Roles of miRNAs in Colorectal Cancer: Therapeutic Implications and Clinical Opportunities

Amir Mehrgou1*, Shima Ebadollahi2, Khaled Seidi3, Mohammad Hosein Ayoubi-Joshaghani4,5, Amirhossein Ahmadieh Yazdi6, Peyman Zare7,8, Mehdi Jaymand9, Rana Jahanban-Esfahlan10,11*

1Department of Medical Genetics and Molecular Biology, Faculty of Medicine, Iran University of Medical Sciences, Tehran, Iran.
2Department of Biochemistry and Biophysics, Faculty of Medicine, Babol University of Medical Sciences, Babol, Iran.
3Biotechnology Research Center, Tabriz University of Medical Sciences, 9841 Tabriz, Iran.
4Drug Applied Research Center, Tabriz University of Medical Sciences, 9841 Tabriz, Iran.
5Research Center for Molecular Medicine, Hamadan University of Medical sciences, Hamadan, Iran.
6Nano Drug Delivery Research Center, Health Technology Institute, Kermanshah University of Medical Sciences, Kermanshah, Iran.
7Department of Medical Genetics and Molecular Biology, Faculty of Medicine, Iran University of Medical Sciences, Tehran, Iran.
8Stem Cell Research Center, Tabriz University of Medical Sciences, 9841 Tabriz, Iran.
9Department of Medical Biotechnology, Faculty of Advanced Medical Sciences, Tabriz University of Medical Sciences, Tabriz, Iran.

Abstract
Colorectal cancer (CRC) is one of the most disseminated diseases across the globe engaging the digestive system. Various therapeutic methods from traditional to the state-of-the-art ones have been applied in CRC patients, however, the attempts have been unfortunate to lead to a definite cure. MiRNAs are a smart group of non-coding RNAs having the capabilities of regulating and controlling coding genes. By utilizing this stock-in-trade biomolecules, not only disease’s symptoms can be eliminated, there may also be a good chance for the complete cure of the disease in the near future. Herein, we provide a comprehensive review delineating the therapeutic relationship between miRNAs and CRC. To this, various clinical aspects of miRNAs which act as a tumor suppressor and/or an oncogene, their underlying cellular processes and clinical outcomes, and, in particular, their effects and expression level changes in patients treated with chemo- and radiotherapy are discussed. Finally, based on the results deducted from scientific research studies, therapeutic opportunities based on targeting/utilizing miRNAs in the preclinical as well as clinical settings are highlighted.

Introduction
Colorectal cancer (CRC) is one of the most prevalent gastrointestinal malignancies across the world, with over 1.2 million newly reported cases of this disease each year. CRC ranks the third frequent cancer in the globe and is a key cause of cancer-attributed mortality. Moreover, CRC is the second and third most common cancer among women and men, respectively. Despite all of the medical breakthroughs in the early diagnosis and treatment of this cancer, almost 50% of patients pass away in the 5-year period following the diagnosis due to the metastasis and relapse caused by resistance to treatment. In this regard, one of the primary reasons is that most patients are not diagnosed in the early stages of the disease, and as a result of poor prognosis they would not meet a satisfactory clinical outcome.

CRC is often caused by the accumulation of genetic/epigenetic changes in genes coding for tumor suppressors, oncogenes, and DNA repair pathways. Further, these mutations drive oncogene activation as well as the silencing of tumor suppressor genes. These alterations lead to several changes in cellular processes such as cell proliferation, apoptosis, invasion, and metastasis. The eventual result is the transformation of epithelial cells into adenocarcinoma. Meanwhile, metastasis and drug resistance are among the most common causes of CRC mortality. In metastasis, cancer cells acquire the appearance and the properties of mesenchymal cells by a phenomenon known as epithelial-mesenchymal transition (EMT) which separates them from the primary...
tumor tissue. Thereafter, these cells reach the secondary target tissue by overcoming the physiological barriers. Metastatic cells can cross physiological barriers through steps of (i) local invasion, (ii) intravasation (the invasion of cancerous cells through the basal membrane into blood or lymphatic vessels, which facilitates the migration of cancerous cells from their primary sites), (iii) survival in the circulatory system, and (iv) extravasation. The cancerous cells enter organs from blood or lymphatic circulations through extravasation and (v) colonization in the secondary target tissue. Finally (vi), metastatic cells undergo a phenomenon called mesenchymal-epithelial transition (MET) to create a new tumor mass. Therefore, MET process, in which the cells obtain the appearance and the properties of epithelial cells, is the opposite of the EMT process.

Regarding drug resistance, though the process has not been fully uncovered yet, it is suggested that it could be caused by the stem- and stem-like cells. Since metastasis is one of the most important causes of death in CRC patients, the detection of its molecular mechanisms would give a more in-depth insight into CRC prevention and treatment. According to different studies, two of the effective primary treatments for CRC are surgery and chemotherapy. A particular example of surgical treatments is radical surgery, which entails the removal of the blood supply, lymph nodes, and sometimes parts of the structures adjacent to the tumor or cancer tissues. Nevertheless, only 50% of patients with CRC benefit from this treatment while the other 50% experience relapse or tumor metastasis to the other parts of the body. Chemotherapy is another major, and the most common, treatment for CRC. Chemotherapy can be classified into two categories: administration of traditional treatments with unknown cytotoxic effects, and the use of inhibitors of specific molecular pathways in cancer cells. Examples of chemotherapeutic agents for CRC are 5-FU (fluorouracil) and alkylating agents such as oxaliplatin. However, the clinical outcome of this treatment is not satisfactory in all CRC cases due to the development of resistance to chemical agents and the lack of a specific mechanism for diagnosing patients who will definitely benefit from chemotherapy. Hence, there is a considerable need for noninvasive markers for the diagnosis and treatment of cancers, especially CRC with a high morbidity and mortality rate.

**miRNAs biogenesis, origin and function in cancer**

MiRNAs are a large family of single-stranded, short, non-coding endogenous RNAs with a length of approximately 21 to 23 nucleotides. They are generated through the multi-phase biogenesis of the miRNA duplex complex, which itself is produced through the processing of pre-miRNAs using the RNase III Dicer enzyme in endogenous hairpin transcriptions.

Pri-miRNAs are also broken down into 70-85 nucleotide pre-miRNAs and are then cut into temporary double-stranded mRNAs in the cytoplasm. One of the strands carries a mature mRNA sequence with 22 nucleotides in length, and the other is called the complementary strand. These two strands are separated by the microRNP (miRNA plus ribonucleoprotein) complex. During this process, one strand is transformed into an active miRNA and the rest of the strands are decomposed. MiRNAs are hardly degraded due to their small sizes, and are more stable and resistant to chemical, physical, and environmental pressures than the messenger RNAs. A specific region with a length of 2 to 8 nucleotides called the seed sequence at the 5’ end of miRNA sequences, is essential for specific base pairing with the target mRNA molecules. Therefore, miRNAs suppress the expression of 30% of the protein-coding genes by forming incomplete hybrids with specific sites in the 3’UTR regions in the messenger RNA, influencing the mRNA stability. The general mechanism of miRNAs in the animal and mammal cells could be framed through two pathways. One mechanism involves the inhibition of translation following the formation of a complex similar to the RISC (RNA-interference-induced silencing complex). The other mechanism affects the expression of the mRNA-splicing gene.

Based on their origin, the new classification for miRNAs follows the (i) cellular, and (ii) cell-free circulatory miRNAs. Accordingly, RNAs can be extracted from cells/tissues (cellular miRNAs), as well as from bodily liquids such as urine, serum, and plasma (circulatory miRNAs). Mature miRNAs can be secreted from the original cell into the circulation as free, in complex with other proteins/lipids, or being packaged into the extra vesicular particles known as exosomes. Monitoring levels of cell-free miRNAs has emerged as a valuable prognostic and diagnostic tool in cancer (Figure 1).

The malfunction and ectopic expression of the miRNAs profile in many forms of cancer could be attributed to a number of mechanisms such as deletion in the fragile regions of the gene, where more than 52% of miRNA genes which are linked to cancer suppression, are accumulated. This malfunction might also be related to hereditary or acquired mutations in miRNA genes or methylation in the miRNA promoters. Targeting miRNAs as clinical biomarkers may represent a strategy for increasing specificity in overcoming drug resistance.

MiRNAs are extremely protected in all species and play important roles as the translational controllers in vertebrae, worms, and plants. These small molecules are involved in a wide range of cellular and biological processes in CRC, such as inflammation, stress response, migration, cellular differentiation, cell cycle progression, apoptosis, metabolism, changes in extracellular matrix regulators, MET transcription factors, and the onset/progression of cancer. They can also affect tumor survival as well as pathophysiological processes such as chemoresistance, chemosensitivity, and resistance to radiotherapy.
The variations of miRNA expressions in CRC

The performance of each miRNA is considerably determined by the cellular and tissue environments. Dysregulated expression of miRNAs is demonstrated in different malignancies including CRC. MiRNAs can serve as oncogenes and/or tumor suppressors in patients suffering from cancers such as CRC depending on the tissue context. A selection of these miRNAs is listed in Table 1 and Table 2, based upon their expression changes and functions. Molecular pathways and their implication in CRC pathogenesis and therapy outcome are discussed in detail in the next sections.

The Effect of miRNAs on cellular processes involved in CRC development, progression, and drug resistance

MiRNAs and their expression regulation is essential in several human diseases, and cancer in particular, as their involvement in various tumorigenesis processes such as angiogenesis, migration, proliferation, and EMT has been confirmed.8,17,38,50,51

The exogenous expression of Mir-1 suppresses invasive attributes such as migration, proliferation, growth, and metastasis of CRC cells in vitro. Mir-1 inhibits metastasis in CRC cases by targeting LASP1. In addition, mir-1 prevents tumor progression through dephosphorylation of ERK1/2 and AKT in the MAPK/ERK and PI3K/AKT pathways. Mir-1 also suppresses EMT and increases MET by reducing mesenchymal markers such as fibronectin and elevating the epithelial markers such as E-cadherin.8 Mir-7 regulates cell proliferation in vitro.8 Mir-9 is transcribed from the mir-9-1/9-2, 9-3 genes, and the CpG island methylation in mir-9-1 is believed to be associated with lymphatic metastasis in CRC samples and cell lines.52 Mir-9 is shown to act as a tumor suppressor gene, as its increased expression is shown to correlate with the decreased expression of UHRF1, which is involved in DNA methylation, and cell proliferation in CRC tissue samples. Meanwhile, mir-9 expression can counteract UHRF1 function, and promotes the apoptosis of CRC cells in vitro.8

