro RNAs as prognostic markers of chemoresistance in colorectal cancer

According to literature, some miRNAs are related to the quality of responses to chemotherapy, surveillance, and CRC recurrence used as predictive markers. MiR218 is one of these miRNAs whose expression is related to a better response to 5-FU in CRC [171]. MiR10b overexpression is also related to 5-FU-resistance in CRC cells. This miRNA can be considered as a predictive marker of survival and response to 5-FU in CRC [172].

MiR625-3P is another miRNA that can be considered as a predictive marker of CRC chemoresistance. It seems that the overexpression of this miRNA is associated with a weaker response to Oxaliplatin in metastatic CRC [173]. This miRNA plus miR-342-3p miR-501-3p, and miR-328-3p can also be used as relapse predictive biomarkers [174]. It seems that the serum and tissue levels of miR429 are increased in CRC patients compared to healthy subjects, and such overexpression is associated with a weaker response to 5-FU, so this miRNA can also be considered as a predictive biomarker of response to chemotherapy in CRC [175]. MiR148a can also be used as a predictor of response to treatment and overall survival in CRC. It seems that the downregulation of this miRNA is associated with a weaker response to treatment and lower overall survival [176]. Also, the miR215 downregulation is associated with the recurrence of CRC and a weaker response to 5-FU, and this miRNA can be used as an independent predictive marker for the recurrence of CRC, following radical surgery [177]. Besides, miR-21-5p predicts the responding to neoadjuvant chemo-radiotherapy in colorectal cancer with 78% sensitivity and 86% specificity [178]. MiR29C can also be used as an early-relapsed predictive marker for colorectal cancer, as [179] has shown that the serum level of this miRNA is significantly increased in early-relapsed colorectal cancer patients compared to non-early relapsed patients [179]. MiR141 and miR125b can also be used as predictive markers for overall survival in colorectal cancer [180,181]. MiR126 is another miRNA that can be used as a predictive biomarker for chemotherapy responses in colorectal cancer. [182] has studied that this miRNA could predict responding to Capecitabine and Oxaliplatin in colorectal cancer with a positive predictive value of 90% and a negative predictive value of 71% [182]. In this case, [183] has provided that changes in miR126 serum levels are related to the response to chemotherapy during the CRC treatment course. In addition, a direct correlation has been observed between the expression of this miRNA and tumor size in CRC patients [183]. on the whole, it seems that miRNAs can be used as predictive markers for responding to chemotherapy, overall survival, and recurrence of colorectal cancer.

5. Conclusion and further direction

Colorectal cancer is one of the most common cancers in men and women. Chemotherapy is one of the oldest approaches to treating colorectal cancer, but chemotherapy drugs fail to treat colorectal cancer effectively in many cases, and the patient dies after a while due to cancer relapses. One of the reasons for the failure of cancer chemotherapy is the resistance of cancer cells to chemotherapy drugs. Cancer cells resist chemotherapy with various mechanisms such as the overexpression of ABC transporters and the efflux of chemotherapy drugs, overexpression of thymidylate synthase, overexpression of anti-apoptotic proteins, and resistance to apoptosis. Colorectal cancer stem cells show strong resistance to chemotherapy as the main cause of the recurrence of colorectal cancer. The attenuation of the aforementioned mechanisms and the increasing chemosensitivity of CRC cells are one of the most important research goals in recent years in colorectal cancer treatment. A significant number of studies have shown that miRNAs are related to different mechanisms of chemoresistance and signaling pathways that are involved in chemoresistance, while these small molecules can be used as therapeutic tools and targets to overcome CRC chemoresistance. In addition, miRNAs seem to be able to serve as prognostic markers for responding to chemotherapy, surveillance, and recurrence of colorectal cancer. To enter these studies into clinical trials and to benefit cancer patients with drug resistance, future studies should look for ways to the optimization of miRNA delivery systems and produce injectable, high stabile miRNA mimics simultaneously with chemotherapy treatments. It would be possible to pave the way for clinical use of these molecules as a new solution to overcome chemoresistance in colorectal cancer in future by conducting further studies, achieving the more accurate perception of the role of various miRNAs in colorectal cancer, and finding more effective solutions for effective delivery of RNA mimics and antagomiRS to the tumor site.

Abbreviations

CRC	Colorectal cancer
ABC transporters	ATP-binding cassette transporters
CSC	cancer stem cells
IBD	inflammatory bowel disease
5-FU	5-fluorouracil
dUMP	Deoxyuridine monophosphate
MDR1	Multidrug resistance protein 1
Pgp	P-glycoprotein
MRP1	Multidrug resistance-associated protein 1
GST	Glutathione S transferase
DSBs	DNA double-strand breaks
EMT	Epithelial-mesenchymal transition
PER3	Period circadian regulator 3.

CRediT authorship contribution statement

Mostafa Vaghari-Tabari and Maryam Majidinia participated in writting article. Durdi Qujeq and Amin Safa participated in the data collecting. Zatollah Asemi and Forough Alemi participated in language editing. Ramin Mohamadzadeh and Nilofar Targhazeh participated in figure design. Bahman Yousefi participated in the study design and revising. All authors read and approved the final manuscript.

Declaration of competing interest

The authors declare that there are no conflict of interest.

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References

[1] F. Bray, J. Ferlay, I. Soerjomataram, R.L. Siegel, L.A. Torre, A. Jemal, Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries, CA Cancer J. Clin. 68 (2018) 394–424, https://doi.org/10.3322/caac.21492 PubMed PMID: 30207593.

[2] R. Dolatkhah, M.H. Somi, M.J. Bonyadi, I. Asvadi Kermani, F. Farassati, S. Dastgiri, Colorectal cancer in Iran: molecular epidemiology and screening strategies, J. Cancer Epidemiol. 2015 (2015) 643020, , https://doi.org/10.1155/2015/643020 (PubMed PMID: 25685149; PubMed Central PMCID: PMCPMC4312646).

[3] S. Narayan, D. Roy, Role of APC and DNA mismatch repair genes in the development of colorectal cancers, Mol. Cancer 2 (2003) 41, https://doi.org/10.1186/1476-4598-2-41 (PubMed PMID: 14672538; PubMed Central PMCID: PMCPMC317355).

[4] L. Roncucci, F. Mariani, Prevention of colorectal cancer: how many tools do we have in our basket? Eur. J. Intern. Med. 26 (2015) 752–756, https://doi.org/10.1016/j.ejim.2015.08.019 (PubMed PMID: 26499755).

[5] S.I. Grivennikov, F. Cominelli, Colitis-associated and sporadic colon cancers: different diseases, different mutations? Gastroenterology 150 (2016) 808–810, https://doi.org/10.1053/j.gastro.2016.02.062 (PubMed PMID: 26924087).

[6] H. Yamagishi, H. Kuroda, Y. Imai, H. Hiraishi, Molecular pathogenesis of sporadic colorectal cancers, Chin. J. Cancer 35 (2016) 4, https://doi.org/10.1186/s40880-015-0066-y (PubMed PMID: 26738600; PubMed Central PMCID: PMCPMC4704376).

[7] I.A. Issa, M. Noureddine, Colorectal cancer screening: an updated review of the available options, World J. Gastroenterol. 23 (2017) 5086–5096, https://doi.org/10.3748/wjg.v23.i28.5086 (PubMed PMID: 28811705; PubMed Central PMCID: PMCPMC5537177).

[9] H. Brenner, M. Kloor, C.P. Pox, Colorectal cancer, Lancet 383 (2014) 1490–1502.

[10] A. Sakatani, F. Sonohara, A. Goel, Melatonin-mediated downregulation of thymidylate synthase as a novel mechanism for overcoming 5-fluorouracil associated chemoresistance in colorectal cancer cells, Carcinogenesis (2018), https://doi.org/10.1093/carcin/bgy186 (PubMed PMID: 30590435).

[11] S. Moein, M. Vaghari-Tabari, D. Qujeq, M. Majidinia, S.M. Nabavi, B. Yousefi, MiRNAs and inflammatory bowel disease: an interesting new story, J. Cell. Physiol. 234 (2019) 3277–3293, https://doi.org/10.1002/jcp.27173 (PubMed PMID: 30417350).

[12] W. Xu, H. Jiang, F. Zhang, J. Gao, J. Hou, MicroRNA-330 inhibited cell proliferation and enhanced chemosensitivity to 5-fluorouracil in colorectal cancer by directly targeting thymidylate synthase, Oncol. Lett. 13 (2017) 3387–3394, https://doi.org/10.3892/ol.2017.5895 (PubMed PMID: 28521444; PubMed Central PMCID: PMCPMC5431319).

[13] J. Brierley, The evolving TNM cancer staging system: an essential component of cancer care, CMAJ 174 (2006) 155–156, https://doi.org/10.1503/cmaj.045113 (PubMed PMID: 16415456; PubMed Central PMCID: PMCPMC1329448).

