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MicroRNAs as novel predictive biomarkers and therapeutic targets in colorectal cancer

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molecule multi-kinase inhibitor regorafenib. One of the major problems for the management of CRC is the inherent or acquired resistance to therapeutic approaches. The discovery of microRNAs (miRNAs), a class of small, endogenous, non-coding, single-stranded RNAs that play a role as post-transcriptional regulators, has added new dimensions to the diagnosis and treatment of cancer. Because miRNAs are important regulators of carcinogenesis, progression, invasion, angiogenesis and metastases in CRC, they might serve as potential predictive and prognostic factors and even as therapeutic targets themselves. Several miRNAs are already known to be dysregulated in CRCs and have been linked to biological processes involved in tumor progression and response to anti-cancer therapies. This review summarizes current therapeutic approaches for treating CRC and highlights the role of miRNAs as novel predictive biomarkers and potential drug targets in CRC patients.

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Key words: Colorectal cancer; MicroRNAs; 5-fluorouracil; Epidermal growth factor receptor; Targeted therapy

Abstract

Colorectal cancer (CRC) is the third most common cancer in western countries. Despite significant improvement in available treatment options, CRC still remains the second leading cause of cancer-related death. Traditionally, 5-fluorouracil has been used as the main chemotherapy drug for treatment of metastatic CRC (mCRC). However, during the last two decades more effective chemotherapeutic agents such as oxaliplatin, irinotecan and the monoclonal antibodies cetuximab, panitumumab and bevacizumab have been used in clinical practice. More recently, the therapeutic armamentarium has been supplemented by the monoclonal antibodies bevacizumab, cetuximab and panitumumab as well as the protein-trap aflibercept and the small

Core tip: In this review article, we summarize the status quo of the current literature regarding microRNAs and their role in resistance against anti-cancer drugs in colorectal cancer. This Review Article explains how microRNAs influence colorectal cancer, and how these small molecules might be useful as predictive factors and drug targets by themselves.

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INTRODUCTION

Colorectal cancer (CRC) is the third most common cancer in western societies with about 1.2 million new cases and 608700 deaths estimated to have occurred in 2008^[1]. Outcomes for patients with mCRC still remain poor, with an average survival of less than 30 mo^[2]. The majority of CRC cases arise from dysplastic adenomatous polyps. The process of transformation includes a few essential events characterized by the activation of oncogenes such as *KRAS* (Kirsten rat sarcoma viral oncogene homolog), *c-MYC* (v-myc avian myelocytomatosis viral oncogene homolog) and *NRAS* (neuroblastoma RAS viral oncogene homolog) and by inactivation of tumor suppressor genes [e.g., *p53* (tumor protein p53) and *APC* (adenomatous polyposis coli)] or DNA repair genes such as *hMSH2* (human mutS homolog 2) or *hMSLH1*^[3]. Although 5-fluorouracil (5-FU) has proven to be moderately effective in CRC as a monotherapy, its combination with the chemotherapeutic drugs oxaliplatin and irinotecan improved the therapeutic outcome. During the last few years, the combination of chemotherapeutic agents with more effective systemic agents such as bevacizumab, panitumumab or cetuximab has been established in clinical practice and improved survival rates in patients with CRC^[4,5].