Example of miRNA with dual action is MiRNA-873. While it acts as an oncogene to derive lung adenocarcinoma...
cell migration and proliferation by targeting SRC kinase signaling inhibitor. Its expression shows a decreased level in mouse CRC samples, human CRC clinical specimens, and highly metastatic CRC cell lines. Mechanistically, MiR-873 suppresses CRC metastasis by targeting ELK1 and STRN4 to inhibit metastasis. Other important CRC-related MiRNA is Mir-145. It regulates the renewal property of stem cells and diminishes the pluripotency factors such as Oct4, Sox2, and Nanog through which it inhibits the stemness features of cells. Mir-145 also promotes cell proliferation, and decreases sensitivity to the clinical regimens that are based on 5-FU and oxaliplatin in the HT-29 and HCT116 cell lines. Additional miRNA linked with stem cell-like properties is Mir-21. It inhibits TiAM1, MMP2, and MMP9, and also promotes the increased apoptosis in the SW620 cells by promoting the caspase-9 and caspase-7 apoptotic proteins and PARP. Moreover, mir-22 inhibits autophagy in SW620 and RKO cells by reducing the expression of autophagy

Table 1. MiRNA as tumor suppressors in CRC.

| MiRNAs as Tumor Suppressor | Function in CRC | Ref. |
|---------------------------|----------------|-----|
| Mir-1                     | Suppress EMT transition and metastasis via the MAPK and PI3K/AKT pathway | 8   |
| Mir-9                     | modulates CRC cell proliferation and apoptosis by regulation of UHRF1 | 9,10|
| Mir-10b*                  | Suppresses growth and metastasis by targeting FGF13 | 11  |
| Let-7                     | Reduce levels of oncoproteins MYC, HMGA2, and IGF1 | 12  |
| Mir-15a                   | Reduce BCL2 and SOX2 to inhibit tumor growth | 13  |
| Mir-22                    | Increase 5-FU sensitivity by promoting apoptosis and inhibiting autophagy in CRC cells | 14  |
| Mir-27a                   | Elicits tumor-suppressive effects by targeting SGPP1 and Smad2 | 15  |
| MirR-27a-3p               | Controls apoptosis and proliferation via targeting BTG1 | 16  |
| Mir-29c                   | Mediates EMT transition during metastasis via regulation of β-catenin/PTP4A and GNA13 signaling | 17  |
| Mir-30a                   | Suppresses migration and invasion by reducing PIK3CD | 18  |
| Mir-30a                   | Target insulin receptor substrate 2 | 19  |
| Mir-30a-5p                | Suppresses metastasis by targeting ITGB3 | 20  |
| Mir-30b                   | Targets KRAS, PIK3CD, and BCL2 | 21  |
| Mir-31                    | Inhibits autophagy in cancer-associated fibroblasts, increase the radiosensitivity and inhibit cancer growth | 22  |
| Mir-34a                   | Modulates E2F pathway to induce senescence-like growth arrest | 23  |
| Mir-34a                   | Suppresses the invasion and migration by enhancing EGR1 and inhibiting vimentin | 24  |
| Mir-124                   | Inhibit STAT3 to suppress the growth of human CRC | 25  |
| Mir-119p-5p               | Exerts tumor suppressor function by targeting NOTCH1 | 26  |
| Mir-143                   | inhibit cell invasion and migration via targets MACC1 | 27  |
| Mir-152                   | Acts as a tumor suppressor gene by targeting | 28  |
| Mir-203                   | Targets EIF5A2 to suppress cell proliferation, migration, and invasion | 29  |
| Mir-203                   | Suppresses ZNF217 upregulation in CRC and its oncogenicity | 30  |
| Mir-218                   | Target the PI3K/AKT/mTOR signaling to inhibit the invasion and migration of colon cancer cells | 31  |
| Mir-218                   | Targets cFLIP to promote apoptosis | 32  |
| Mir-363-3p                | Suppresses the EMT transition and inhibits metastasis by targeting Sox4 | 33  |
| Mir-519b-3p               | Modulates the uMCKWnt signaling pathway to inhibit the proliferation and invasion | 34  |
| Mir-873                   | Targets ELK1 and STRN4 to inhibit metastasis | 35  |
| MiR-125b                  | Suppresses CKS1B expression to inhibit the proliferation and migration | 36  |

*miRNA with oncogenic/tumor-suppressive dual-action
Table 2. Oncomirs involved in CRC pathogenesis

| miRNAs as Tumor Suppressor | Function in CRC                                                                 | Ref. |
|----------------------------|--------------------------------------------------------------------------------|------|
| Mir-10b*                   | TWIST-1 induces upregulation of miR-10b and reduce E-cadherin to promote metastatic phenotype acquisition | 37   |
| MIR-9, mir-31, mir-182     | Promote proliferation and tumor cell survival                                   | 30   |
| Mir-17                    | promotes cell proliferation, tumor growth, and cell cycle progression by targeting the RND1 tumor suppressor gene | 33   |
| Mir-23a                   | Its inhibition activates APAF-1/caspase-9 apoptotic pathway to promotes 5-FU chemosensitivity | 39   |
| Mir-23b                   | Its expression regulates EMT transition and causes oxaliplatin-resistant       | 40   |
| Mir-106b                  | induces cell radioresistance via the activating PI3K/AKT, decreasing PTEN and p21 and upregulation of stemness-related genes (CD133, Sox2) | 41   |
| Mir-124                   | Targets iASPP to regulates the cells proliferation                              | 42   |
| Mir-125b, mir-137         | Its expression upregulates in response to capecitabine chemoradiotherapy which causes drug resistance of rectal cancer | 43   |
| Mir-135a                  | Promotes growth and invasion via metastasis suppressor 1                        | 44   |
| Mir-135b                  | Causes proliferation, invasion, and apoptosis by deregulation of PTEN/PI3K pathway, and upregulation of SRC | 45   |
| Mir-153                   | Produce MMP9 to promote invasiveness and inhibits FOXO3a to cause drug resistance | 46   |
| Mir-181b                  | miR-181b functions as an oncomir in CRC by targeting PDCD4                      | 47   |
| Mir-224                   | promotes tumor growth and cell proliferation by accelerating the G1-S phase transition via AKT/FOXO3a signaling activation, p21Cip1/p27Kip1 downregulation, cyclin D1 upregulation, and PHLP1 and PHLP2 repression | 48   |
| mir-501-3p                | Promotes progression by activation of Wnt/β-catenin signaling                   | 49   |

*miRNA with oncogenic/tumor-suppressive dual-action.

marker LC3-II which increases their sensitivity to 5-FU treatment in vitro and in vivo. Similar to the actions of mir-22 which can counteract the action of autophagy inhibitors by targeting B-cell translocation gene 1 (BTG1), recently mir-27a-3p depletion has also been shown to increase apoptosis and reduce proliferation of colon cancer cells by upregulating BTG1 and suppressing ERK/MEK signaling pathway. In contrast, Mir-23a expression is shown to suppresses the apoptosis induced by 5-FU through the APAF1/caspase9 pathway in the HCT-116 and HT-29 cell lines. Mir-27a can block cell proliferation, colonization, and growth of CRC tumors by targeting SGPP1, Smad2, and STAT3. The upregulation of mir-27a is associated with distant metastasis and histopathologic stages.

Mir-29c blocks metastasis and invasion in CRC by diminishing the expression of GNA13 and PTP4A1 genes and suppressing the β-catenin pathway. Mir-29c also limits cell migration by increasing epithelial markers such as E-cadherin and β-catenin and reducing mesenchymal markers such as fibronectin and vimentin which cause MET-related morphologic changes. Mir-29c-3p is a critical target of the P53 gene and regulates the expression of Pleckstrin Homology-Like Domain Family Member 2 (PHLD2), which is involved in colon cancer metastasis in CRC patients. Mir-30a is known to prevent various pathways in CRC including migration, invasion, cell growth, cell proliferation, and metastasis. This action is mediated by reduced phosphorylation of akt by targeting insulin receptor substrate 2 in vitro. Another important target of mir-30a is the Transmembrane-4-L-six-family-1 (TM4SF1), the up-regulation of which in CRC tumor specimens is shown to be associated with advanced stage and lymph node metastasis. Mir 30a expression suppresses invasion of CRC cancer cells by targeting TM4SF1 as well as VEGF and E-cadherin as EMT regulators. In addition, miR-30a-5p is found to inhibit colon metastasis through restraining integrin β3. As another member of mir-30 family, Mir-30b inhibits cell proliferation and tumor growth by enhancing the cell population in the G0/G1 phase and inhibiting transition from G2/M and S phases. It also increases apoptosis by suppressing BCL-2 activity, KRAS, PIK3CD. Furthermore, suppression of mir-31 expression diminishes cell migration and invasion. The increased expression of mir-31 in the CRC HT29 cell line, which carries the TP53 mutation, exerts a strong anti-apoptotic effect. However, the anti-apoptotic effect of increased Mir-31 expression in SW480 and HCT116, which have an intact and functional TP53 pathway, is weaker or absent. Mir-103/107 is overexpressed in CRC where it leads to elevated metastasis by targeting metastatic suppressors such as death-associated protein kinase and Krüppel-like factor 4. Equally, Mir-106b enhances cell proliferation and tumor growth in vitro and in vivo. It also increases resistance to radiation by functioning as a DNA repair agent, and reduces apoptosis by promoting BCL2 expression. When mir-106b expression is increased, p21 acts as a DNA damaging agent in SW620 cells and reverses resistance to radiation, which also involves PTEN. Moreover, mir-106b promotes the self-renewal and stemness properties in cells under both normal and radiated conditions. Mir-124 increases apoptosis and diminishes tumor growth in vitro and in vivo by targeting STAT3 and inhibitor of apoptosis-stimulating protein of p53 (iASPP), and limits cell proliferation and colonization in the CRC.
cell lines.\textsuperscript{25,42} Mir-125b is essential for the continued proliferation of differentiated cells, while both mir-125a and mir-125b decrease migration and invasion in rectal cancer.\textsuperscript{43} Moreover, in vitro investigations have recognized that mir-125b elicits an oncogenic role in the therapeutic resistance and progression in CRC by inhibiting critical proteins such as P53 and BAK1 (Bcl2L7).\textsuperscript{61,62}

Mir-129 enhances apoptosis by suppression of Bcl-2, and by blocking 5-FU-targeted proteins such as TS and E2F3, eventually stopping cell growth and cell cycle progression in CRC patients.\textsuperscript{63} Mir-130b restrains cell invasion and migration in CRC by suppressing integrin β1.\textsuperscript{64} Furthermore, Mir-135a increases cell proliferation in the SW480 and SW620 cell lines by metastasis suppressor 1.\textsuperscript{65} Mir-135b promotes proliferation, invasion, migration, and neo-angiogenesis in CRC patients by elevating IL-8.\textsuperscript{45} Low levels of Mir-137 are required for the maintenance of the tumor state in rectal cancer.\textsuperscript{66} By targeting IGF-1R, mir-139 reduces invasion, migration, and metastasis \textit{in vitro} and \textit{in vivo}. Mir-139 expression is linked to the tumor stage, the involvement of lymph nodes, and vascular invasion.\textsuperscript{67}