[14] Vahid Shafiei-Irannejad, Nasser Samadi, Roya Salehi, Bahman Yousefi, Mahdi Rahimi, Abolfazl Akbarzadeh, Reversion of Multidrug Resistance by Co-Encapsulation of Doxorubicin and Metformin in Poly(lactide-co-glycolide)-d-α-tocopheryl Polyethylene Glycol 1000 Succinate Nanoparticles, Pharm. Res. 35 (2018) 119–127, https://doi.org/10.1007/s11095-018-2404-7 (PubMed PMID: 28280604; PubMed Central PMCID: PMCPMC5334064).

[16] J. Mishra, J. Drummond, S.H. Quazi, S.S. Karanki, J.J. Shaw, B. Chen, et al., Prospective of colon cancer treatments and scope for combinatorial approach to enhanced cancer cell apoptosis, Crit. Rev. Oncol. Hematol. 86 (2013) 232–250, https://doi.org/10.1016/j.critrevonc.2012.09.014 (PubMed PMID: 23098684; PubMed Central PMCID: PMCPMC3561496).

[17] A. Varghese, Chemotherapy for stage II colon cancer, Clin. Colon Rectal Surg. 28 (2015) 256–261, https://doi.org/10.1055/s-0035-1564430 (PubMed PMID: 26648796; PubMed Central PMCID: PMCPMC4655109).

[18] D.B. Longley, D.P. Harkin, P.G. Johnston, 5-fluorouracil: mechanisms of action and clinical strategies, Nat. Rev. Cancer 3 (2003) 330–338, https://doi.org/10.1038/nrc1074 (PubMed PMID: 12724731).

[19] M. Hassan, H. Watari, A. AbuAlmaaty, Y. Ohba, N. Sakuragi, Apoptosis and molecular targeting therapy in cancer, Biomed. Res. Int. 2014 (2014) 150845, , https://doi.org/10.1155/2014/150845 (PubMed PMID: 25013758; PubMed Central PMCID: PMCPMC4075070).

[20] T. Alcindor, N. Beauger, Oxaliplatin: a review in the era of molecularly targeted therapy, Curr. Oncol. 18 (2011) 18–25 (PubMed PMID: 21331278; PubMed Central PMCID: PMCPMC3031353).

[21] W. Chen, J. Dong, J. Haiech, M.C. Kilhoffer, M. Zeniou, Cancer stem cell quiescence and plasticity as major challenges in cancer therapy, Stem Cells Int. 2016 (2016) 1740936, , https://doi.org/10.1155/2016/1740936 (PubMed PMID: 27418931; PubMed Central PMCID: PMCPMC4932171).

[22] D. Sargent, A. Sobrero, A. Grothey, M.J. O'Connell, M. Buyse, T. Andre, et al., Evidence for cure by adjuvant therapy in colon cancer: observations based on individual patient data from 20,898 patients on 18 randomized trials, J. Clin. Oncol. 27 (2009) 872–877, https://doi.org/10.1200/jco.2008.19.5362 (PubMed PMID: 19124803; PubMed Central PMCID: PMCPMC2738431).

[23] K.P. Locher, Mechanistic diversity in ATP-binding cassette (ABC) transporters, Nat. Struct. Mol. Biol. 23 (2016) 487–493, https://doi.org/10.1038/nsmb.3216 (PubMed PMID: 27273632).

[24] E. Hinoshita, T. Uchiumi, K. Taguchi, N. Kinukawa, M. Tsuneyoshi, Y. Maehara, et al., Increased expression of an ATP-binding cassette superfamily transporter, multidrug resistance protein 2, in human colorectal carcinomas, Clin. Cancer Res. 6 (2000) 2401–2407 (PubMed PMID: 10873092).

[25] S.C. Linn, G. Giaccone, MDR1/P-glycoprotein expression in colorectal cancer, Eur. J. Cancer 31A (1995) 1291–1294 (PubMed PMID: 7577038).

[26] K.A. Jung, B.H. Choi, M.K. Kwak, The c-MET/PI3K signaling is associated with cancer resistance to doxorubicin and photodynamic therapy by elevating BCRP/ABCG2 expression, Mol. Pharmacol. 87 (2015) 465–476, https://doi.org/10.1124/mol.114.096065 (PubMed PMID: 25534417).

[27] M. Prenkert, B. Uggla, E. Tina, U. Tidefelt, H. Strid, Rapid induction of P-glycoprotein mRNA and protein expression by cytarabine in HL-60 cells, Anticancer Res. 29 (2009) 4071–4076 (PubMed PMID: 19846953).

[28] Maryam Majidinia, Russel Reiter J, Seyed Kazem Shakouri, Bahman Yousefi, et al., The role of melatonin, a multitasking molecule, in retarding the processes of ageing, Ageing Res. Rev. 48 (2018) 198–213, https://doi.org/10.1158/0008-5472.can-11-0221 (PubMed PMID: 21652540; PubMed Central PMCID: PMCPMC3395026).

[29] Q. Guo, T. Grimmig, G. Gonzalez, A. Giobbie-Hurder, G. Berg, N. Carr, et al., ATP-binding cassette member B5 (ABCB5) promotes tumor cell invasiveness in human colorectal cancer, J. Biol. Chem. 293 (2018) 11166–11178, https://doi.org/10.1074/jbc.RA118.003187 (PubMed PMID: 29789423; PubMed Central PMCID: PMCPMC6052213).

[30] Z. Wang, L. Zhang, Z. Ni, J. Sun, H. Gao, Z. Cheng, et al., Resveratrol induces AMPK-dependent MDR1 inhibition in colorectal cancer HCT116/L-OHP cells by preventing activation of NF-kappaB signaling and suppressing cAMP-responsive element transcriptional activity, Tumour Biol. 36 (2015) 9499–9510, https://doi.org/10.1007/s13277-015-3636-3 (PubMed PMID: 26124005).

[31] J. Wang, W. Wang, H. Cai, B. Du, L. Zhang, W. Ma, et al., MACC1 facilitates chemoresistance and cancer stem celllike properties of colon cancer cells through the PI3K/AKT signaling pathway, Mol. Med. Rep. 16 (2017) 8747–8754, https://doi.org/10.3892/mmr.2017.7721 (PubMed PMID: 28990068; PubMed Central PMCID: PMCPMC5779950).

[32] Bahman Yousefi, Nasser Samadi, Yasin Ahmadi, Akt and p53R2, partners that dictate the progression and invasiveness of cancer, DNA Repair 22 (2014) 24–29, https://doi.org/10.1016/j.dnarep.2014.07.001 (PubMed PMID: 25833940; PubMed Central PMCID: PMCPMC4382731).

[33] J.D. Uys, P.J. Mulholland, D.M. Townsend, Glutathione and redox signaling in substance abuse, Biomed. Pharmacother. 68 (2014) 799–807, https://doi.org/10.1016/j.biopha.2014.06.001 (PubMed PMID: 25027386; PubMed Central PMCID: PMCPMC4455547).

[34] A.D. Kim, R. Zhang, X. Han, K.A. Kang, M.J. Piao, Y.H. Maeng, et al., Involvement of glutathione and glutathione metabolizing enzymes in human colorectal cancer cell lines and tissues, Mol. Med. Rep. 12 (2015) 4314–4319, https://doi.org/10.3892/mmr.2015.3902 (PubMed PMID: 26059756).

[35] S.C. Barranco, R.R. Perry, M.E. Durm, M. Quraishi, A.L. Werner, S.G. Gregorcyk, et al., Relationship between colorectal cancer glutathione levels and patient survival: early results, Dis. Colon Rectum 43 (2000) 1133–1140 (PubMed PMID: 10950013).

[36] B. Jamali, M. Nakhjavani, L. Hosseinzadeh, S. Amidi, N. Nikounezhad, H.S. F, Intracellular GSH alterations and its relationship to level of resistance following exposure to cisplatin in cancer cells, Iran J. Pharm. Res. 14 (2015) 513–519 (PubMed PMID: 25901159; PubMed Central PMCID: PMCPMC4403068).

[37] N. Traverso, R. Ricciarelli, M. Nitti, B. Marengo, A.L. Furfaro, M.A. Pronzato, et al., Role of glutathione in cancer progression and chemoresistance, Oxidative Med. Cell. Longev. 2013 (2013) 972913, , https://doi.org/10.1155/2013/972913 (PubMed PMID: 23766865; PubMed Central PMCID: PMCPMC3673338).

[38] Z. Zhu, S. Du, Y. Du, J. Ren, G. Ying, Z. Yan, Glutathione reductase mediates drug resistance in glioblastoma cells by regulating redox homeostasis, J. Neurochem. 144 (2018) 93–104, https://doi.org/10.1111/jnc.14250 (PubMed PMID: 29105080).

[39] B. Cai, S.H. Chang, E.B. Becker, A. Bonni, Z. Xia, p38 MAP kinase mediates apoptosis through phosphorylation of BimEL at Ser-65, J. Biol. Chem. 281 (2006) 25215–25222, https://doi.org/10.1074/jbc.M512627200 (PubMed PMID: 16818494).

[40] H. Bulus, S. Oguztuzun, G. Guler Simsek, M. Kilic, A.O. Ada, S. Gol, et al., Expression of CYP and GST in human normal and colon tumor tissues, Biotech. Histochem. 94 (2019) 1–9, https://doi.org/10.1080/10520295.2018.1493220 (PubMed PMID: 30092668).