CURRENT COLORECTAL CANCER TREATMENT REGIMENS

5-fluorouracil

5-FU is one of the main chemotherapeutic drugs used for treatment of CRC^[6,7]. It exhibits its cytotoxicity by incorporating fluoronucleotides into RNA and DNA molecules, but its main toxic effects are mediated by inhibiting the nucleotide synthetic enzyme thymidylate synthase (TYMS)^[7]. However, one of the major problems in managing progressed colorectal cancer is both the inherent and acquired failure of 5-FU-based therapy. Several analyses of 5-FU resistance in CRC have focused on genes involved in pharmacodynamic and pharmacokinetic pathways. One main point has been the activity of TYMS, a key therapeutic target of 5-FU. CRCs that are resistant to 5-FU-based chemotherapy have been shown to possess greater TYMS enzymatic activity than cancers that are sensitive to this therapy^[8]. High levels of *TYMS* mRNA or protein expression in liver metastases have also been linked to lack of clinical response to 5-FU *in vivo*^[9]. Moreover, a meta-analysis of 24 studies demonstrated that low expression levels of TYMS in metastatic colorectal tumors are associated with greater sensitivity to fluoropyrimidine-based chemotherapy^[10]. Additionally, the activity of thymidine phosphorylase (TP), a key enzyme that catalyzes the transformation from 5-FU prodrugs of 5'-deoxy-5-fluorouridine (5'-DFUR) to 5-FU, is closely linked to failure of 5-FU and targeted therapy in CRC cells^[11].

EGFR inhibitors

The epidermal growth factor receptor (EGFR) belongs to the ErbB family of receptors that are able to promote tumor cell proliferation in diverse epithelial malignancies^[12]. For this reason, EGFR has become an important target in oncology. Monoclonal antibodies against EGFR are used as a standard therapy for some types of solid tumors. The chimeric IgG1 mouse/human antibody cetuximab and the human IgG2 antibody panitumumab are considered to be equally effective in mCRC. However, it has been extensively reported that primary resistance to these agents is mediated by mutations in downstream signaling molecules^[13]. Misale *et al.*^[14] showed that the development of resistance to anti-EGFR treatment in CRC is associated with molecular alterations of *KRAS*. Although *KRAS* mutations confer strong resistance to anti-EGFR antibodies, not all CRC patients with *KRAS* wildtype (*KRAS*wt) benefit from these agents. Therefore, there is a need for novel biomarkers to better identify which *KRAS*wt patients would benefit from this therapy^[15]. A few studies have shown that high EGFR gene copy number could be a potential favorable marker for anti-EGFR therapy in CRC, as patients with low gene copy number are unlikely to respond to anti-EGFR agents^[16,17]. Very recently, rare mutations in exons 3 and 4 in the both the *KRAS* gene and *NRAS* gene have demonstrated predictive potential in regards to panitumumab treatment^[18].

VEGF targeted therapy

Angiogenesis is widely regarded as an important therapeutic target in many different types of cancer, including CRC^[19]. It has been suggested that inhibition of angiogenesis in tumors can influence the development of new tumor blood vessels and probably lead to normalization of the existing tumor vasculature. The vascular endothelial growth factor (VEGF) is a pro-angiogenic factor that plays a key role in tumor vascular development^[20]. VEGF-neutralizing antibodies can prevent the binding to and activation of VEGFR1 (vascular endothelial growth factor receptor 1), VEGFR2 (vascular endothelial growth factor receptor 2) and the co-receptors NP1 (Neuropilin 1) and NP2 (Neuropilin 2). Bevacizumab, a humanized monoclonal antibody that binds to all isoforms of VEGF, is the first anti-angiogenic therapy approved for treatment of CRC^[21,22]. It has also been used in combination with common chemotherapeutic agents, such as 5-FU and capecitabine as well as irinotecan and oxaliplatin^[23]. Resistance to combinatorial therapy in CRC treatment may be due to resistance to bevacizumab, resistance to the chemotherapeutic with which bevacizumab was administered or a resistance to both. As observed, several pathways in addition to the VEGF pathway are involved in angiogenesis. Therefore, mechanisms of resistance to anti-angiogenic therapy may also include VEGF-independent anti-angiogenesis pathways^[24].