Mir-139-5p can promote cell cycle arrest in phase G0/G1 via the upregulation of p21Cip1/Waf1 and p27Kip1. It also escalates apoptosis through the extrinsic apoptosis pathway, including the caspase-3, caspase-7, and caspase-8 proteins and the cleaved PARP. Notch is an important target of this miRNA, as well. Furthermore, mir-139-5p plays a role in the inhibition of invasion and migration by reducing matrix metalloproteinases (MMP7) and MMP9 in mice.\textsuperscript{78}

Moreover, Mir-143 prevents cell growth by suppressing oncogenic proteins such as KRAS, metastasis-associated in colon cancer-1 (MACC1), C-myc, and IRS-1, and can limit invasion and metastasis in CRC.\textsuperscript{27,65,66} Downregulation of mir-143 is linked to distant metastasis and tumor relapse in CRC patients.\textsuperscript{69} Mir-150 inhibits tumor growth \textit{in vitro} and \textit{in vivo} by inhibiting DKC1 and AKT2, and increasing tumor suppressors such as Bim and P53 in vivo.\textsuperscript{70} Mir-153 promotes invasion in CRC by increasing MMP-9, which is a key destructor of the extracellular matrix and is significantly involved in CRC invasion. Moreover, mir-153 reduces apoptosis and increases resistance to chemotherapy by decreasing caspase-3 in the SW480 cell line treated with cisplatin. Also, mir-153 has been observed to be up-regulated in CRC, leading to elevated invasion.\textsuperscript{66} Mir-155 is linked to lymphatic metastasis and promotes invasion and migration by targeting claudin-1. Mir-155 also serves as an EMT mediator by inhibiting E-cadherin and increasing ZEB1.\textsuperscript{71} Mir-155 together with mir-193, target RAD51 which is involved in DNA repair.\textsuperscript{72}

The overexpression of mir-181b through direct binding to tumor suppressor RASSF1A boosts its expression in CRC cells.\textsuperscript{73} On the other hand, mir-181b has the most potential pre-proliferation effect on the HT-29 cell line, which increases cell proliferation by more than four times.\textsuperscript{10}

Mir-15B and Mir-182 elicit anti-apoptotic properties. Mir-182 promotes progression of CRC by increasing cell survival.\textsuperscript{10} The increased expression of Mir-185 and the decreased expression of Mir-133B are linked with the development of metastatic conditions in CRC cases.\textsuperscript{74} Mir-200c, mir-212, and mir-363-3p have been recognized as EMT regulators. Anti-metastatic potential is attributed to targeting ZEB1, ETS1 and FLT1 and EMT markers E-cadherin and vimentin by mir-200c.\textsuperscript{75} Superoxide dismutase (MnSOD) targeting by mir-212 \textsuperscript{75} and Sox-4 targeting by mir-363-3p in CRC in tissue specimens, in vitro and in vivo.\textsuperscript{15}

The expression of miRNAs such as miR-200,\textsuperscript{74} miR-135,\textsuperscript{75} and miR-34a\textsuperscript{23,24} regulate cell survival, proliferation, invasion, and metastasis in CRC. A recent study indicated that mir-34a inhibited the invasion and migration of SW620 cells by blocking vimentin and increasing early growth response protein 1 (EGR1).\textsuperscript{44} MiRNA-1258 elicits tumor-suppressive effects and suppresses the proliferation and migration of human CRC Cells by inhibiting cyclin-dependent kinase regulatory subunit 1B (CKS1B).\textsuperscript{82} Also, miR-501-3p promotes CRC progression by activation of Wnt/β-catenin signaling and through reducing expression of their target genes, cyclin D1 and c-Myc \textit{in vitro}.\textsuperscript{83}

Mir-203 reduces cell proliferation and growth and increases apoptosis and cellular senescence. It also causes oxaliplatin resistance of CRC cells by downregulating DNA damage response mediators, ataxia telangiectasia mutated (ATM) kinases.\textsuperscript{76} The increased mir-218 expression precludes the growth, motility, and invasion of LoVo CRC cells.\textsuperscript{31}

Mir-218 induces the apoptosis of SW1417 cells by increasing caspase-8 expression and inhibiting cellular c-Fas-associated death domain-like interleukin-1β-converting (c-FLIP) regulator.\textsuperscript{62} Mir-222 increases cell proliferation and migration and reduces apoptosis.\textsuperscript{77} Mir-223 improves the cellular proliferation of CRC cells \textit{in vitro} and \textit{in vivo}.\textsuperscript{80} Mir-224 increases cell proliferation and tumorigenesis by suppressing two tumor suppressors named PHLPP1 and PHLPP2 \textit{in vitro} and \textit{in vivo}. In addition, mir-224 promotes cell survival.\textsuperscript{48}

Dysregulated mir-224 expression is associated with declined chemoradiosensitivity in CRC. Therefore, mir-224 has pro-metastatic characteristics rather than anti-metastatic role in CRC.\textsuperscript{79} Mir-297 induces sensitivity to several chemotherapeutics \textit{in vitro} and \textit{in vivo}.\textsuperscript{80} Mir-378 constrains cell growth in the transition from phase G1 to S, and decreases cell life and colonization in the HT-29 and HCT-116 cell lines.\textsuperscript{81}

Mir-519 reduces cell proliferation by controlling the levels of RNA-binding protein HUR. HUR regulates the translational efficiency and stability of mRNAs encoding key elements of the cellular growth, proliferation, and survival pathways. HUR also uses alternative
Roles of miRNAs in colorectal cancer

Advanced Pharmaceutical Bulletin, 2021, Volume 11, Issue 2

polyadenylation sites to modulate its own expression. 

miRNAs expression changes determine treatment outcomes

Chemotherapy

It is well accepted that miRNAs confer strong regulatory effects on survival rate by regulating the pathways for chemical resistance and sensitivity. 

In addition, the existing pieces of evidence suggest that changes in the expression of miRNAs are in fact responses to chemotherapeutic agents. These changes, which are made during chemotherapeutic regimens such as 5-FU, have been observed in the human CRC cell lines. 

Mir-7 is capable of suppressing EGRF in vitro and making CRC patients, who develop resistance to EGFR inhibitors such as cetuximab, regain sensitivity to these drugs. 

For more than 50 years, advanced CRC patients have been using fluoropyrimidine-based chemotherapeutic agents such as 5-FU. Nishida et al. found that the expression of mir-10b is a strong indicator for measuring the sensitivity to the conventional chemotherapy regimens based on 5-FU. 

Mir-17-5p results in chemoresistance in CRC patients by inhibiting the PTEN gene through binding to two regions in the 3′UTR region of this gene. Hence, the Mir-17-5p antisense oligonucleotide can be a promising solution for overcoming chemoresistance in these patients. 

MIR-21 is one of the most significant miRNAs with oncogenic activity in CRC. This miRNA exerts its effect by constraining the clinical effect of 5-FU-based chemotherapeutic regimens. In addition, mir-21 is downregulated in the CRC cell lines treated with 5-FU. 

From another angle, Mir-22 potentiates chemosensitivity to paclitaxel. Particularly, it diminishes chemoresistance to this drug in CRC patients who carry mutated P53 through the PTEN signaling pathway. MIR-22, through suppressing the target enzyme of 5-FU (Thymidylate synthase (TS)), escalates the apoptosis induced by this medicine in SW620 cells and elevates the sensitivity of CRC cells to 5-FU. Moreover, treatment with 5-FU upregulates MIR-22 in RKO cells and facilitates apoptosis. 

Additionally, the inhibition of MIR-22 also reduces the 5-FU-related apoptosis in RKO cells. Furthermore, MIR-22 can sensitize cells to 5-FU by preventing autophagy. Based on the results from the in vivo experiments, MIR-22 reduces the average weight of CRC tumors by elevating chemosensitivity to 5-FU. 

In the condition of 5-FU treatment, the expression of mir-23 in C.20.22 and HC.21 CRC cells, and mir-23a expression in HT29 and HCT.116 colon carcinoma cells, are escalated. The increase in apoptosis induced by 5-FU through the in vitro administration of mir-23a antisense supports the finding that mir-23 functions as a 5-FU-based drug resistance agent. 

Mir-23a and mir-497 have been recognized as regulators in 5-FU treatment. Mir-497, miR-139-5p, and mir-23a sensitize CRC cells to 5-FU by serving as tumor suppressors. 

The suppression of mir-31 declines the resistance to 5-FU in HCT116 cells. 

Mir-129 leads CRC cells to be sensitized to 5-FU in vitro and in vivo in two ways; either by (i) downregulating Bcl-2 expression, which leads to high apoptosis rate; or by (ii) suppressing the E2F3 protein. 

Mir-139-5p sensitizes CRC cells to 5-FU through inducing apoptosis and inhibiting the expression of mir-139-5p targets NOTCH-1 gene and its downstream MDR-associated genes, MRPl, and Bcl-2 

Mir-140 creates resistance to the 5-FU in CRC patients. 

Also, the downregulation of mir-148a reduces sensitivity to 5-FU and oxaliplatin. 

A high level of mir-625-3p declines the response to oxaliplatin in patients suffering from metastatic CRC. 

The upregulation of mir-153 enhances resistance to platinum-based treatments such as oxaliplatin and cisplatin through inhibiting FOXO3. This miRNA reduces the apoptotic effect of these drugs. 

According to the findings reported by Nakajima et al., let-7 and miR-181b are linked to the response to 5-FU treatment. 

Mir-203 influences the response of CRC cells to 5-FU by inhibiting TYSMs, and inhibits tumor growth. 

It also positively regulates the CRC cell responses to paclitaxel, which affects the cell cycle, by reducing AKT. Mir-203 induces cellular senescence and causes delayed cell growth. However, miR-203 can contribute to the increase in the acquired resistance to oxaliplatin in CRC cells. 

Mir-19b, miR-34, and miR-192/215 are other miRNAs determining the resistance to 5-FU. Some of the miRNAs linked to the oxaliplatin resistance are miR-20 and miR-1915. 

Mir-433 sensitizes HeLa cell to 5-FU by reducing TYSM expression, and is downregulated in CRC tissues and cell lines. 

Mir-433 targets MACC1 to promote apoptosis and decrease the viability of CRC cells. 

Svoboda et al. reported that let-7e, miR-99a, miR-215, miR-450b-5p, and miR-196b are involved in the CRC response to chemotherapy. 

It was reported that mir-99 impedes pro-survival/anti-apoptotic pathways through affecting Bcl-2 and mTOR targets. 

The upregulation of miR-592 has been observed in CRC patients with a healthy MMR (Mismatch Repair) system as compared to patients with defective MMR system. Moreover, cells with defective MMRs and a reduced level of miR-592 are resistant to some chemotherapeutic agents such as 5-FU and some platinum compounds such as cisplatin and carboplatin. 

Mir-129 expression is decreased in doxorubicin-insensitive colon cancer cell lines. 

Mir-127 is shown to inhibit proto-oncogene Bcl-6 activity. Lower levels of miR-150 in CRC tissue samples correlates with chemoresistance and shorter survival. 