[41] L. Sawers, M.J. Ferguson, B.R. Ihrig, H.C. Young, P. Chakravarty, C.R. Wolf, et al., Glutathione S-transferase P1 (GSTP1) directly influences platinum drug chemosensitivity in ovarian tumour cell lines, Br. J. Cancer 111 (2014) 1150–1158, https://doi.org/10.1038/bjc.2014.386 (PubMed PMID: 25010864; PubMed Central PMCID: PMCPMC4453841).

[42] S. Popat, A. Matakidou, R.S. Houlston, Thymidylate synthase expression and prognosis in colorectal cancer: a systematic review and meta-analysis, J. Clin. Oncol. 22 (2004) 529–536, https://doi.org/10.1200/jco.2004.05.064 (PubMed PMID: 14752076).

[43] M. Kornmann, W. Schwabe, S. Sander, M. Kron, J. Strater, S. Polat, et al., Thymidylate synthase and dihydropyrimidine dehydrogenase mRNA expression levels: predictors for survival in colorectal cancer patients receiving adjuvant 5-fluorouracil, Clin. Cancer Res. 9 (2003) 4116–4124 (PubMed PMID: 14519634).

[44] D. Salonga, K.D. Danenberg, M. Johnson, R. Metzger, S. Groshen, D.D. Tsao-Wei, et al., Colorectal tumors responding to 5-fluorouracil have low gene expression levels of dihydropyrimidine dehydrogenase, thymidylate synthase, and thymidine phosphorylase, Clin. Cancer Res. 6 (2000) 1322–1327 (PubMed PMID: 10778957).

[45] N. Kugimiya, E. Harada, Y. Suehiro, A. Suga, Y. Takemoto, K. Hamano, Determination of thymidine phosphorylase expression level facilitates recurrence risk stratification in stage II/III colorectal cancer following adjuvant