MIRNA BIOGENESIS AND FUNCTION

MiRNAs are a class of small, endogenous, non-coding, single-stranded RNAs that play a role as post-transcriptional regulators by suppressing the translation or inducing the mRNA degradation of their target genes^[25]. Dysregulated miRNA expression in human cancers plays a role in carcinogenesis mainly by regulating their mRNA targets, which could be oncogenes or tumor suppressors^[26]. Various combinations of miRNAs are expressed in different cell types and regulate cell-specific target genes. MiRNAs regulate about one-third of all human genes and a single miRNA can target around 200 or more transcripts that are key regulators of multiple signaling pathways in the cell^[27,28]. Aberrational miRNA expression patterns, commonly seen in human diseases including various types of cancer, can serve as prognostic factors and may have implications for cancer stem cell regulation^[29-32]. More than 50% of known human miRNA genes are localized in fragile chromosomal regions that are susceptible to amplification, deletion or translocation during cancer development^[33].

MiRNAs are transcribed as long primary transcripts called pri-miRNAs and are processed into precursor miRNAs (pre-miRNAs) in the nucleus by the enzyme Drosha. These short hairpin RNAs of approximately 70 nt are then translocated to the cytoplasm where they are cleaved by the enzyme Dicer to generate the miRNA duplex^[34,35]. Afterwards, the miRNA is unwound by a helicase and one of the strands is defined as the mature strand while the other one is quickly degraded. The mature miRNA is incorporated into an RNA-induced silencing complex (RISC) that mediates gene silencing^[36].

MiRNAs are important regulators of oncogenesis, progression, invasion, angiogenesis and metastasis in colorectal cancer. Both upregulation and downregulation have been linked to carcinogenesis in CRC^[37]. Many proteins that play a role in key signaling pathways of CRC seem to be influenced by miRNA regulation, such as members of the Wnt/beta-catenin and phosphatidylinositol-3-kinase (PI-3-K) pathways, KRAS, p53, extracellular matrix regulators as well as epithelial-mesenchymal transition (EMT) proteins and transcription factors^[26,38,39].

New findings suggest that miRNAs could be linked to sensitivity to chemotherapeutic drugs in tumor cells. For this reason, researchers are interested in the potential role of miRNAs in pharmacogenomics^[40]. A recent study by Pardini *et al.*^[41] provided evidence that a modulation of the expression of base excision repair (BER) genes, such as a post-transcriptional change caused by microRNAs, could influence the efficiency of this repair system. Single-nucleotide polymorphisms (SNP) within the 3'-untranslated regions (UTR) of target genes could lead to an alteration in binding of specific miRNAs that modulate gene expression. Such changes could affect cancer prognosis and therapy outcomes. Hence, characterization of polymorphisms in miRNA-related genes or target sites might afford a basis for miRNA-based

therapy approaches.

In the next few pages, we will discuss particular miRNAs which have been experimentally proven to play a role in drug resistance in the past few years.

MIRNAS AND THEIR INVOLVEMENT IN RESISTANCE TO ANTI-CANCER THERAPIES

Let-7

Clinical trials have demonstrated that KRAS mutations are negative predictive biomarkers for EGFR-targeted therapy in CRC. Mechanisms of post-transcriptional downregulation of mutated KRAS might therefore be of clinical relevance in patients with mCRC^[42,43]. The members of the *let-7* family are known to target KRAS and their involvement in response to EGFR-targeted therapy has already been reported^[44]. Upregulation of *let-7* expression levels might provide a survival advantage by inhibiting mutated KRAS under EGFR-targeted therapy. In addition, *let-7* may reveal further favorable effects by regulating other genes such as the cell cycle regulators, *Myc*, *Bcl-2* (B-cell CLL/lymphoma 2), integrins and signal transducers. Ruzzo *et al.*^[45] analyzed the expression levels of *let-7a* in colorectal carcinomas with mutated KRAS and in mCRC patients treated with cetuximab and irinotecan. Their study revealed that intra-tumor expression of *let-7a* correlates with tumor response and overall survival in mCRC patients treated with anti-EGFR-based therapy in both KRAS mutant and wildtype populations. Moreover, they showed that downregulation of *let-7e* and *let-7b* can potentially be used to predict resistance to the monoclonal antibody cetuximab. Cappuzzo *et al.*^[46] investigated whether microRNAs can predict sensitivity to EGFR-targeting monoclonal antibodies in patients with mCRC. They identified the cluster *Let-7c/miR-99a/miR-125b* as a signature linked to an outcome different from that of EGFR targeting therapies. In the first cohort, patients with high-intensity signatures showed a significantly longer progression-free survival and longer overall survival. Moreover, in the KRAS wild-type population, high-intensity signature patients had a significantly longer progression-free survival, as demonstrated in the validation cohort. Therefore, the *miR-99a/let-7c/miR-125b* signature could improve the selection of patients with KRAS wild-type mCRC for treatment with EGFR targeting therapies.