Radiation therapy

Intrinsic and acquired resistance to radiation is a challenging barrier to the clinical management of CRC. The acquisition of resistance to radiation is a complex process comprising an increase in the expression of DNA repair proteins, and dysregulation in signaling pathways,
angiogenesis, CSCs, and autophagy.\textsuperscript{102} MiRNAs may serve to predict and modify cancer treatments such as radiotherapy.\textsuperscript{102} Recent findings are also indicative of the substantial role of miRNAs in the cellular responses against ionizing radiation.\textsuperscript{103}

Lin28-let7 mediates radiation resistance in CRC cancer cells by activating K-Ras.\textsuperscript{104} Moreover, the combined functions of let7g and mir-9 can increase resistance to radiotherapy through the suppression of NF-kappaB1.\textsuperscript{105} MIR-101 sensitizes CRC cells to radiation by targeting ATM and \textit{in vitro} and \textit{in vivo}.\textsuperscript{106} The clonogenic assay is a cell biology technique that determines the effectiveness of specific agents on cell survival and proliferation. This assay revealed that the upregulation of MIR-106b results in an increase in resistance, while its downregulation leads to an increase in sensitivity to ionizing radiation in CRC patients. Therefore, it is concluded that cells with upregulated mir-106b have stronger DNA repair systems. Besides, mir-106b induces this resistance by increasing AKT and reducing PTEN in the PTEN-P13K/AKT pathway.\textsuperscript{101} MIR-124 increases CRC cells’ sensitivity to ionizing radiation and promotes cell apoptosis in radiotherapy by declining the expression of PRRX1. Moreover, mir-124 suppresses Bcl-2, and the synergy between MIR-124 and ionizing radiation drastically diminishes Bcl-2 expression and eventually leads to apoptosis.\textsuperscript{101}

The effect of miRNAs on CRC clinical responses and procedure

MiRNAs are implicated in various stages of tumorigenesis, form early CRC development to acquiring drug resistance and metastasis\textsuperscript{13} as well as the survival rate of CRC patients. A high level of let-7 is linked to a shorter lifetime and is contradictory to let-7 role as a tumor suppressor.\textsuperscript{66} The in-situ hybridization results suggest a sharp decrease in the expression of mir-9 in CRC tissues compared to healthy counterparts. Patients experiencing reduced expression of mir-9 have poor clinical outcomes.\textsuperscript{5} MiR-17-5P reduces the survival of CRC patients by deactivating PTEN.\textsuperscript{74} Schetter et al have demonstrated that mir-21 overexpression is linked to poor clinical outcomes and low survival rate in colon adenocarcinoma patients.\textsuperscript{107}

MIR-21 also plays a substantial role in the pathogenesis of CRC. Suppression of PTEN is controlled by miR-21, which is associated with reinforcement of the PI3K pathway and the advancement of CRC.\textsuperscript{66}

Low expression of miR-30b is linked to low differentiation and the advanced stage of TNM clinical classification. Moreover, patients with upregulated miR-30b survive longer than patients with low expression of this miRNA.\textsuperscript{21} MiR-93 can also prevent the early relapse of CRC.\textsuperscript{108}

Research findings have revealed that chaotic mir-106a expression, independent of the tumor stage, can function as a DFS (disease-free survival) and OS (overall survival) marker.\textsuperscript{107} There was no considerable difference in the expressions of miR-129 in the healthy tissues and adenomas in stages I and II of cancer, but miR-129 levels dropped significantly in stages III and IV of cancer, revealing the relationship between reduced expression of mir-129 and CRC progression.\textsuperscript{12} The poor survival of CRC patients is also connected with the declined expression of mir-133B.\textsuperscript{71} Although there are contrasting reports for relation of mir-139-5P with the CRC progression, Zhang et al. reported a decreased level of this miRNA with advanced CRC.\textsuperscript{26} Moreover, expression changes of miR-21, miR-31, miR-143, and miR-145 are closely involved in the pathological and clinical characteristics of CRC.\textsuperscript{10,56,109}

The downregulated mir-150 is linked to poor clinical outcomes in patients with stages I and II of CRC. Hence, increased mir-150 activity contributes to the prevention of tumorigenesis in populations prone to CRC, such as people suffering from familial adenomatous polyposis (FAP).\textsuperscript{67} The upregulated mir-153 in advanced CRC is linked to cancer progression and the tumor spreads to distant and nodal organs.\textsuperscript{46} Overexpression of mir-185 is significantly linked with the low survival rate in CRC cases.\textsuperscript{21} Moreover, high expression of mir-29a and mir-362-3p elongates DFS.\textsuperscript{10,111}

Mir-451 can be used as a marker for predicting drug resistance (e.g. response to irinotecan) and relapse in CRC cases.\textsuperscript{112} Equally, the elevated levels of miR-3 and reduced expression of mir-592 are linked to poor responses to treatment.\textsuperscript{68}

MiRNAs as biomarkers in CRC patients

MiRNAs are used as novel biomarkers in CRC patients. These smart molecules are used as prognostic and diagnostic biomarkers for the risk assessment of cancer and the analysis of response to treatment, and are even considered as therapeutic agents and targets.\textsuperscript{113} The dysregulation of miRNAs is also involved in the development and progression of CRC.\textsuperscript{21} The declined expression of mir-7 is associated with CRC progression and poor prognosis in CRC patients. Moreover, mir-7 can be considered a useful marker for sensitivity to cetuximab.\textsuperscript{6} Also, the downregulated mir-9 in CRC tissues is linked to CRC prognosis.\textsuperscript{114} High expression of mir-15 is known as a marker for poor prognosis in CRC cases.\textsuperscript{115} Mir-17-5b is known as a biomarker that demonstrates the prognosis and prediction of chemotherapy in CRC cases. This miRNA is particularly associated with the final stage of CRC and a worse survival rate.\textsuperscript{49} The increased expression of mir-21 in CRC tumor tissues is considered as a biomarker for the advanced stage of this disease, and poor cellular differentiation and response to chemotherapy.\textsuperscript{116} Therefore, this miRNA provides a diagnostic value for CRC.\textsuperscript{21} In addition, the expression of mir-31, similar to mir-21, is linked to the disease stage.\textsuperscript{10} Mir-34a may function as a non-invasive biomarker for CRC.\textsuperscript{24} Furthermore, Wang et al. carried out a microarray test to show that the expression of mir-106b is enhanced in
Roles of miRNAs in colorectal cancer

CRC cases with lymphatic metastasis.\textsuperscript{117} The dysregulation of mir-139-5p in the early stage of CRC has also been reported.\textsuperscript{26} Several research results have indicated that mir-15b, mir-181b, mir-191, and mir-200c may play a role in the CRC development and its progression, and so they may also be involved as non-invasive markers in the prognosis of this disease.\textsuperscript{113}

Mir-218 and miR-152 are linked to the TNM stage of CRC and a decrease in their expression has been observed in patients with poor prognosis.\textsuperscript{28,118} Also, miR-224 promotes cell metastasis and proliferation through the Wnt/\(\beta\)-catenin pathway. These results demonstrate that the increase in the expression of mir-224 is considered to be linked to the severe phenotype of CRC, which includes its invasive characteristics and poor prognosis in patients suffering from CRC.\textsuperscript{46,119}

Importantly, recent advances in single-cell analysis have opened a new horizon in the non-invasive analysis of bodily fluids for the detection of cancer biomarkers, including circulatory miRNAs.\textsuperscript{120,121} This field, which is referred to as “liquid biopsy”, combined with newly-emerged nanobiosensors,\textsuperscript{122,123} and lab-on-chip and microfluidics devices\textsuperscript{124} has enabled researchers and clinicians to analyze low amounts of samples to gain valuable information regarding active and/or non-active disease state (Figure 2, Table 3). Circulatory miRNA with diagnostic/prognostic potential in CRC in recently reviewed by.\textsuperscript{120}

**Conclusion**

CRC is one of the prevalent cancers in which the benefits of using miRNAs as a non-invasive diagnostic and prognostic tool can be reaped. In the sense of liquid biopsy, circulatory levels of miRNA are applied as a non-invasive

---

**Table 3. Circulatory miRNA as valuable diagnostic/prognostic in CRC patients**

| miRNA         | Type                          | Expression pattern in CRC | Clinical value                                                                                     | Ref. |
|---------------|-------------------------------|---------------------------|----------------------------------------------------------------------------------------------------|------|
| mir-125b      | Plasma exosomes               | Increased                 | Early detection of resistance to first-line chemotherapy (leucovorin, oxaliplatin, fluorouracil) in patients with advanced/recurrent CRC/ biomarker for PFS | 125  |
| Mir-21        | Plasma exosomes, primary tumor tissues, liver metastasis tissues | Increased                 | A prognostic factor for OS rates in patients with TNM stage IV and DFS rates with TNM stage II or III in CRC patients | 126  |
| miR-125B-2-3p | Tissue                        | Decreased                 | Prediction of CRC cell sensitivity to first-line chemotherapy (fluorouracil, oxaliplatin, CPT-11)    | 127  |
| miR-652-3p, miR-328-3p, miR-342-3p, miR-501-3p | Plasma                      | Increased                 | Prediction of OS rates and tumor relapse of stage I-III                                              | 128  |
| miR-652-3p    | Serum, plasma, tissue         | Increased                 | Biomarker for chemo (multi-tyrosine kinase inhibitor regorafenib) - refractive metastatic CRC          | 129  |
| Mir-1290      | Tissues, serum                | Increased                 | Correlation with tumor aggressiveness and poor prognosis. Independent prognostic factor and an independent predictor for tumor recurrence. | 130  |
| Mir-122       | Serum exosome                 | Increased                 | A new diagnostic and prognostic biomarker in CRC patients with liver metastasis                     | 131  |
| miR-150-5p    | Serum exosome                 | Decreased                 | Association with poor differentiation, advanced TNM stage, positive lymph node metastasis and poor survival rates in CRC patients | 132  |
| miR-1290, miR-320d | Plasma            | Increased                 | Early diagnosis of CRC                                                                             | 133  |
| miRNA-320d    | Serum exosome                 | Increased                 | Diagnostic biomarker for metastatic CRC                                                             | 134  |
| miR-182, miR-20a | Tissue, plasma samples       | Increased                 | Diagnostic biomarker for early CRC                                                                 | 135  |
| miR-27a, miR-130a | Serum exosome               | Increased                 | Higher levels of these miRNA can be used for early detection and predicting prognosis of CRC          | 136  |
| miR-103a-3p, miR-18a-5p, miR-127-3p, miR-17-5p | Tissue                        | Increased                 | Diagnostic biomarker for early CRC                                                                  | 137  |
| miR-17-5p, miR-18b-5p, miR-181a-5p, miR-18a-5p | Plasma exosomes              | Increased                 | Diagnostic biomarker for early CRC                                                                  | 138  |
| miR-19a-3p, miR-21-5p, miR-425-5p | Serum, tissue, serum exosome | Increased                 | Diagnostic biomarker for early CRC                                                                  | 139  |
| miR-92a-3p, miR-17-5p | Serum                        | Increased                 | Predicting biomarker for CRC staging and grading                                                    | 140  |
| Mir-200c      | Serum                         | Increased                 | CRC prognosis and predicting metastasis                                                              | 141  |
| miR-200c-3p, miR-141-3p, miR-143-3p | Tissue, serum               | Increased                 | Differentiation of advanced adenoma from CRC                                                        | 142  |
| Mir-203       | Serum                         | Increased                 | Prognostic biomarker for distant metastasis, higher tumor stage, poor survival rate                  | 143  |

Abbreviations: OS, overall survival; DFS, disease-free survival; PFS, progression-free survival.