chemotherapy with oral fluoropyrimidines, Oncol. Lett. 17 (2019) 5267–5274.
[46] J.Y. Ahn, J.S. Lee, H.Y. Min, H.Y. Lee, Acquired resistance to 5-fluorouracil via HSP90/Src-mediated increase in thymidylate synthase expression in colon cancer, Oncotarget 6 (2015) 32622–32633, https://doi.org/10.18632/oncotarget.5327 (PubMed PMID: 26416450; PubMed Central PMCID: PMCPMC4741717).
[47] R. Douard, S. Moutereau, P. Pernet, M. Chimingqi, Y. Allory, P. Manivet, et al., Sonic Hedgehog-dependent proliferation in a series of patients with colorectal cancer, Surgery 139 (2006) 665–670, https://doi.org/10.1016/j.surg.2005.10.012 (PubMed PMID: 16701100).
[48] V. Varghese, L. Magnani, N. Harada-Shoji, F. Mauri, R.M. Szydlo, S. Yao, et al., FOXM1 modulates 5-FU resistance in colorectal cancer through regulating TYMS expression, Sci. Rep. 9 (2019) 1505, https://doi.org/10.1038/s41598-018-38017-0 (PubMed PMID: 30728402; PubMed Central PMCID: PMCPMC6365533).
[49] T. Xie, J. Geng, Y. Wang, L. Wang, M. Huang, J. Chen, et al., FOXM1 evokes 5-fluorouracil resistance in colorectal cancer depending on ABCC10, Oncotarget 8 (2017) 8574–8589, https://doi.org/10.18632/oncotarget.14351 (PubMed PMID: 28051999; PubMed Central PMCID: PMCPMC5352423).
[50] A. Marechal, L. Zou, DNA damage sensing by the ATM and ATR kinases, Cold Spring Harb. Perspect. Biol. 5 (2013), https://doi.org/10.1101/cshperspect.a012716 (PubMed PMID: 24003211; PubMed Central PMCID: PMCPMC3753707).
[51] T. Abbas, A. Dutta, p21 in cancer: intricate networks and multiple activities, Nat. Rev. Cancer 9 (2009) 400–414, https://doi.org/10.1038/nrc2657 PubMed PMID: 19440234; PubMed Central PMCID: PMCPMC2722839.
[52] J.D. Amaral, J.M. Xavier, C.J. Steer, C.M. Rodrigues, The role of p53 in apoptosis, Discov. Med. 9 (2010) 145–152 (PubMed PMID: 20193641).
[53] R. Mathew, V. Karantza-Wadsworth, E. White, Role of autophagy in cancer, Nat. Rev. Cancer 7 (2007) 961–967, https://doi.org/10.1038/nrc2254 (PubMed PMID: 17972889; PubMed Central PMCID: PMCPMC2866167).
[54] S. Fulda, Tumor resistance to apoptosis, Int. J. Cancer 124 (2009) 511–515, https://doi.org/10.1002/ijc.24064 (PubMed PMID: 19003982).
[55] K. Matsuura, K. Canfield, W. Feng, M. Kurokawa, Metabolic regulation of apoptosis in Cancer, Int. Rev. Cell Mol. Biol. 327 (2016) 43–87, https://doi.org/10.1016/bs.ircmb.2016.06.006 (PubMed PMID: 27692180; PubMed Central PMCID: PMCPMC5819894).
[56] Y. Jin-Song, W. Zhao-Xia, L. Cheng-Yu, L. Xiao-Di, S. Ming, G. Yuan-Yuan, et al., Prognostic significance of Bcl-xL gene expression in human colorectal cancer, Acta Histochem. 113 (2011) 810–814, https://doi.org/10.1016/j.acthis.2011.01.002 (PubMed PMID: 21277008).
[57] A.L. Scherr, G. Gdynia, M. Salou, P. Radhakrishnan, K. Duglova, A. Heller, et al., Bcl-xL is an oncogenic driver in colorectal cancer, Cell Death Dis. 7 (2016) e2342, https://doi.org/10.1038/cddis.2016.233 (PubMed PMID: 27537525; PubMed Central PMCID: PMCPMC5108319).
[58] S. Violette, L. Poulain, E. Dussaulx, D. Pepin, A.M. Faussat, J. Chambaz, et al., Resistance of colon cancer cells to long-term 5-fluorouracil exposure is correlated to the relative level of Bcl-2 and Bcl-X(L) in addition to Bax and p53 status, Int. J. Cancer 98 (2002) 498–504 (PubMed PMID: 11920608).
[59] D.W. Wu, C.C. Huang, S.W. Chang, T.H. Chen, H. Lee, Bcl-2 stabilization by paxillin confers 5-fluorouracil resistance in colorectal cancer, Cell Death Differ. 22 (2015) 779–789, https://doi.org/10.1038/cdd.2014.170 (PubMed PMID: 25323586; PubMed Central PMCID: PMCPMC4392075).
[60] M. Nakayama, M. Oshima, Mutant p53 in colon cancer, J. Mol. Cell Biol. (2018), https://doi.org/10.1093/jmcb/mjy075 (PubMed PMID: 30496442; PubMed Central PMCID: PMCPMC6487790).
[61] A.F. Sarasqueta, G. Forte, W.E. Corver, N.F. de Miranda, D. Ruano, R. van Eijk, et al., Integral analysis of p53 and its value as prognostic factor in sporadic colon cancer, BMC Cancer 13 (2013) 277, https://doi.org/10.1186/1471-2407-13-277 (PubMed PMID: 23739040; PubMed Central PMCID: PMCPMC3682902).
[62] J. Benhattar, J.P. Cerottini, E. Saraga, G. Metthez, J.C. Givel, p53 mutations as a possible predictor of response to chemotherapy in metastatic colorectal carcinomas, Int. J. Cancer 69 (1996) 190–192, https://doi.org/10.1002/(sici)1097-0215(19960621)69:3<190::aid-ijc7>3.0.co;2-v (PubMed PMID: 8682586).
[63] J. Boyer, E.G. McLean, S. Aroori, P. Wilson, A. McCulla, P.D. Carey, et al., Characterization of p53 wild-type and null isogenic colorectal cancer cell lines resistant to 5-fluorouracil, oxaliplatin, and irinotecan, Clin. Cancer Res. 10 (2004) 2158–2167 (PubMed PMID: 15041737).
[64] V.A. Stamelos, C.W. Redman, A. Richardson, Understanding sensitivity to BH3 mimetics: ABT-737 as a case study to foresee the complexities of personalized medicine, J. Mol. Signal. 7 (2012) 1–15.
[65] J.W. Yang, Q.H. Zhang, T. Liu, Autophagy facilitates anticancer effect of 5-fluorouracil in HCT-116 cells, J. Cancer Res. Ther. 14 (2018), https://doi.org/10.4103/0973-1482.204898 S1141-S7. (PubMed PMID: 30539860).
[66] X. Sui, N. Kong, X. Wang, Y. Fang, X. Hu, Y. Xu, et al., JNK confers 5-fluorouracil resistance in p53-deficient and mutant p53-expressing colon cancer cells by inducing survival autophagy, Sci. Rep. 4 (2014) 4694, https://doi.org/10.1038/srep04694 (PubMed PMID: 24733045; PubMed Central PMCID: PMCPMC3986705).
[67] C.A. Martz, K.A. Ottina, K.R. Singleton, J.S. Jasper, S.E. Wardell, A. Peraza-Penton, et al., Systematic identification of signaling pathways with potential to confer anticancer drug resistance, Sci. Signal. 7 (2014) ra121, https://doi.org/10.1126/scisignal.aaa1877 (PubMed PMID: 25538079; PubMed Central PMCID: PMCPMC4353587).
[68] J. Cui, W. Jiang, S. Wang, L. Wang, K. Xie, Role of Wnt/beta-catenin signaling in drug resistance of pancreatic cancer, Curr. Pharm. Des. 18 (2012) 2464–2471 (PubMed PMID: 22372504).