Salendo *et al.*^[47] performed a genome-wide miRNA profiling in 12 colorectal cancer cell lines and established an individual in vitro signature for chemoradiosensitivity. Their study demonstrated that high expression of *let-7g* was linked with a good prognosis in rectal cancer patients. This finding suggests that *let7g* expression may serve as potential predictive biomarker.

MiR-126

An increasing number of studies proposed *miR-126*

as a player in the regulation of angiogenesis, a process that has already been considered as a target for development of novel drugs. High expression of *miR-126* has already been associated with increased vascular endothelial growth factor A (VEGF-A) mediated signaling in endothelial cells and a higher blood vessel integrity^[48]. Additionally, *miR-126* has been identified as a putative tumor suppressor in primary tumors^[49-51]. Hansen *et al*^[48] investigated the role of *miR-126* as a predictive marker in patients with CRC in relation to first-line treatment with capecitabine, a precursor of 5-FU, and oxaliplatin (XELOX). They demonstrated a significant relationship between expression of *miR-126* in the primary tumor and sensitivity to first-line XELOX treatment. Low expression of *miR-126* might therefore lead to tumor vessels with decreased integrity followed by an increase in interstitial pressure, which may explain the lower sensitivity in patients treated with XELOX. A recent study by Hansen *et al*^[52] revealed that high expression of *miR-126* in mCRC patients was strongly related to a longer progression-free survival. Their results confirm their previous findings on the prognostic value of *miR-126* in mCRC. As VEGF-A may be a target of *miR-126*, the results of their study might provide predictive information in regards to next-generation anti-angiogenic therapy approaches.

MiR-31

Several studies revealed that *miR-31* is upregulated in CRC, but there is little known about its role in modulating tumor cell response to chemotherapeutic drugs. Wang *et al*^[53] showed that the treatment of HCT-116 colon cancer cells with an anti-*miR-31* inhibitor increased the sensitivity to 5-FU as early as 24 hours after exposure without affecting cell proliferation. Combination of 5-FU treatment with a respective negative control did not lead to a reduction in cell viability. The apoptosis rate of HCT-116 cells treated with both 5-FU and the anti-*miR-31* inhibitor was the highest among respective control groups, indicating that these agents inhibited proliferation *via* the apoptotic mechanism.

MiR-192/miR-215

The expression levels of *miR-192* and -215 were shown to be significantly reduced in CRC tissues compared to non-tumor counterparts. Furthermore, Chiang *et al*^[54] demonstrated that low expression levels of *miR-192* and -215 are related to increased tumor size in CRC. Thus, *miR-129* and *miR-215* could be useful biomarkers in the carcinogenesis of CRC. In addition, *miR-192* and *miR-215* were reported to negatively regulate CRC cell proliferation^[55]. Boni *et al*^[40] showed that *miR-192* and -215 downregulate TYMS expression and thus increase resistance to 5-FU in CRC cell lines. TYMS plays a role in normal cell function and is a potential target for chemotherapeutic drugs such as 5-FU. Transcriptional and translational regulation of TYMS most likely affect cell chemosensitivity. Additionally, they demonstrated that *miR-192* and *miR-215* inhibit progression into the S phase, play a role in cell cycle con-

trol and prevent sensitivity to 5-FU. Zhang *et al*^[56] identified a set of 6 miRNAs including *miR-215* which could serve as an authentic prognostic and predictive tool for determination of disease recurrence in patients with stage II colon cancer. *miR-215* could potentially predict which patients would benefit from adjuvant chemotherapy, which can in turn facilitate patient consultation and help individualize management of patients with this disease.