---
method for screening of CRC. Generally, several hundred miRNAs are observed to be drastically dysregulated in this disease. The miRNAs target a wide range of molecular pathways in normal and cancerous cells. Therefore, this significant feature makes these molecules good candidates for playing a role as biomarkers for differentiating stages of the disease. Also, taking advantage of these smart molecules as therapeutic hallmarks, CRC patients could be detected easier and sooner, meanwhile, the clinical status and the efficiency of clinical interventions for them could be meticulously monitored while they are receiving clinical regimens. However, the specificity and sensitivity of the discussed method are not approved as same as those of routine clinical ones. Accordingly, this method could not be an undisputed substitution for colonoscopy or other commonly-used diagnostic methods, nor for chemotherapy and radiotherapy as standard treatment methods yet, but as a complement to them. Furthermore, technological advances that allow for single-cell analysis of CRC biomarkers such as cell-free miRNA would allow effective screening and predict disease state. Equally it affords clinicians to adopt the most appropriate therapeutic regimes before cancer can progress into an advanced disease.

Ethical Issues
Not applicable.

Conflict of interest
The authors declare no conflicts of interest.

Authors’ contribution
AM and ShE have written the initial draft, KhS and MHAJ collected the data. AhA has drawn the figures. MJ, PZ and RJE have revised, edited and polished the final draft for intellectual content.

References
1. Rawla P, Sunkara T, Barsouk A. Epidemiology of colorectal cancer: incidence, mortality, survival, and risk factors. Prz Gastroenterol 2019;14(2):89-103. doi: 10.5114/pg.2018.81072
2. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2019. CA Cancer J Clin 2019;69(1):7-34. doi: 10.3322/caac.21551
3. Jahanban-Esfahlan R, Seidi K, Manjili MH, Jahanban-Esfahlan A, Javaheri T, Zare P. Tumor cell dormancy; threat or opportunity in the fight against cancer. Cancers (Basel) 2019;11(8):1207. doi: 10.3390/cancers11081207
4. Baghban R, Roshangar L, Jahanban-Esfahlan R, Seidi K, Ebrahimi-Kalan A, Jaymand M, et al. Tumor microenvironment complexity and therapeutic implications at a glance. Cell Commun Signal 2020;18(1):59. doi: 10.1186/s12967-020-0530-4
5. Majidinia M, Ghazizadeh Darband S, Kaviani M, Nahavi SM, Jahanban-Esfahlan R, Yousefi B. Cross-regulation between Notch signaling pathway and miRNA machinery in cancer. DNA Repair (Amst) 2018;66-67:30-41. doi: 10.1016/j.dnarep.2018.04.002
6. Suto T, Yokobori T, Yajima R, Morita H, Fujii T, Yamaguchi S, et al. MicroRNA-7 expression in colorectal cancer is associated with poor prognosis and regulates cestuximab sensitivity via EGFR regulation. Carcinogenesis 2015;36(3):338-45. doi: 10.1093/carcin/bgu242
7. Turchinovich A, Weiz L, Burwinkel B. Extracellular miRNAs: the mystery of their origin and function. Trends Biochem Sci 2012;37(11):460-5. doi: 10.1016/j.tibs.2012.08.003
8. Xu L, Zhang Y, Wang H, Zhang G, Ding Y, Zhao L. Tumor suppressor miR-1 restrains epithelial-mesenchymal transition and metastasis of colorectal carcinoma via the MAPK and PI3K/AKT pathway. J Transl Med 2014;12:244. doi: 10.1186/s12967-014-0244-8
9. Zhu M, Xu Y, Ge M, Gui Z, Yan F. Regulation of UHRF1 by miRNA-9 modulates colorectal cancer cell proliferation and apoptosis. Cancer Sci 2015;106(7):833-9. doi: 10.1111/cas.12689
10. Cekaite L, Rantala JK, Bruun J, Guriby M, Agesen TH, Danielsen SA, et al. MiR-9, -31, and -182 deregulation promote proliferation and tumor cell survival in colon cancer. Neoplasia 2012;14(9):868-79. doi: 10.1593/neo.121094
11. Song JJ, Li W. MiR-10b suppresses the growth and metastasis of colorectal cancer cell by targeting FGF13. Eur Rev Med Pharmacol Sci 2019;23(2):576-87. doi: 10.26355/eurev_201901_16870
12. Mizuno R, Kawada K, Sakai Y. The molecular basis and therapeutic potential of let-7 microRNAs against colorectal cancer. Can J Gastroenterol Hepatol 2018;2018:5769591. doi: 10.1155/2018/5769591
13. Gopalan V, Ebrahimi F, Islam F, Vider J, Qallandar OB, Pillai S, et al. Tumour suppressor properties of miR-15a and its regulatory effects on BCL2 and SOX2 proteins in colorectal carcinomas. Exp Cell Res 2018;370(2):245-53. doi: 10.1016/j.yexcr.2018.06.025
14. Zhang H, Tang J, Li C, Kong J, Wang J, Wu Y, et al. MiR-22 regulates 5-FU sensitivity by inhibiting autophagy and promoting apoptosis in colorectal cancer cells. Cancer Lett 2015;356(2 Pt B):781-90. doi: 10.1016/j.canlet.2014.10.029
15. Bao Y, Chen Z, Guo Y, Feng Y, Li Z, Han W, et al. Tumor suppressor microRNA-27a in colorectal carcinogenesis

Figure 2. Concept and significance of liquid biopsy using circulatory miRNA for CRC personalized medicine. Adopted from MDPI: Cancers. Copyright (2019).
Roles of miRNAs in colorectal cancer

and progression by targeting SGPP1 and Smad2. PLoS One 2014;9(8):e105991. doi: 10.1371/journal.pone.0105991

16. Su C, Huang DP, Liu JW, Liu WY, Cao YO. miR-27a-3p regulates proliferation and apoptosis of colon cancer cells by potentially targeting BTG1. Oncol Lett 2019;18(3):2825-34. doi: 10.3892/ol.2019.10629

17. Zhang X, Mai SJ, Huang XX, Wang FW, Liao YJ, Lin MC, et al. MiR-29c mediates epithelial-to-mesenchymal transition in colorectal cancer: metastasis via PTPTA4 and GNA13 regulation of β-catenin signaling. Ann Oncol 2014;25(11):2196-204. doi: 10.1093/annonc/mdu439

18. Zhong M, Bian Z, Wu Z. miR-30a suppresses cell migration and invasion through downregulation of PIK3CD in colorectal carcinoma. Cell Physiol Biochem 2013;31(2-3):209-18. doi: 10.1159/000334336

19. Zhang Q, Tang Q, Qin D, Yu L, Huang R, Lv G, et al. Role of microRNA 30a targeting insulin receptor substrate 2 in colorectal tumorigenesis. Mol Cell Biol 2015;35(6):988-1000. doi: 10.1128/mcb.01242-14

20. Wei W, Yang Y, Cai J, Cui K, Li RX, Wang H, et al. MiR-30a-5p suppresses tumor metastasis of human colorectal cancer by targeting ITGB3. Cell Physiol Biochem 2016;39(3):1165-76. doi: 10.1159/000447823

21. Liao WT, Ye YP, Zhang NJ, Li TT, Wang SY, Cui YM, et al. MicroRNA-30b functions as a tumour suppressor in human colorectal cancer by targeting KRAS, PIK3CD and BCL2. J Pathol 2014;232(4):415-27. doi: 10.1002/path.4309

22. Yang X, Xu X, Zhu J, Zhang S, Wu Y, Wu Y, et al. miR-31 affects colorectal cancer cells by inhibiting autophagy in cancer-associated fibroblasts. Oncotarget 2016;7(48):79617-28. doi: 10.18632/oncotarget.12873

23. Tazawa H, Tsuchiya N, Izumiya M, Nakagama H. Tumor-suppressive miR-34a induces senescence-like growth arrest through modulation of the E2F pathway in human colon cancer cells. Proc Natl Acad Sci U S A 2007;104(39):15472-7. doi: 10.1073/pnas.0707351104

24. Zhu W, Long JL, Yin YT, Guo HN, Jiang EP, Li YL, et al. MicroRNA-34a suppresses the invasion and migration of colorectal cancer cells by enhancing EGR1 and inhibiting vimentin. Exp Ther Med 2019;18(4):2459-66. doi: 10.3892/etm.2019.7826

25. Zhang J, Lu Y, Yue X, Li H, Luo X, Wang Y, et al. MiR-124 suppresses growth of human colorectal cancer by inhibiting STAT3. PLoS One 2013;8(8):e70300. doi: 10.1371/journal.pone.0070300

26. Zhang L, Dong Y, Zhu N, Tsoi H, Zhao Z, Wu CW, et al. microRNA-139-5p exerts tumor suppressor function by targeting NOTCH1 in colorectal cancer. Mol Cancer 2014;13:124. doi: 10.1186/1476-4598-13-12

27. Zhang Y, Wang Z, Chen M, Peng L, Wang X, Ma Q, et al. MicroRNA-143 targets MACC1 to inhibit cell invasion and migration in colorectal cancer. Mol Cancer 2012;11:23. doi: 10.1186/1476-4598-11-23

28. Li B, Xie Z, Li B. Mir-152 functions as a tumor suppressor in colorectal cancer by targeting PIK3R3. Tumour Biol 2016;37(8):10075-84. doi: 10.1007/s13277-016-4888-2

29. Deng B, Wang B, Fang J, Zhu X, Cao Z, Lin Q, et al. MiRNA-203 suppresses cell proliferation, migration and invasion in colorectal cancer via targeting of E1F5a2. Sci Rep 2016;6(1):28301. doi: 10.1038/srep28301

30. Li Z, Du L, Dong Z, Yang Y, Zhang X, Wang L, et al. Mir-203 suppresses ZNF217 upregulation in colorectal cancer and its oncogenicity. PLoS One 2015;10:e0116170. doi: 10.1371/journal.pone.0116170

31. Zhang X, Shi H, Tang H, Fang Z, Wang J, Cui S. miR-218 inhibits the invasion and migration of colon cancer cells by targeting the PI3K/Akt/mTOR signaling pathway. Int J Mol Med 2015;35(5):1301-8. doi: 10.3892/immm.2015.2126