[69] P. Godwin, A.M. Baird, S. Heavey, M.P. Barr, K.J. O'Byrne, K. Gately, Targeting nuclear factor-kappa B to overcome resistance to chemotherapy, Front. Oncol. 3 (2013) 120, https://doi.org/10.3389/fonc.2013.00120 (PubMed PMID: 23720710; PubMed Central PMCID: PMCPMC3655421).
[70] N. Chikazawa, H. Tanaka, T. Tasaka, M. Nakamura, M. Tanaka, H. Onishi, et al., Inhibition of Wnt signaling pathway decreases chemotherapy-resistant side-population colon cancer cells, Anticancer Res. 30 (2010) 2041–2048 (PubMed PMID: 20651349).
[71] M. Kobayashi, R. Funayama, S. Ohnuma, M. Unno, K. Nakayama, Wnt-beta-catenin signaling regulates ABCC3 (MRP3) transporter expression in colorectal cancer, Cancer Sci. 107 (2016) 1776–1784, https://doi.org/10.1111/cas.13097 (PubMed PMID: 27709738; PubMed Central PMCID: PMCPMC5198960).
[72] B. Liu, T. Xu, X. Xu, Y. Cui, X. Xing, Biglycan promotes the chemotherapy resistance of colon cancer by activating NF-kappaB signal transduction, Mol. Cell. Biochem. 449 (2018) 285–294, https://doi.org/10.1007/s11010-018-3365-1 (29761248).
[73] Z. Wang, X. Zhao, W. Wang, Y. Liu, Y. Li, J. Gao, et al., ZBTB7 evokes 5-fluorouracil resistance in colorectal cancer through the NFkappaB signaling pathway, Int. J. Oncol. 53 (2018) 2102–2110, https://doi.org/10.3892/ijo.2018.4521 (PubMed PMID: 30106136).
[74] E. Kukcinaviciute, V. Jonusiene, A. Sasnauskiene, D. Dabkeviciene, E. Eidenaite, A. Laurinavicius, Significance of Notch and Wnt signaling for chemoresistance of colorectal cancer cells HCT116, J. Cell. Biochem. 119 (2018) 5913–5920, https://doi.org/10.1002/jcb.26783 (PubMed PMID: 29637602).
[75] R. Xu, J. Yin, Y. Zhang, S. Zhang, Annexin A3 depletion overcomes resistance to oxaliplatin in colorectal cancer via the MAPK signaling pathway, J. Cell. Biochem. (2019), https://doi.org/10.1002/jcb.28720 (PubMed PMID: 30998268).
[76] K. Yang, K. Gao, G. Hu, Y. Wen, C. Lin, X. Li, CTGF enhances resistance to 5-FU-mediating cell apoptosis through FAK/MEK/ERK signal pathway in colorectal cancer, Onco. Targets Ther. 9 (2016) 7285–7295, https://doi.org/10.2147/ott.s108929 (PubMed PMID: 27942222; PubMed Central PMCID: PMCPMC5138041).
[77] J. Xu, S. Zhang, R. Wang, X. Wu, L. Zeng, Z. Fu, Knockdown of PRDX2 sensitizes colon cancer cells to 5-FU by suppressing the PI3K/AKT signaling pathway, Biosci. Rep. 37 (2017), https://doi.org/10.1042/bsr20160447 (PubMed PMID: 28432271; PubMed Central PMCID: PMCPMC5426286).
[78] H. Won, S. Lim, M. Jang, Y. Kim, M.A. Rashid, K.R. Jyothi, et al., Peroxiredoxin-2 upregulated by NF-kappaB attenuates oxidative stress during the differentiation of muscle-derived C2C12 cells, Antioxid. Redox Signal. 16 (2012) 245–261, https://doi.org/10.1089/ars.2011.3952 (PubMed PMID: 21902453).
[79] A. Cort, T. Ozben, L. Saso, C. De Luca, L. Korkina, Redox control of multidrug resistance and its possible modulation by antioxidants, Oxidative Med. Cell. Longev. 2016 (2016) 4251912, , https://doi.org/10.1155/2016/4251912 (PubMed PMID: 26881027; PubMed Central PMCID: PMCPMC4736404).
[80] K. Maiese, New insights for oxidative stress and diabetes mellitus, Oxidative Med. Cell. Longev. 2015 (2015) 875961, , https://doi.org/10.1155/2015/875961 (PubMed PMID: 26064426; PubMed Central PMCID: PMCPMC4443788).
[81] M. Vaghari Tabari, S. Moein, D. Qujeq, M. Kashifard, J. Shokri Shirvani, K. Hajian Tilaki, et al., Evaluation of the potential antioxidant role of high-density lipoprotein-cholesterol (HDL-C) in patients with ulcerative colitis, Ann. Colorectal Res. 5 (2017) e13699, , https://doi.org/10.5812/acr.13699.
[82] M. Vaghari-Tabari, S. Moein, D. Qujeq, M. Kashifard, K. Hajian-Tilaki, Positive correlation of fecal calprotectin with serum antioxidant enzymes in patients with inflammatory bowel disease: accidental numerical correlation or a new finding? Am J Med Sci 355 (2018) 449–455, https://doi.org/10.1016/j.amjms.2017.12.009 (PubMed PMID: 29753375).
[83] Y. Fu, G. Yang, F. Zhu, C. Peng, W. Li, H. Li, et al., Antioxidants decrease the apoptotic effect of 5-Fu in colon cancer by regulating Src-dependent caspase-7 phosphorylation, Cell Death Dis. 5 (2014) e983, https://doi.org/10.1038/cddis.2013.509 (PubMed PMID: 24407236; PubMed Central PMCID: PMCPMC4040661).
[84] M.R. Sadeghi, F. Jeddi, N. Soozangar, M.H. Somi, N. Samadi, The role of Nrf2-Keap1 axis in colorectal cancer, progression, and chemoresistance, Tumour Biol. 39 (2017), https://doi.org/10.1177/1010428317705510 1010428317705510. (PubMed PMID: 28621229).
[85] X. Bai, Y. Chen, X. Hou, M. Huang, J. Jin, Emerging role of NRF2 in chemoresistance by regulating drug-metabolizing enzymes and efflux transporters, Drug Metab. Rev. 48 (2016) 541–567, https://doi.org/10.1080/03602532.2016.1197239 (PubMed PMID: 27320238).
[86] A. Bansal, M.C. Simon, Glutathione metabolism in cancer progression and treatment resistance, J. Cell Biol. 217 (2018) 2291–2298, https://doi.org/10.1083/jcb.201804161 (PubMed PMID: 29915025; PubMed Central PMCID: PMCPMC6028537).
[87] L.C. Chang, C.W. Fan, W.K. Tseng, J.R. Chen, H.P. Chein, C.C. Hwang, et al., Immunohistochemical study of the Nrf2 pathway in colorectal cancer: Nrf2 expression is closely correlated to Keap1 in the tumor and Bach1 in the normal tissue, Appl. Immunohistochem. Mol. Morphol. 21 (2013) 511–517, https://doi.org/10.1097/PAI.0b013e318282ac20 (PubMed PMID: 23455180).
[88] M.R. Sadeghi, F. Jeddi, N. Soozangar, M.H. Somi, M. Shirmohamadi, V. Khaze, et al., Nrf2/P-glycoprotein axis is associated with clinicopathological characteristics in colorectal cancer, Biomed. Pharmacother. 104 (2018) 458–464, https://doi.org/10.1016/j.biopha.2018.05.062 (PubMed PMID: 29793178).
[89] K.A. Kang, M.J. Piao, K.C. Kim, H.K. Kang, W.Y. Chang, I.C. Park, et al., Epigenetic modification of Nrf2 in 5-fluorouracil-resistant colon cancer cells: involvement of TET-dependent DNA demethylation, Cell Death Dis. 5 (2014) e1183, https://doi.org/10.1038/cddis.2014.149 (PubMed PMID: 24743738; PubMed Central PMCID: PMCPMC4001304).
[90] C. Peitzsch, A. Tyutyunnykova, K. Pantel, A. Dubrovska, Cancer stem cells: the root of tumor recurrence and metastases, Semin. Cancer Biol. 44 (2017) 10–24,