32. Meng Q, Chen Y, Lian B, Shang Y, Yang H. miR-218 promotes apoptosis of SW1417 human colon cancer cells by targeting c-FLIP. Oncol Rep 2018;40(2):916-22. doi: 10.3892/or.2018.6460

33. Hu F, Min J, Cao X, Liu L, Ge Z, Hu J, et al. MiR-363-3p inhibits the epithelial-to-mesenchymal transition and suppresses metastasis in colorectal cancer by targeting Sox4. Biochem Biophys Res Commun 2016;474(1):35-42. doi: 10.1016/j.bbrc.2016.04.055

34. Zhang Y, Sun M, Chen Y, Li B. MiR-519b-3p inhibits the proliferation and invasion in colorectal cancer via modulating the uMtCdk/Wnt signaling pathway. Front Pharmacol 2019;10:741. doi: 10.3389/fphar.2019.00741

35. Fan C, Lin B, Huang Z, Cui D, Zhu M, Ma Z, et al. MicroRNA-873 inhibits colorectal cancer metastasis by targeting ELK1 and STRN4. Oncotarget 2019;10(41):4192-204. doi: 10.18632/oncotarget.24115

36. Hwang JS, Jeong EJ, Choi J, Lee YJ, Jung E, Kim SK, et al. MicroRNA-125b inhibits the proliferation and migration of human colorectal cancer cells through suppressing CKS1B expression. Genes (Basel) 2019;10(11). doi: 10.3390/genesi01101912

37. Abdelmaksoud-Dammak R, Chamtourni T, Triki M, Saadallah-Kallel A, Ayadi W, Charfi S, et al. Overexpression of miR-10b in colorectal cancer patients: correlation with TWIST-1 and E-cadherin expression. Tumour Biol 2017;39(3):101428317695916. doi: 10.1177/1010428317695916

38. Luo H, Zou J, Dong Z, Zeng Q, Wu D, Liu L. Up-regulated miR-17 promotes cell proliferation, tumour growth and cell cycle progression by targeting the RND3 tumour suppressor gene in colorectal carcinoma. Biochem J 2012;442(2):311-21. doi: 10.1042/bj20111517

39. Shang J, Yang F, Wang Y, Wang Y, Xue G, Mei Q, et al. MicroRNA-23a antisense enhances 5-fluorouracil chemosensitivity through APAF-1/caspase-9 apoptotic pathway in colorectal cancer cells. J Cell Biochem 2014;115(4):772-84. doi: 10.1002/jcb.24721

40. Gasiulė S, Dreize N, Kaupinis A, Ražanskas R, Čiupas L, Stankevičius V, et al. Molecular insights into miRNA-driven resistance to 5-fluorouracil and oxaliplatin chemotherapy. miR-23b modulates the epithelial–mesenchymal transition of colorectal cancer cells. J Clin Med 2019;8(12). doi: 10.3390/jcm8122115

41. Zheng L, Zhang Y, Liu Y, Zhou M, Lu Y, Yuan L, et al. MiR-106b induces cell radioresistance via the PTEN/PI3K/AKT pathways and p21 in colorectal cancer. J Transl Med 2015;13:252. doi: 10.1186/s12974-015-0592-z

42. Liu K, Zhao H, Yao H, Lei S, Lei Z, Li T, et al. MicroRNA-124 regulates the proliferation of colorectal cancer cells by targeting iASPP. Biomed Res Int 2013;2013:867537. doi: 10.1155/2013/867537

43. Svoboda M, Izakovicova Holla L, Sefr R, Vrko娃 I, Kocakova I, Tichy B, et al. Micro-RNAs miR125b and...
miR137 are frequently upregulated in response to captopril chemoradiotherapy of rectal cancer. *Int J Oncol* 2008;33(3):541-7. doi: 10.3892/ijo.0000038

44. Zhou W, Li X, Liu F, Xiao Z, He M, Shen S, et al. MiR-135a promotes growth and invasion of colorectal cancer via metastasis suppressor 1 in vitro. *Acta Biochim Biophys Sin (Shanghai)* 2012;44(10):838-46. doi: 10.1093/abbs/gms071

45. Valeri N, Braconi C, Gasparini P, Murgia C, Lampis A, Paulus-Hock V, et al. MicroRNA-135b promotes cancer progression by acting as a downstream effector of oncogenic pathways in colon cancer. *Cancer Cell* 2014;25(4):469-83. doi: 10.1016/j.ccc.2014.03.006

46. Zhang L, Pickard K, Jenei V, Bullock MD, Bruce A, Ritter R, et al. Mir-153 supports colorectal cancer progression via pleiotropic effects that enhance invasion and chemotherapeutic resistance. *Cancer Res* 2013;73(21):6435-47. doi: 10.1158/0008-5472.can-12-3308

47. Liu Y, Uzair Ur R, Guo Y, Liang H, Cheng R, Yang F, et al. Mir-181b functions as an oncomir in colorectal cancer by targeting PDCD4. *Protein Cell* 2016;7(10):722-34. doi: 10.1007/s13238-016-0131-2

48. Liao WT, Ye YP, Zhang NJ, Li TT, Wang SY, Cui YM, et al. MicroRNA-30b functions as a tumour suppressor in human colorectal cancer by targeting KRAS, PIK3CD and BCL2. *J Pathol* 2014;232(4):415-27. doi: 10.1002/path.4309

49. Wu F, Xing T, Gao X, Liu F. miR-501-3p promotes colorectal cancer progression via activation of Wnt/β-catenin signaling. *Int J Oncol* 2019;55(3):671-83. doi: 10.3892/ijj.2019.4852

50. Zhao Y, Miao G, Li Y, Isaij T, Gu J, Li J, et al. MicroRNA-130b suppresses migration and invasion of colorectal cancer cells through downregulation of β1 [corrected]. *PLoS One* 2014;9(2):e87938. doi: 10.1371/journal.pone.0087938

51. Xiong B, Cheng Y, Ma L, Zhang C. MiR-21 regulates biological behavior through the PTEN/PI3 K/Akt signaling pathway in human colorectal cancer cells. *Int J Oncol* 2013;42(1):219-28. doi: 10.3892/ijj.2012.1707

52. Bandres E, Agirre X, Bitarte N, Ramirez N, Zarate R, Roman-Gomez J, et al. Epigenetic regulation of microRNA expression in colorectal cancer. *Int J Cancer* 2009;125(11):2737-43. doi: 10.1002/ijc.24638

53. Gao Y, Xue Q, Wang D, Du M, Zhang Y, Gao S. miR-873 induces lung adenocarcinoma cell proliferation and migration by targeting SRCIN1. *Am J Transl Res* 2017;9(7):2519-26.

54. Fang L, Li H, Wang L, Hu J, Jin T, Wang J, et al. MicroRNA-17-5p promotes chemotherapeutic drug resistance and tumour metastasis of colorectal cancer by repressing PTEN expression. Oncotarget 2014;5(10):2974-87. doi: 10.18632/oncotarget.1614

55. You C, Jin L, Xu Q, Shen B, Jiao X, Huang X. Expression of miR-21 and miR-138 in colon cancer and its effect on cell proliferation and prognosis. *Oncol Lett* 2019;17(2):2271-7. doi: 10.3892/ol.2018.9864

56. Yu Y, Nangia-Makker P, Farhana L, Rajendra SG, Levi E, Majumdar AP. miR-21 and miR-145 cooperate in regulation of colon cancer stem cells. *Mol Cancer* 2015;14:98. doi: 10.1186/s12943-015-0372-7

57. Li B, Song Y, Liu T, Cui YB, Jiang Y, Xie ZS, et al. miRNA-22 suppresses colon cancer cell migration and invasion by inhibiting the expression of T-cell lymphoma invasion and metastasis 1 and matrix metalloproteinases 2 and 9. *Oncol Rep* 2013;29(5):1932-8. doi: 10.3892/or.2013.2300

58. Chen G, Zhou T, Li Y, Yu Z, Sun L. p53 target miR-29c-3p suppresses colon cancer cell invasion and migration through inhibition of PHLD2. *Biochem Biophys Res Commun* 2017;478(1):90-5. doi: 10.1016/j.bbrc.2017.04.023

59. Park YR, Kim SL, Lee MR, Seo SY, Lee JH, Kim SH, et al. MicroRNA-30a-5p (miR-30a) regulates cell motility and EMT by directly targeting oncogenic TM4SF1 in colorectal cancer. *J Cancer Res Clin Oncol* 2017;143(10):1915-27. doi: 10.1007/s00432-017-2440-4

60. Chen HY, Lin YM, Chung HC, Lang YD, Lin CJ, Huang J, et al. miR-103/107 promote metastasis of colorectal cancer by targeting the metastasis suppressors DAPK and KLF4. *Cancer Res* 2012;72(14):3631-41. doi: 10.1158/0008-5472.can-12-0667

61. Nishida N, Yokobori T, Mimori K, Sudo T, Tanaka F, Shibata K, et al. MicroRNA miR-125b is a prognostic marker in human colorectal cancer. *Int J Oncol* 2011;38(5):1437-43. doi: 10.3892/ijo.2011.969

62. Banzhaf-Strathmann J, Edbauer D. Good guy or bad guy? the opposing roles of microRNA 125b in cancer. *Cell Commun Signal* 2014;12:30. doi: 10.1186/1478-811x-12-30

63. Karayaevaz M, Zhai H, Ju J. miR-129 promotes apoptosis and enhances chemosensitivity to 5-fluorouracil in colorectal cancer. *Cell Death Dis* 2013;4(6):e659. doi: 10.1038/cddis.2013.193

64. Shen K, Liang Q, Xu K, Cui D, Jiang L, Yin P, et al. MiR-139 inhibits invasion and metastasis of colorectal cancer by targeting the type I insulin-like growth factor receptor. *Biochem Pharmacol* 2012;84(3):320-30. doi: 10.1016/j.bcp.2012.04.017

65. Ak S, Tunca B, Tsezcan G, Cecener G, Egeli U, Yilmazlar T, et al. MicroRNA expression patterns of tumors in early-onset colorectal cancer patients. *J Surg Res* 2014;191(1):113-22. doi: 10.1016/j.jss.2014.03.057

66. Drebber U, Lay M, Wedemeyer I, Vallböhmer D, Bollschweiler E, Brabender J, et al. Altered levels of the onco-microRNA 21 and the tumor-suppressor microRNAs 143 and 145 in advanced rectal cancer indicate successful neoadjuvant chemoradiotherapy. *Int J Oncol* 2011;39(2):409-15. doi: 10.3892/ijo.2011.1036

67. Ma Y, Zhang P, Wang E, Zhang H, Yang J, Peng J, et al. miR-150 as a potential biomarker associated with prognosis and therapeutic outcome in colorectal cancer. *Gut* 2012;61(10):1447-53. doi: 10.1136/gutjnl-2011-301122

68. Zhang GJ, Xiao HX, Tian HP, Liu ZL, Xiao SS, Zhou Y. Upregulation of microRNA-155 promotes the migration and invasion of colorectal cancer cells through the regulation of claudin-1 expression. *Int J Mol Med* 2013;31(6):1375-80. doi: 10.3892/imjmm.2013.1348

69. Kara M, Yumrutas O, Ozcan O, Celik OI, Bozgeyik E, Bozgeyik I, et al. Differential expressions of cancer-associated genes and their regulatory microRNAs in colorectal carcinoma. *Gene* 2015;567(1):81-6. doi: 10.1016/j.gene.2015.04.065

70. Zhao LD, Zheng WW, Wang GX, Kang XC, Qin L, Ji JJ, et al. Epigenetic silencing of miR-181b contributes to tumorigenicity in colorectal cancer by targeting RASSF1A. *Int J Oncol* 2016;48(5):1977-84. doi: 10.3892/ijo.2016.3414

71. Akçakaya P, Ekelund S, Kolosenko I, Caramuta S, Ozata
Roles of miRNAs in colorectal cancer

DM, Xie H, et al. miR-185 and miR-133b deregulation is associated with overall survival and metastasis in colorectal cancer. Int J Oncl 2011;39(2):311-8. doi: 10.3892/ijo.2011.1043

72. Hur K, Toyiama Y, Takahashi M, Balagué F, Nagasaka T, Koike J, et al. MicroRNA-200c modulates epithelial-to-mesenchymal transition (EMT) in human colorectal metastasis. Gut 2013;62(9):1315-26. doi: 10.1136/gutjnl-2011-301846

73. Meng X, Wu J, Pan C, Wang H, Ying X, Zhou Y, et al. Genetic and epigenetic down-regulation of microRNA-212 promotes colorectal tumor metastasis via dysregulation of MsnD. Gastroenterology 2013;145(2):426-36.e1-6. doi: 10.1053/j.gastro.2013.04.004

74. Burk U, Schubert J, Wellner U, Schmalhofer O, Vincan E, Spaderna S, et al. A reciprocal repression between ZEB1 and members of the miR-200 family promotes EMT and invasion in cancer cells. EMBO Rep 2008;9(6):582-9. doi: 10.1038/embor.2008.74

75. Nagel R, le Sage C, Diosdado B, van der Waal M, Oude Vrielink JA, Bolijn A, et al. Regulation of the adenomatous polyposis coli gene by the miR-135 family in colorectal cancer. Cancer Res 2008;68(14):5795-802. doi: 10.1158/0008-5472.can-08-0951

76. Zhou Y, Wang G, Spizzo R, Ivan C, Mathur R, Hu X, et al. Mir-203 induces oxaliplatin resistance in colorectal cancer cells by negatively regulating atm kinase. Molecular oncology 2014;8(1):93-92. doi: 10.1016/j.molonc.2013.09.004

77. Iida M, Hazama S, Tsunedomi R, Tanaka H, Takenouchi H, Kanekiyo S, et al. Overexpression of miR-221 and miR-222 in the cancer stroma is associated with malignant potential in colorectal cancer. Oncol Rep 2018;40(3):1621-31. doi: 10.3892/or.2018.6575

78. Zhang J, Luo X, Li H, Yue X, Deng L, Cui Y, et al. MicroRNA-223 functions as an oncogene in human colorectal cancer cells. Oncol Rep 2014;32(1):115-20. doi: 10.3892/or.2014.3173

79. Ling H, Pickard K, Ivan C, Isella C, Ikuo M, Mitter R, et al. The clinical and biological significance of MIR-224 expression in colorectal cancer metastasis. Am J Surg Oncol 2012;19(9):3065-71. doi: 10.1045/s10434-012-2246-1

80. Yu X, Li Z, Yu J, Chan MT, Wu WK. Micrornas predict and modulate responses to chemotherapy in colorectal cancer. Cell proliferation 2015;48(5):503-10. doi: 10.1111/cpr.12202

81. Liu H, Yin Y, Hu Y, Feng Y, Bian Z, Yao S, et al. miR-139-5p sensitizes colorectal cancer cells to 5-fluorouracil by targeting NOTCH-1. Pathol Res Pract 2016;212(7):643-9. doi: 10.1016/j.prp.2016.04.011

82. Mosakhani N, Labi L, Borze I, Karjalainen-Lindsberg ML, Sundström J, Ristamäki R, et al. MicroRNA profiling predicts survival in anti-EGFR treated chemoresistant metastatic colorectal cancer patients with wild-type KRAS and BRAF. Cancer Genet 2012;205(11):545-51. doi: 10.1016/j.cancergen.2012.08.003

83. Takahashi M, Cuatrecasas M, Balagué F, Hur K, Toyiama Y, Castells A, et al. The clinical significance of MiR-148a as a predictive biomarker in patients with advanced colorectal cancer. PloS One 2012;7(10):e46684. doi: 10.1371/journal.pone.0046684

84. Rasmussen MH, Jensen NR, Tarpgaard LS, Qvortrup C, Rømer MU, Stenvang J, 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 2013;7(3):637-46. doi: 10.1016/j.molonc.2013.02.016

85. Non-coding MicroRNAs hsa-let-7g and hsa-miR-181b are Associated with Chemoresistance to S-1 in Colon Cancer. Cancer Genomics Proteomics 2006;3(5):317-24.

86. Li T, Gao F, Zhang XP. miR-203 enhances chemosensitivity to 5-fluorouracil by targeting thymidylate synthase in colorectal cancer. Oncol Rep 2015;33(2):607-14. doi: 10.3892/or.2014.3646

87. Nakajima G, Hayashi K, Xi Y, Kudo K, Uchida K, Takasaki K, et al. Non-coding MicroRNAs hsa-let-7g and hsa-miR-192/miR-215 influence 5-fluorouracil resistance through cell cycle-mediated mechanisms complementary to its post-transcriptional thymidylate synthase regulation. Mol Cancer Ther 2010;9(8):2265-75. doi: 10.1158/1535-7163.Mct-10-0061

88. Kurokawa K, Tanahashi T, Ima H, Yamamoto Y, Akaie Y, Nishida K, et al. Role of miR-19b and its target mRNAs in 5-fluorouracil resistance in colon cancer cells. J Gastroenterol 2012;47(8):883-95. doi: 10.1007/s00535-012-0547-6

89. Wang BD, Kline CL, Pastor DM, Olson TL, Frank B, Luu T, et al. Prostate apoptosis response protein 4 sensitizes human colon cancer cells to chemotherapeutic 5-FU through mediation of an NF kappaB and microRNA network. Mol Cancer 2010;9:98. doi: 10.1186/1476-4598-9-98

90. Xu K, Lian J, Zhang FX, Yu MJ, Yue JS, Zhao JS. MicroRNA-378 inhibits cell growth and enhances l-ohp-induced apoptosis in human colorectal cancer. IUBMB life 2014;66(9):645-54. doi: 10.1002/iub.1317

91. Abdelmohsen K, Kim MM, Srikantian S, Mercenko EM, Brennan SE, Wilson GM, et al. miR-519 suppresses tumor growth by reducing HuR levels. Cell Cycle 2010;9(7):1354-9. doi: 10.4161/cc.9.7.11164

92. Nishida N, Yamashita S, Mimori K, Sudo T, Tanaka F, Shibata K, 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 2012;19(9):3065-71. doi: 10.1245/s10434-012-2246-1

93. Yu X, Li Z, Yu J, Chan MT, Wu WK. Micrornas predict and modulate responses to chemotherapy in colorectal cancer. Cell proliferation 2015;48(5):503-10. doi: 10.1111/cpr.12202

94. Liu H, Yin Y, Hu Y, Feng Y, Bian Z, Yao S, et al. miR-139-5p sensitizes colorectal cancer cells to 5-fluorouracil by targeting NOTCH-1. Pathol Res Pract 2016;212(7):643-9. doi: 10.1016/j.prp.2016.04.011

95. Mosakhani N, Labi L, Borze I, Karjalainen-Lindsberg ML, Sundström J, Ristamäki R, et al. MicroRNA profiling predicts survival in anti-EGFR treated chemoresistant metastatic colorectal cancer patients with wild-type KRAS and BRAF. Cancer Genet 2012;205(11):545-51. doi: 10.1016/j.cancergen.2012.08.003

96. Takahashi M, Cuatrecasas M, Balagué F, Hur K, Toyiama Y, Castells A, et al. The clinical significance of MiR-148a as a predictive biomarker in patients with advanced colorectal cancer. PloS One 2012;7(10):e46684. doi: 10.1371/journal.pone.0046684
Nekvindova I, et al. MicroRNA expression profile associated with response to neoadjuvant chemoradiotherapy in locally advanced rectal cancer patients. Radiat Oncol 2012;7:195-. doi: 10.1186/1748-717X-7-195

98. Mueller AC, Sun D, Dutta A. The miR-99 family regulates the DNA damage response through its target SNF2H. Oncogene 2013;32(9):1164-72. doi: 10.1038/onc.2012.131

99. Sarver AL, French AJ, Borrallho PM, Thayanihy V, Oberg AL, Silverstein KA, et al. Human colon cancer profiles show differential microRNA expression depending on mismatch repair status and are characteristic of undifferentiated proliferative states. BMC Cancer 2009;9:401. doi: 10.1186/1471-2407-9-401

100. Qu J, Zhao L, Zhang P, Wang J, Xu N, Mi W, et al. MicroRNA-195 chemosensitizes colon cancer cells to the chemotherapeutic drug doxorubicin by targeting the first binding site of BCL2L2 mRNA. J Cell Physiol 2015;230(3):535-45. doi: 10.1002/jcp.24366

101. Saito Y, Liang G, Egger G, Friedman JM, Chuang JC, Coetzee GA, et al. Specific activation of microRNA-127 with downregulation of the proto-oncogene BCL6 by chromatin-modifying drugs in human cancer cells. Cancer Cell 2006;9(6):435-43. doi: 10.1016/j.ccc.2006.04.020

102. Zhang Y, Zheng L, Huang J, Gao F, Lin X, He L, et al. MiR-124 Radiosensitizes human colon cancer cells by targeting PRX1. PLoS One 2014;9(4):e93917. doi: 10.1371/journal.pone.0093917

103. Szatkowska M, Krupa R. Regulation of DNA Damage Response and Homologous Recombination Repair by microRNA in Human Cells Exposed to Ionizing Radiation. Cancers 2020;12(7):1838

104. Oh JS, Kim JJ, Byun JY, Kim IA. Lin28-let7 modulates radiosensitivity of human cancer cells with activation of K-Ras. Int J Radiat Oncol Biol Phys 2010;76(1):5-8. doi: 10.1016/j.ijrobp.2009.08.028

105. Arora H, Qureshi R, Jin S, Park AK, Park WY, miR-9 and let-7g enhance the sensitivity to ionizing radiation by suppression of NFκB1. Exp Mol Med 2011;43(5):298-304. doi: 10.3858/emm.2011.43.5.031