https://doi.org/10.1016/j.semcancer.2017.02.011 (PubMed PMID: 28257956).
[91] T. Nunes, D. Hamdan, C. Leboeuf, M. El Bouchtaoui, G. Gapihan, T.T. Nguyen, et al., Targeting cancer stem cells to overcome chemoresistance, Int. J. Mol. Sci. 19 (2018), https://doi.org/10.3390/ijms19124036 (PubMed PMID: 30551640; PubMed Central PMCID: PMCPMC6321478).
[92] S. Foersch, M.F. Neurath, Colitis-associated neoplasia: molecular basis and clinical translation, Cell. Mol. Life Sci. 71 (2014) 3523–3535, https://doi.org/10.1007/s00018-014-1636-x (PubMed PMID: 24830703).
[93] M.I. James, C. Iwuji, G. Irving, A. Karmokar, J.A. Higgins, N. Griffin-Teal, et al., Curcumin inhibits cancer stem cell phenotypes in ex vivo models of colorectal liver metastases, and is clinically safe and tolerable in combination with FOLFOX chemotherapy, Cancer Lett. 364 (2015) 135–141, https://doi.org/10.1016/j.canlet.2015.05.005 (PubMed PMID: 25979230; PubMed Central PMCID: PMCPMC4510144).
[94] Setareh Rezatabar, Ansar Karimian, Vahid Rameshknia, Hadi Parsian, Maryam Majidinai, Tayebeh Azramezani Kopi, et al., RAS/MAPK signaling functions in oxidative stress, DNA damage response and cancer progression, J. Cell. Physiol. 235 (2019) 1–10, https://doi.org/10.1002/jcp.28334 (PubMed PMID: 31097715; PubMed Central PMCID: PMCPMC6522523).
[95] S. Toden, Y. Okugawa, T. Jascur, D. Wodarz, N.L. Komarova, C. Buhrmann, et al., Curcumin mediates chemosensitization to 5-fluorouracil through miRNA-induced suppression of epithelial-to-mesenchymal transition in chemoresistant colorectal cancer, Carcinogenesis 36 (2015) 355–367, https://doi.org/10.1093/carcin/bgv006 (PubMed PMID: 25653233; PubMed Central PMCID: PMCPMC4400529).
[96] T. Zhang, K. Wang, J. Zhang, X. Wang, Z. Chen, C. Ni, et al., Huaier aqueous extract inhibits colorectal cancer stem cell growth partially via downregulation of the Wnt/beta-catenin pathway, Oncol. Lett. 5 (2013) 1171–1176, https://doi.org/10.3892/ol.2013.1145 (PubMed PMID: 23599758; PubMed Central PMCID: PMCPMC3629070).
[97] F. Zhang, H. Sun, S. Zhang, X. Yang, G. Zhang, T. Su, Overexpression of PER3 inhibits self-renewal capability and chemoresistance of colorectal cancer stem-like cells via inhibition of notch and beta-catenin Signaling, Oncol. Res. 25 (2017) 709–719, https://doi.org/10.3727/096504016x14772331883976 (PubMed PMID: 27983919).
[98] G. Yang, O. Jiang, D. Ling, X. Jiang, P. Yuan, G. Zeng, et al., MicroRNA-522 reverses drug resistance of doxorubicin-induced HT29 colon cancer cell by targeting ABCB5, Mol. Med. Rep. 12 (2015) 3930–3936, https://doi.org/10.3892/mmr.2015.3890 (PubMed PMID: 26043974).
[99] H. Zhou, C. Lin, Y. Zhang, X. Zhang, C. Zhang, P. Zhang, et al., miR-506 enhances the sensitivity of human colorectal cancer cells to oxaliplatin by suppressing MDR1/P-gp expression, Cell Prolif. 50 (2017), https://doi.org/10.1111/cpr.12341 (PubMed PMID: 28217977).
[100] K. Ikemura, M. Yamamoto, S. Miyazaki, H. Mizutani, T. Iwamoto, M. Okuda, MicroRNA-145 post-transcriptionally regulates the expression and function of P-glycoprotein in intestinal epithelial cells, Mol. Pharmacol. 83 (2013) 399–405, https://doi.org/10.1124/mol.112.081844 (PubMed PMID: 23166305).
[101] H. Sui, G.X. Cai, S.F. Pan, W.L. Deng, Y.W. Wang, Z.S. Chen, et al., miR200c attenuates P-gp-mediated MDR and metastasis by targeting JNK2/c-Jun signaling pathway in colorectal cancer, Mol. Cancer Ther. 13 (2014) 3137–3151, https://doi.org/10.1158/1535-7163.mct-14-0167 (PubMed PMID: 25205654).
[102] X. Li, X. Li, D. Liao, X. Wang, Z. Wu, J. Nie, et al., Elevated microRNA-23a expression enhances the chemoresistance of colorectal cancer cells with microsatellite instability to 5-fluorouracil by directly targeting ABCF1, Curr. Protein Pept. Sci. 16 (2015) 301–309 (PubMed PMID: 25929864).
[103] J. Shang, F. Yang, Y. Wang, Y. Wang, G. Xue, Q. Mei, et al., MicroRNA-23a antisense enhances 5-fluorouracil chemosensitivity through APAF-1/caspase-9 apoptotic pathway in colorectal cancer cells, J. Cell. Biochem. 115 (2014) 772–784, https://doi.org/10.1002/jcb.24721 (PubMed PMID: 24249161).
[104] K. Xu, X. Liang, K. Shen, D. Cui, Y. Zheng, J. Xu, et al., miR-297 modulates multidrug resistance in human colorectal carcinoma by down-regulating MRP-2, Biochem. J. 446 (2012) 291–300, https://doi.org/10.1042/bj20120386 (PubMed PMID: 22676135).
[105] M. Chen, D. Li, N. Gong, H. Wu, C. Su, C. Xie, et al., miR-133b down-regulates ABCC1 and enhances the sensitivity of CRC to anti-tumor drugs, Oncotarget 8 (2017) 52983–52994, https://doi.org/10.18632/oncotarget.17677 (PubMed PMID: 28881788; PubMed Central PMCID: PMCPMC5581087).
[106] K.K. To, W.W. Leung, S.S. Ng, Exploiting a novel miR-519c-HuR-ABCG2 regulatory pathway to overcome chemoresistance in colorectal cancer, Exp. Cell Res. 338 (2015) 222–231, https://doi.org/10.1016/j.yexcr.2015.09.011 (PubMed PMID: 26386386).
[107] K.K. To, W.W. Leung, S.S. Ng, A novel miR-203-DNMT3b-ABCG2 regulatory pathway predisposing colorectal cancer development, Mol. Carcinog. 56 (2017) 464–477, https://doi.org/10.1002/mc.22508 (PubMed PMID: 27253631).
[108] W.W. Shen, Z. Zeng, W.X. Zhu, G.H. Fu, MiR-142-3p functions as a tumor suppressor by targeting CD133, ABCG2, and Lgr5 in colon cancer cells, J. Mol. Med. (Berl) 91 (2013) 989–1000, https://doi.org/10.1007/s00109-013-1037-x (PubMed PMID: 23619912).
[109] B. Chen, D. Zhang, J. Kuai, M. Cheng, X. Fang, G. Li, Upregulation of miR-199a/b contributes to cisplatin resistance via Wnt/beta-catenin-ABCG2 signaling pathway in ALDHA1(+) colorectal cancer stem cells, Tumour Biol. 39 (2017), https://doi.org/10.1177/1010428317715155 1010428317715155. (PubMed PMID: 28639895).
[110] C. Lin, L. Xie, Y. Lu, Z. Hu, J. Chang, miR-133b reverses cisplatin resistance by targeting GSTP1 in cisplatin-resistant lung cancer cells, Int. J. Mol. Med. 41 (2018) 2050–2058, https://doi.org/10.3892/ijmm.2018.3382 (PubMed PMID: 29328427; PubMed Central PMCID: PMCPMC5810210).
[111] M. Ghanbarian, A. Afgar, R. Yadegarazari, R. Najafi, L. Teimoori-Toolabi, Through oxaliplatin resistance induction in colorectal cancer cells, increasing ABCB1 level accompanies decreasing level of miR-302c-5p, miR-3664-5p and miR-129-5p, Biomed. Pharmacother. 108 (2018) 1070–1080, https://doi.org/10.1016/j.biopha.2018.09.112 (PubMed PMID: 30372807).
[112] T. Li, F. Gao, X.P. Zhang, miR-203 enhances chemosensitivity to 5-fluorouracil by targeting thymidylate synthase in colorectal cancer, Oncol. Rep. 33 (2015) 607–614, https://doi.org/10.3892/or.2014.3646 (PubMed PMID: 25482885).
[113] Z. Sun, N. Zhou, Q. Han, L. Zhao, C. Bai, Y. Chen, et al., MicroRNA-197 influences 5-fluorouracil resistance via thymidylate synthase in colorectal cancer, Clin. Transl. Oncol. 17 (2015) 876–883, https://doi.org/10.1007/s12094-015-1318-7 (PubMed PMID: 26055341).
[114] Q. Chen, Y. Mao, F. Meng, L. Wang, H. Zhang, W. Wang, et al., Rs7911488 modified the efficacy of capecitabine-based therapy in colon cancer through altering miR-1307-3p and TYMS expression, Oncotarget 8 (2017) 74312–74319, https://doi.org/10.18632/oncotarget.19670 (PubMed PMID: 29088787; PubMed Central PMCID: PMCPMC5650342).
[115] V. Boni, N. Bitarte, I. Cristobal, R. Zarate, J. Rodriguez, E. Maiello, et al., miR-192/miR-215 influence 5-fluorouracil resistance through cell cycle-mediated mechanisms complementary to its post-transcriptional thymidilate synthase regulation, Mol. Cancer Ther. 9 (2010) 2265–2275, https://doi.org/10.1158/1535-7163.mct-10-0061 (PubMed PMID: 20647341).
[116] J. Chai, W. Dong, C. Xie, L. Wang, D.L. Han, S. Wang, et al., MicroRNA-494 sensitizes colon cancer cells to fluorouracil through regulation of DPYD, IUBMB Life 67 (2015) 191–201, https://doi.org/10.1002/iub.1361 (PubMed PMID: 25873402).
[117] X. Meng, R. Fu, miR-206 regulates 5-FU resistance by targeting Bcl-2 in colon cancer cells, Onco. Targets Ther. 11 (2018) 1757–1765, https://doi.org/10.2147/ott.s159093 (PubMed PMID: 29636622; PubMed Central PMCID: PMCPMC5881530).
[118] Z. Tong, N. Liu, L. Lin, X. Guo, D. Yang, Q. Zhang, miR-125a-5p inhibits cell proliferation and induces apoptosis in colon cancer via targeting BCL2, BCL2L12 and MCL1, Biomed. Pharmacother. 75 (2015) 129–136, https://doi.org/10.1016/j.biopha.2015.07.036 (PubMed PMID: 26297542).
[119] H. Zhang, Y. Li, Q. Huang, X. Ren, H. Hu, H. Sheng, et al., MiR-148a promotes apoptosis by targeting Bcl-2 in colorectal cancer, Cell Death Differ. 18 (2011) 1702–1710, https://doi.org/10.1038/cdd.2011.28 (PubMed PMID: 21455217; PubMed Central PMCID: PMCPMC3190106).
[120] H. Yao, Q. Sun, J. Zhu, miR-1271 enhances the sensitivity of colorectal cancer cells to cisplatin, Exp. Ther. Med. 17 (2019) 4363–4370, https://doi.org/10.3892/etm.2019.7501 (PubMed PMID: 31086572; PubMed Central PMCID: PMCPMC6489001).
[121] P.M. Borralho, B.T. Kren, R.E. Castro, I.B. da Silva, C.J. Steer, C.M. Rodrigues, MicroRNA-143 reduces viability and increases sensitivity to 5-fluorouracil in HCT116 human colorectal cancer cells, FEBS J. 276 (2009) 6689–6700, https://doi.org/10.1111/j.1742-4658.2009.07383.x (PubMed PMID: 19843160).
[122] H. Nakano, T. Miyazawa, K. Kinoshita, Y. Yamada, T. Yoshida, Functional screening identifies a microRNA, miR-491 that induces apoptosis by targeting Bcl-X(L) in colorectal cancer cells, Int. J. Cancer 127 (2010) 1072–1080, https://doi.org/10.1002/ijc.25143 (PubMed PMID: 20039318).
[123] Y. Dong, J. Zhao, C.W. Wu, L. Zhang, X. Liu, W. Kang, et al., Tumor suppressor functions of miR-133a in colorectal cancer, Mol. Cancer Res. 11 (2013) 1051–1060, https://doi.org/10.1158/1541-7786.mcr-13-0061 (PubMed PMID: 23723074).
[124] C. Feng, L. Zhang, Y. Sun, X. Li, L. Zhan, Y. Lou, et al., GDPD5, a target of miR-195-5p, is associated with metastasis and chemoresistance in colorectal cancer, Biomed. Pharmacother. 101 (2018) 945–952, https://doi.org/10.1016/j.biopha.2018.03.028 (PubMed PMID: 29635904).
[125] J. Han, Z. Liu, N. Wang, W. Pan, MicroRNA-874 inhibits growth, induces apoptosis and reverses chemoresistance in colorectal cancer by targeting X-linked inhibitor of apoptosis protein, Oncol. Rep. 36 (2016) 542–550, https://doi.org/10.3892/or.2016.4810 (PubMed PMID: 27221209).
[126] Y. Akao, S. Noguchi, A. Iio, K. Kojima, T. Takagi, T. Naoe, Dysregulation of microRNA-34a expression causes drug-resistance to 5-FU in human colon cancer DLD-1 cells, Cancer Lett. 300 (2011) 197–204, https://doi.org/10.1016/j.canlet.2010.10.006 (PubMed PMID: 21067862).
[127] Y. Li, C. Li, D. Li, L. Yang, J. Jin, B. Zhang, lncRNA KCNQ1OT1 enhances the chemoresistance of oxaliplatin in colon cancer by targeting the miR-34a/ATG4B pathway, Onco. Targets Ther. 12 (2019) 2649–2660, https://doi.org/10.2147/ott.s188054 (PubMed PMID: 31040703; PubMed Central PMCID: PMCPMC6462170).
[128] D. Xian, Y. Zhao, LncRNA KCNQ1OT1 enhanced the methotrexate resistance of colorectal cancer cells by regulating miR-760/PPP1R1B via the cAMP signalling pathway, J. Cell. Mol. Med. 23 (2019) 3808–3823, https://doi.org/10.1111/jcmm.14071 (PubMed PMID: 30997746).
[129] J.K. Dhanoa, R.S. Sethi, R. Verma, J.S. Arora, C.S. Mukhopadhyay, Long noncoding RNA: its evolutionary relics and biological implications in mammals: a review, J. Anim. Sci. Technol. 60 (2018) 25, https://doi.org/10.1186/s40781-018-0183-7 (PubMed PMID: 30386629; PubMed Central PMCID: PMCPMC6201556).
[130] M. Karaayvaz, H. Zhai, J. Ju, miR-129 promotes apoptosis and enhances chemosensitivity to 5-fluorouracil in colorectal cancer, Cell Death Dis. 4 (2013) e659, https://doi.org/10.1038/cddis.2013.193 (PubMed PMID: 23744359; PubMed Central PMCID: PMCPMC3702282).
[131] N. Wu, A. Fesler, H. Liu, J. Ju, Development of novel miR-129 mimics with enhanced efficacy to eliminate chemoresistant colon cancer stem cells, Oncotarget 9 (2018) 8887–8897, https://doi.org/10.18632/oncotarget.22322 (PubMed PMID:

29507661; PubMed Central PMCID: PMCPMC5823633).
[132] X.W. Li, S.J. Qiu, X. Zhang, Overexpression of miR-215-3p sensitizes colorectal cancer to 5-fluorouracil induced apoptosis through regulating CXCR1, Eur. Rev. Med. Pharmacol. Sci. 22 (2018) 7240–7250, https://doi.org/10.26355/eurrev_201811_16258 (PubMed PMID: 30468467).
[133] D.L. Chen, Y.X. Lu, J.X. Zhang, X.L. Wei, F. Wang, Z.L. Zeng, et al., Long non-coding RNA UICLM promotes colorectal cancer liver metastasis by acting as a ceRNA for microRNA-215 to regulate ZEB2 expression, Theranostics 7 (2017) 4836–4849, https://doi.org/10.7150/thno.20942 (PubMed PMID: 29187907; PubMed Central PMCID: PMCPMC5706103).
[134] J. Merhautova, P. Vychytilova-Faltejskova, R. Demlova, O. Slaby, Systemic administration of miRNA mimics by liposomal delivery system in animal model of colorectal carcinoma, Physiol. Res. 65 (2016) S481-S8. (PubMed PMID: 28006930).
[135] H. Wu, Q. Zou, H. He, Y. Liang, M. Lei, Q. Zhou, et al., Long non-coding RNA PCAT6 targets miR-204 to modulate the chemoresistance of colorectal cancer cells to 5-fluorouracil-based treatment through HMGA2 signaling, Cancer Med. 8 (2019) 2484–2495, https://doi.org/10.1002/cam4.1809 (PubMed PMID: 30938104).
[136] Z. Xiao, Z. Qu, Z. Chen, Z. Fang, K. Zhou, Z. Huang, et al., LncRNA HOTAIR is a prognostic biomarker for the proliferation and chemoresistance of colorectal cancer via MiR-203a-3p-mediated Wnt/ss-catenin signaling pathway, Cell. Physiol. Biochem. 46 (2018) 1275–1285, https://doi.org/10.1159/000489110 (PubMed PMID: 29680837).
[137] Y.L. Ren, W. Zhang, Propofol promotes apoptosis of colorectal cancer cells via alleviating the suppression of lncRNA HOXA11-AS on miRNA let-7i, Biochem. Cell Biol. (2019), https://doi.org/10.1139/bcb-2018-0235 (PubMed PMID: 31013434).
[138] S. Zhou, W. Ye, Y. Zhang, D. Yu, Q. Shao, J. Liang, et al., miR-144 reverses chemoresistance of hepatocellular carcinoma cell lines by targeting Nrf2-dependent antioxidant pathway, Am. J. Transl. Res. 8 (2016) 2992–3002 (PubMed PMID: 27508019; PubMed Central PMCID: PMCPMC4969435).
[139] K.A. Jung, S. Lee, M.K. Kwak, NFE2L2/NRF2 activity is linked to mitochondria and AMP-activated protein kinase Signaling in cancers through miR-181c/mitochondria-encoded cytochrome c oxidase regulation, Antioxid. Redox Signal. 27 (2017) 945–961, https://doi.org/10.1089/ars.2016.6797 (PubMed PMID: 28383996).
[141] J. Han, J. Li, K. Tang, H. Zhang, B. Guo, N. Hou, et al., miR-338-3p confers 5-fluorouracil resistance in p53 mutant colon cancer cells by targeting the mammalian target of rapamycin, Exp. Cell Res. 360 (2017) 328–336, https://doi.org/10.1016/j.yexcr.2017.09.023 (PubMed PMID: 28928082).
[142] Y. Zhang, L. Geng, G. Talmon, J. Wang, MicroRNA-520g confers drug resistance by regulating p21 expression in colorectal cancer, J. Biol. Chem. 290 (2015) 6215–6225, https://doi.org/10.1074/jbc.M114.620252 (PubMed PMID: 25616665; PubMed Central PMCID: PMCPMC4358260).
[143] Y. He, J. Wang, J. Wang, V.Y. Yung, E. Hsu, A. Li, et al., MicroRNA-135b regulates apoptosis and chemoresistance in colorectal cancer by targeting large tumor suppressor kinase 2, Am. J. Cancer Res. 5 (2015) 1382–1395 (PubMed PMID: 26101704; PubMed Central PMCID: PMCPMC4473317).
[144] M. Liu, Q. Tang, M. Qiu, N. Lang, M. Li, Y. Zheng, et al., miR-21 targets the tumor suppressor RhoB and regulates proliferation, invasion and apoptosis in colorectal cancer cells, FEBS Lett. 585 (2011) 2998–3005, https://doi.org/10.1016/j.febslet.2011.08.014 (PubMed PMID: 21872591).
[145] Y. Zhang, G. Talmon, J. Wang, MicroRNA-587 antagonizes 5-FU-induced apoptosis and confers drug resistance by regulating PPP2R1B expression in colorectal cancer, Cell Death Dis. 6 (2015) e1845, https://doi.org/10.1038/cddis.2015.200 (PubMed PMID: 26247730; PubMed Central PMCID: PMCPMC4558495).
[146] H. Zhang, J. Tang, C. Li, J. Kong, J. Wang, Y. Wu, et al., MiR-22 regulates 5-FU sensitivity by inhibiting autophagy and promoting apoptosis in colorectal cancer cells, Cancer Lett. 356 (2015) 781–790, https://doi.org/10.1016/j.canlet.2014.10.029 (PubMed PMID: 25449431).
[147] S. Tan, H. Shi, M. Ba, S. Lin, H. Tang, X. Zeng, et al., miR-409-3p sensitizes colon cancer cells to oxaliplatin by inhibiting Beclin-1-mediated autophagy, Int. J. Mol. Med. 37 (2016) 1030–1038, https://doi.org/10.3892/ijmm.2016.2492 (PubMed PMID: 26935807).
[148] H. Zhai, A. Fesler, Y. Ba, S. Wu, J. Ju, Inhibition of colorectal cancer stem cell survival and invasive potential by hsa-miR-140-5p mediated suppression of Smad2 and autophagy, Oncotarget 6 (2015) 19735–19746, https://doi.org/10.18632/oncotarget.3771 (PubMed PMID: 25980495; PubMed Central PMCID: PMCPMC4637317).
[149] X. Yu, W. Shi, Y. Zhang, X. Wang, S. Sun, Z. Song, et al., CXCL12/CXCR4 axis induced miR-125b promotes invasion and confers 5-fluorouracil resistance through enhancing autophagy in colorectal cancer, Sci. Rep. 7 (2017) 42226, , https://doi.org/10.1038/srep42226 (PubMed PMID: 28176874; PubMed Central PMCID: PMCPMC5296742).
[150] M.J. Nyhan, T.R. O'Donovan, A.W. Boersma, E.A. Wiemer, S.L. McKenna, MiR-193b promotes autophagy and non-apoptotic cell death in oesophageal cancer cells, BMC Cancer 16 (2016) 101, https://doi.org/10.1186/s12885-016-2123-6 (PubMed PMID: 26878873; PubMed Central PMCID: PMCPMC4754993).
[151] L. Huangfu, H. Liang, G. Wang, X. Su, L. Li, Z. Du, et al., miR-183 regulates autophagy and apoptosis in colorectal cancer through targeting of UVRAG, Oncotarget 7 (2016) 4735–4745, https://doi.org/10.18632/oncotarget.6732 (PubMed PMID: 26717041; PubMed Central PMCID: PMCPMC4826239).
[152] L. Liu, D. Wang, Y. Qiu, H. Dong, X. Zhan, Overexpression of microRNA-15 increases the chemosensitivity of colon cancer cells to 5-fluorouracil and oxaliplatin by inhibiting the nuclear factor-kappaB signalling pathway and inducing apoptosis, Exp. Ther. Med. 15 (2018) 2655–2660, https://doi.org/10.3892/etm.2017.5675 (PubMed PMID: 29467857; PubMed Central PMCID: PMCPMC5792766).
[153] P.M. Borralho, A.E. Simoes, S.E. Gomes, R.T. Lima, T. Carvalho, D.M. Ferreira, et al., miR-143 overexpression impairs growth of human colon carcinoma xenografts in mice with induction of apoptosis and inhibition of proliferation, PLoS One 6 (2011) e23787, , https://doi.org/10.1371/journal.pone.0023787 (PubMed PMID: 21901135; PubMed Central PMCID: PMCPMC3162002).
[154] P. Li, X. Zhang, L. Wang, L. Du, Y. Yang, T. Liu, et al., lncRNA HOTAIR contributes to 5FU resistance through suppressing miR-218 and activating NF-kappaB/TS signaling in colorectal cancer, Mol. Ther. Nucleic Acids. 8 (2017) 356–369, https://doi.org/10.1016/j.omtn.2017.07.007 (PubMed PMID: 28918035; PubMed Central PMCID: PMCPMC5537205).
[155] S. Liu, X. Sun, M. Wang, Y. Hou, Y. Zhan, Y. Jiang, et al., A microRNA 221- and 222-mediated feedback loop maintains constitutive activation of NFkappaB and STAT3 in colorectal cancer cells, Gastroenterology 147 (2014) 847–859 e11 https://doi.org/10.1053/j.gastro.2014.06.006 (PubMed PMID: 24931456; PubMed Central PMCID: PMCPMC4839969).
[156] H. Liu, Y. Yin, Y. Hu, Y. Feng, Z. Bian, S. Yao, et al., miR-139-5p sensitizes colorectal cancer cells to 5-fluorouracil by targeting NOTCH-1, Pathol. Res. Pract. 212 (2016) 643–649, https://doi.org/10.1016/j.prp.2016.04.011 (PubMed PMID: 27173050).
[157] Y. Jin, M. Wang, H. Hu, Q. Huang, Y. Chen, G. Wang, Overcoming stemness and chemoresistance in colorectal cancer through miR-195-5p-modulated inhibition of notch signaling, Int. J. Biol. Macromol. 117 (2018) 445–453, https://doi.org/10.1016/j.ijbiomac.2018.05.151 (PubMed PMID: 29852230).
[158] Q. Li, X. Liang, Y. Wang, X. Meng, Y. Xu, S. Cai, et al., miR-139-5p inhibits the epithelial-mesenchymal transition and enhances the chemotherapeutic sensitivity of colorectal cancer cells by downregulating BCL2, Sci. Rep. 6 (2016) 27157, , https://doi.org/10.1038/srep27157 (PubMed PMID: 27244080; PubMed Central PMCID: PMCPMC4886683).
[159] X. Lin, S. Wang, M. Sun, C. Zhang, C. Wei, C. Yang, et al., miR-195-5p/NOTCH2-mediated EMT modulates IL-4 secretion in colorectal cancer to affect M2-like TAM polarization, J. Hematol. Oncol. 12 (2019) 20, https://doi.org/10.1186/s13045-019-0708-7 (PubMed PMID: 30808369; PubMed Central PMCID: PMCPMC6390326).
[160] L.Y. Wan, J. Deng, X.J. Xiang, L. Zhang, F. Yu, J. Chen, et al., miR-320 enhances the sensitivity of human colon cancer cells to chemoradiotherapy in vitro by targeting FOXM1, Biochem. Biophys. Res. Commun. 457 (2015) 125–132, https://doi.org/10.1016/j.bbrc.2014.11.039 (PubMed PMID: 25446103).
[161] J. Li, Y. Chen, J. Zhao, F. Kong, Y. Zhang, miR-203 reverses chemoresistance in p53-mutated colon cancer cells through downregulation of Akt2 expression, Cancer Lett. 304 (2011) 52–59, https://doi.org/10.1016/j.canlet.2011.02.003 (PubMed PMID: 21354697).
[162] J. Li, Y. Zhang, J. Zhao, F. Kong, Y. Chen, Overexpression of miR-22 reverses paclitaxel-induced chemoresistance through activation of PTEN signaling in p53-mutated colon cancer cells, Mol. Cell. Biochem. 357 (2011) 31–38, https://doi.org/10.1007/s11010-011-0872-8 (PubMed PMID: 21594648).
[163] L. Fang, H. Li, L. Wang, J. Hu, T. Jin, J. Wang, et al., MicroRNA-17-5p promotes chemotherapeutic drug resistance and tumour metastasis of colorectal cancer by repressing PTEN expression, Oncotarget 5 (2014) 2974–2987, https://doi.org/10.18632/oncotarget.1614 (PubMed PMID: 24912422; PubMed Central PMCID: PMCPMC4102784).
[164] G. Liu, J. Zhou, M. Dong, Down-regulation of miR-543 expression increases the sensitivity of colorectal cancer cells to 5-fluorouracil through the PTEN/PI3K/AKT pathway, Biosci. Rep. 39 (2019), https://doi.org/10.1042/bsr20190249 (PubMed PMID: 30842340; PubMed Central PMCID: PMCPMC6430726).
[165] Y. Yu, P. Nangia-Makker, L. Farhana, G.R. S, E. Levi, A.P. Majumdar, miR-21 and miR-145 cooperation in regulation of colon cancer stem cells, Mol. Cancer 14 (2015) 98, https://doi.org/10.1186/s12943-015-0372-7 (PubMed PMID: 25928322; PubMed Central PMCID: PMCPMC4415383).
[166] Y. Jin, Z. Jiang, X. Guan, Y. Chen, Q. Tang, G. Wang, et al., miR-450b-5p suppresses stemness and the development of chemoresistance by targeting SOX2 in colorectal cancer, DNA Cell Biol. 35 (2016) 249–256, https://doi.org/10.1089/dna.2015.3120 (PubMed PMID: 26845645).
[167] S. Jiang, D. Miao, M. Wang, J. Lv, Y. Wang, J. Tong, MiR-30-5p suppresses cell chemoresistance and stemness in colorectal cancer through USP22/Wnt/beta-catenin signaling axis, J. Cell. Mol. Med. 23 (2019) 630–640, https://doi.org/10.1111/jcmm.13968 (PubMed PMID: 30338942; PubMed Central PMCID: PMCPMC6307779).
[168] K. Hur, Y. Toiyama, M. Takahashi, F. Balaguer, T. Nagasaka, J. Koike, et al., MicroRNA-200c modulates epithelial-to-mesenchymal transition (EMT) in human colorectal cancer metastasis, Gut 62 (2013) 1315–1326, https://doi.org/10.1136/gutjnl-2011-301846 (PubMed PMID: 22735571; PubMed Central PMCID: PMCPMC3787864).
[169] Y. Yu, S.S. Kanwar, B.B. Patel, P.S. Oh, J. Nautiyal, F.H. Sarkar, et al., MicroRNA-21 induces stemness by downregulating transforming growth factor beta receptor 2 (TGFbetaR2) in colon cancer cells, Carcinogenesis 33 (2012) 68–76, https://doi.org/10.1093/carcin/bgr246 (PubMed PMID: 22072622; PubMed Central PMCID: PMCPMC3276336).
[170] D. Cheng, S. Zhao, H. Tang, D. Zhang, H. Sun, F. Yu, et al., MicroRNA-20a-5p promotes colorectal cancer invasion and metastasis by downregulating Smad4, Oncotarget 7 (2016) 45199–45213, https://doi.org/10.18632/oncotarget.9900 (PubMed PMID: 27286257; PubMed Central PMCID: PMCPMC5216716).
[171] P.L. Li, X. Zhang, L.L. Wang, L.T. Du, Y.M. Yang, J. Li, et al., MicroRNA-218 is a prognostic indicator in colorectal cancer and enhances 5-fluorouracil-induced

apoptosis by targeting BIRC5, Carcinogenesis 36 (2015) 1484–1493, https://doi.org/10.1093/carcin/bgv145 (PubMed PMID: 26442524).
[172] N. Nishida, S. Yamashita, K. Mimori, T. Sudo, F. Tanaka, K. Shibata, et al., MicroRNA-10b is a prognostic indicator in colorectal cancer and confers resistance to the chemotherapeutic agent 5-fluorouracil in colorectal cancer cells, Ann. Surg. Oncol. 19 (2012) 3065–3071, https://doi.org/10.1245/s10434-012-2246-1 (PubMed PMID: 22322955).
[173] M.H. Rasmussen, N.F. Jensen, L.S. Tarpgaard, C. Qvortrup, M.U. Romer, J. Stenvang, et al., High expression of microRNA-625-3p is associated with poor response to first-line oxaliplatin based treatment of metastatic colorectal cancer, Mol. Oncol. 7 (2013) 637–646, https://doi.org/10.1016/j.molonc.2013.02.016 (PubMed PMID: 23506979; PubMed Central PMCID: PMCPMC5528477).
[174] D. Ji, M. Qiao, Y. Yao, M. Li, H. Chen, Q. Dong, et al., Serum-based microRNA signature predicts relapse and therapeutic outcome of adjuvant chemotherapy in colorectal cancer patients, EBioMedicine 35 (2018) 189–197, https://doi.org/10.1016/j.ebiom.2018.08.042 (PubMed PMID: 30166271; PubMed Central PMCID: PMCPMC6156709).
[175] S.J. Dong, X.J. Cai, S.J. Li, The clinical significance of MiR-429 as a predictive biomarker in colorectal cancer patients receiving 5-fluorouracil treatment, Med. Sci. Monit. 22 (2016) 3352–3361 (PubMed PMID: 27654003; PubMed Central PMCID: PMCPMC5036382).
[176] M. Takahashi, M. Cuatrecasas, F. Balaguer, K. Hur, Y. Toiyama, A. Castells, et al., The clinical significance of MiR-148a as a predictive biomarker in patients with advanced colorectal cancer, PLoS One 7 (2012) e46684, , https://doi.org/10.1371/journal.pone.0046684 (PubMed PMID: 23056401; PubMed Central PMCID: PMCPMC3463512).
[177] S. Li, J. Gao, J. Gu, J. Yuan, D. Hua, L. Shen, MicroRNA-215 inhibits relapse of colorectal cancer patients following radical surgery, Med. Oncol. 30 (2013) 549, https://doi.org/10.1007/s12032-013-0549-0 (PubMed PMID: 23532818).
[178] C.M. Lopes-Ramos, A. Habr-Gama, S. Quevedo Bde, N.M. Felicio, F. Bettoni, F.C. Koyama, et al., Overexpression of miR-21-5p as a predictive marker for complete tumor regression to neoadjuvant chemoradiotherapy in rectal cancer patients, BMC Med. Genet. 7 (2014) 68, https://doi.org/10.1186/s12920-014-0068-7 (PubMed PMID: 25496125; PubMed Central PMCID: PMCPMC4279677).
[179] I.P. Yang, H.L. Tsai, C.W. Huang, M.Y. Huang, M.F. Hou, S.H. Juo, et al., The functional significance of microRNA-29c in patients with colorectal cancer: a potential circulating biomarker for predicting early relapse, PLoS One 8 (2013) e66842, , https://doi.org/10.1371/journal.pone.0066842 (PubMed PMID: 23840538; PubMed Central PMCID: PMCPMC3696003).
[180] H. Cheng, L. Zhang, D.E. Cogdell, H. Zheng, A.J. Schetter, M. Nykter, et al., Circulating plasma MiR-141 is a novel biomarker for metastatic colon cancer and predicts poor prognosis, PLoS One 6 (2011) e17745, , https://doi.org/10.1371/journal.pone.0017745 (PubMed PMID: 21445232; PubMed Central PMCID: PMCPMC3060165).
[181] N. Nishida, T. Yokobori, K. Mimori, T. Sudo, F. Tanaka, K. Shibata, et al., MicroRNA miR-125b is a prognostic marker in human colorectal cancer, Int. J. Oncol. 38 (2011) 1437–1443, https://doi.org/10.3892/ijo.2011.969 (PubMed PMID: 21399871).
[182] T.F. Hansen, F.B. Sorensen, J. Lindebjerg, A. Jakobsen, The predictive value of microRNA-126 in relation to first line treatment with capecitabine and oxaliplatin in patients with metastatic colorectal cancer, BMC Cancer 12 (2012) 83, https://doi.org/10.1186/1471-2407-12-83 (PubMed PMID: 22397399; PubMed Central PMCID: PMCPMC3311029).
[183] T.F. Hansen, A.L. Carlsen, N.H. Heegaard, F.B. Sorensen, A. Jakobsen, Changes in circulating microRNA-126 during treatment with chemotherapy and bevacizumab predicts treatment response in patients with metastatic colorectal cancer, Br. J. Cancer 112 (2015) 624–629, https://doi.org/10.1038/bjc.2014.652 (PubMed PMID: 25584492; PubMed Central PMCID: PMCPMC4333496).