106. Yan D, Ng WL, Zhang X, Wang P, Zhang Z, Mo YY, et al. Targeting DNA-PKcs and ATM with miR-101 sensitizes tumors to radiation. Plos One 2010;5(7):e11397. doi: 10.1371/journal.pone.0011397

107. Schetter AJ, Leung SY, Sohn JJ, Zanetti KA, Bowman ED, Yanaiba N, et al. MicroRNA expression profiles associated with prognosis and therapeutic outcome in colon adenocarcinoma. JAMA 2008;299(4):425-36. doi: 10.1001/jama.299.4.425

108. Yang J-P, Tsai H-L, Hou M-F, Chen K-C, Tsai P-C, Huang Y, et al. MicroRNA-93 inhibits tumor growth and early relapse of human colorectal cancer by affecting genes involved in the cell cycle. Carcinogenesis 2012;33(8):1522-30. doi: 10.1093/carcin/bgs166

109. Ardila HJ, Sanabria-Salas MC, Meneses X, Rios R, Huertas-Muñoz A, Serrano AL. Circulating miR-141-3p, miR-143-3p and miR-200c-3p are differentially expressed in colorectal cancer and advanced adenomas. Mol Clin Oncol 2019;11(2):201-7. doi: 10.3892/mco.2019.1876

110. Peng Q, Feng Z, Shen Y, Zhu J, Zou L, Shen Y, et al. Integrated analyses of microRNA-29 family and the related combination biomarkers demonstrate their widespread influence on risk, recurrence, metastasis and survival outcome in colorectal cancer. Cancer Cell Int 2019;19:181-. doi: 10.1186/s12935-019-0907-x

111. Christensen LL, Tobiasen H, Holm A, Schepeler T, Ostenfeld MS, Thorsen K, et al. MiRNA-362-3p induces cell cycle arrest through targeting of E2F1, USF2 and PTPN1 and is associated with recurrence of colorectal cancer. Int J Cancer 2013;133(1):67-78. doi: 10.1002/ijc.28010

112. Bitarte N, Bandres E, Boni V, Zarate R, Rodriguez J, Gonzalez-Huarriz M, et al. MicroRNA-451 is involved in the self-renewal, tumorigenicity, and chemoresistance of colorectal cancer stem cells. Stem Cells 2011;29(11):1661-71. doi: https://doi.org/10.1002/stem.741

113. To KK, Tong CW, Wu M, Cho WC. MicroRNAs in the prognosis and therapy of colorectal cancer: From bench to bedside. World J Gastroenterol 2018;24(27):2949-73. doi: 10.3748/wjg.v24.i27.2949

114. Ahmed FE, Ahmed NC, Vos PW, Bonnerup C, Atkins JN, Casey M, et al. Diagnostic microRNA markers to screen for sporadic human colon cancer in stool: I. Proof of principle. Cancer Genomics Proteomics 2013;10(3):93-113

115. Xiao G, Tang H, Wei W, Li J, Ge J. Abrerant Expression of MicroRNA-15a and MicroRNA-16 Synergistically Associates with Tumor Progression and Prognosis in Patients with Colorectal Cancer. Gastroenterol Res Pract 2014;2014:364549. doi: 10.1155/2014/364549

116. Li Liu K, Li G, Fan C, Zhou X, Wu B, Li J. Increased expression of microRNA-21 and its association with chemotherapeutic response in human colorectal cancer. J Int Med Res 2011;39(6):2288-95. doi: 10.1177/147323001103900626

117. Wang YX, Zhang XY, Zhang BF, Yang CQ, Shen XM, Gao HJ, Initial study of microRNA expression profiles of colon cancer without lymph node metastasis. J Dig Dis 2010;11(1):50-4. doi: 10.1111/j.1751-2980.2009.00413.x

118. Yu H, Gao G, Jiang L, Guo L, Lin M, Jiao X, et al. Decreased expression of miR-218 is associated with poor prognosis in patients with colorectal cancer. Int J Clin Exp Pathol 2013;6(12):2904-11.

119. Li T, Lai Q, Wang S, Cai J, Xiao Z, Deng D, et al. MicroRNA-224 sustains Wnt/β-catenin signaling and promotes aggressive phenotype of colorectal cancer. J Exp Clin Cancer Res 2016;35:21. doi: 10.1186/s13046-016-0287-1

120. Rapado-González O, Álvarez-Castro A, López-López R, Iglesias-Canel J, Suárez-Cunqueiro MM, Muñedo-Romay L. Circulating microRNAs as promising biomarkers in colorectal cancer. Cancer (Basel) 2019;11(7). doi: 10.3390/cancers11070898

121. Wills B, Gorse E, Lee V. Role of liquid biopsies in colorectal cancer. Curr Probl Cancer 2018;42(6):593-600. doi: 10.1016/j.curprobcan.2018.08.004

122. Jahanban-Esfahlan R, Seidi K, Jaymand M, Alizadeh E, Majdi H, et al. Dynamic DNA nanostructures in biomedicine: Beauty, utility and limits. Nanotechnol Sci Appl 2015;8:101. doi: 10.1515/ntsa-2015-0083

123. Jahanban-Esfahlan A, Jahanban-Esfahlan R, Seidi K, Jaymand M, Alizadeh E, Majdi H, et al. Dynamic DNA nanostructures for cancer theranostics: recent progress in design and applications. Nanotechnol Sci Appl 2019;12:25-46. doi: 10.2147/ntsa.s227193

124. Ayoubi-Joshaghani MH, Dianat-Moghadam H, Seidi K,
Roles of miRNAs in colorectal cancer

Jahanban-Esfahalan A, Zare P, Jahanban-Esfahalan R. Cell-free protein synthesis: the transition from batch reactions to minimal cells and microfluidic devices. *Biotechnol Bioeng* 2020;117(4):1204-29. doi: 10.1002/bit.27248

125. Yagi T, Inuma H, Hayama T, Matsuda K, Nozawa K, Tsukamoto M, et al. Plasma exosomal microRNA-125b as a monitoring biomarker of resistance to mFOLFOX6-based chemotherapy in advanced and recurrent colorectal cancer patients. *Mol Clin Oncol* 2019;11(4):416-24. doi: 10.3892/mco.2019.1191

126. Tsukamoto M, Inuma H, Yagi T, Matsuda K, Hashiguchi Y. Circulating exosomal microRNA-21 as a biomarker in each tumor stage of colorectal cancer. *Oncology* 2017;92(6):360-70. doi: 10.1159/000463387

127. Lu JH, Zuo ZX, Wang W, Zhao Q, Qiu MZ, Luo HY, et al. A two-microRNA-based signature predicts first-line chemotherapy outcomes in advanced colorectal cancer patients. *Cell Death Discov* 2018;4:116. doi: 10.1038/s41420-018-0133-7

128. Ji D, Qiao M, Yao Y, Li M, Chen H, Dong Q, et al. Serum-based microRNA signature predicts relapse and therapeutic outcome of adjuvant chemotherapy in colorectal cancer patients. *EBioMedicine* 2018;35:189-97. doi: 10.1016/j.ebiom.2018.08.042

129. Hedayat S, Khan K, Cunningham D, Vlachogiannis G, Lampis A, Marchetti S, et al. Abstract LB-305: circulating miR-652-3p as a biomarker of resistance to regorafenib in metastatic colorectal cancer patients. *Cancer Res* 2019;79(13 Suppl):LB-305. doi: 10.1158/1538-7445.am2019-lb-305

130. Imaoka H, Toiyama Y, Fujikawa H, Hiro J, Saigusa S, Tanaka K, et al. Circulating microRNA-1290 as a novel diagnostic and prognostic biomarker in human colorectal cancer. *Ann Oncol* 2016;27(10):1879-86. doi: 10.1093/annonc/mdw279

131. Sun L, Liu X, Pan B, Hu X, Zhu Y, Su Y, et al. Serum exosomal miR-122 as a potential diagnostic and prognostic biomarker of colorectal cancer with liver metastasis. *J Cancer* 2020;11(3):630-7. doi: 10.7150/jca.33022

132. Zou SL, Chen YL, Ge ZZ, Qu YY, Cao Y, Kang ZX. Downregulation of serum exosomal miR-150-5p is associated with poor prognosis in patients with colorectal cancer. *Cancer Biomark* 2019;26(1):69-77. doi: 10.3233/cbm-190156

133. Liu X, Xu X, Pan B, He B, Chen X, Zeng K, et al. Circulating miR-1290 and miR-320d as novel diagnostic biomarkers of human colorectal cancer. *J Cancer* 2019;10(1):43-50. doi: 10.7150/jca.26723

134. Tang Y, Zhao Y, Song X, Song X, Niu L, Xie L. Tumor-derived exosomal miRNA-320d as a biomarker for metastatic colorectal cancer. *J Clin Lab Anal* 2019;33(9):e23004. doi: 10.1002/jcla.23004

135. Liu X, Xu T, Hu X, Chen X, Zeng K, Sun L, et al. Elevated circulating miR-182 acts as a diagnostic biomarker for early colorectal cancer. *Cancer Manag Res* 2018;10:857-65. doi: 10.2147/cmar.s158016

136. Liu X, Pan B, Sun L, Chen X, Zeng K, Hu X, et al. Circulating exosomal miR-27a and miR-130a act as novel diagnostic and prognostic biomarkers of colorectal cancer. *Cancer Epidemiol Biomarkers Prev* 2018;27(7):746-54. doi: 10.1158/1055-9965.epi-18-0067

137. Zhang H, Zhu M, Shan X, Zhou X, Wang T, Zhang J, et al. A panel of seven-miRNA signature in plasma as potential biomarker for colorectal cancer diagnosis. *Gene* 2019;687:246-54. doi: 10.1016/j.gene.2018.11.055

138. Zhu M, Huang Z, Zhu D, Zhou X, Shan X, Qi LW, et al. A panel of microRNA signature in serum for colorectal cancer diagnosis. *Oncotarget* 2017;8(10):17081-91. doi: 10.18632/oncotarget.15059

139. Fu F, Jiang W, Zhou L, Chen Z. Circulating exosomal miR-17-5p and miR-92a-3p predict pathologic stage and grade of colorectal cancer. *Transl Oncol* 2018;11(2):221-32. doi: 10.1016/j.tranon.2017.12.012

140. Toiyama Y, Hur K, Tanaka K, Inoue Y, Kusunoki M, Boland CR, et al. Serum miR-200c is a novel prognostic and metastasis-predictive biomarker in patients with colorectal cancer. *Ann Surg* 2014;259(4):735-43. doi: 10.1097/SLA.0b013e3182a6909d

141. Hur K, Toiyama Y, Okugawa Y, Ide S, Imaoka H, Boland CR, et al. Circulating microRNA-203 predicts prognosis and metastasis in human colorectal cancer. *Gut* 2017;66(4):654-65. doi: 10.1136/gutjnl-2014-308737