MiR-148a

It has been shown that *miR-148a* is a pro-apoptotic miRNA in CRC which acts by targeting *Bcl-2*, a regulator of apoptosis. In addition, several in vitro studies have demonstrated that *miR-148a* functions as a tumor suppressor by targeting several genes such as *PXR* (nuclear receptor subfamily 1, group I, member 2), *TGIF2* (TGFB-induced factor homeobox 2), *MSX1* (msh homeobox 1), *CDC25B* (cell division cycle 25B), *DNMT1* [DNA (cytosine-5-methyltransferase 1)] and *DNMT3b* [DNA (cytosine-5-methyltransferase 3 beta)]^[57]. Takahashi *et al*^[58] showed that low expression of *miR-148a* is significantly linked to an unfavorable outcome in treatment of stage III CRC patients with 5-FU. They also demonstrated the link between decreased *miR-148a* expression and poorer sensitivity and survival rate in patients with stage IV CRC treated with oxaliplatin combined with 5-FU. Stage IV CRC patients that showed a high *miR-148a* expression level were shown to benefit from chemotherapeutic drugs, indicating that *miR-148a* may have predictive value in the assessment of response to CRC treatment. In addition, their data suggested that downregulation of *miR-148a* is mediated by DNA methylation. Takahashi *et al*^[58] showed that there is a significant and independent association between *miR-148a* methylation and poor survival in stage IV patients. Therefore, the methylation status of *miR-148a* might be a potential prognostic marker in CRC. Kjersem *et al*^[59] investigated microRNAs in plasma as potential predictive markers for sensitivity to oxaliplatin-based chemotherapy. Their study revealed that a high expression level of *miR-148a* is associated with a decrease in progression-free survival. The results of their study suggest that *miR-148* could serve as a non-invasive biomarker for predicting outcomes in mCRC patients treated with 5-FU and oxaliplatin-based chemotherapy.

MiR-21

Upregulated *miR-21* expression is associated with some types of human cancer, including CRC. It has been demonstrated that *miR-21* regulates several tumor suppressors such as p21, TGF-beta receptor II and B-cell leukemia/lymphoma 2-associated X protein. Moreover, overexpression of *miR-21* is linked to poor response to 5-FU-based chemotherapy. Valeri *et al*^[60] found an inverse expressional correlation of *miR-21* and the tumor suppressor hMSH2. They demonstrated that *miR-21* directly targets the 3' UTR of *hMSH2* mRNA and significantly reduces its protein expression. CRC cells that showed high expression levels of *miR-21* have decreased hMSH2

protein expression and revealed significantly reduced 5-FU-induced G2/M damage arrest and apoptosis. This indicates a characteristic defect in the core mismatch repair system, suggesting that *miR-21* might act as a regulator of genes associated with cell-cycle arrest and/or drug resistance. In addition, Deng *et al.*^[61] showed that forced *miR-21* expression in HT-29 colon cancer cells significantly inhibited apoptosis, enhanced cell proliferation and invasion and increased resistance to the chemotherapeutic agent 5-FU. Moreover, they demonstrated that silencing of *miR-21* inverted these effects on HT-29 cells and restored the sensitivity to 5-FU.

MiR-129

Reduced *miR-129* expression levels have been reported in several tumor cell lines and primary tumors including CRC^[62]. Karaayvaz *et al.*^[63] demonstrated that *miR-129* expression was clearly lower in CRC patients. There was no significant difference between adenoma and stage I and II carcinomas. They observed that *miR-129* expression was dramatically reduced in stage III and IV cancers. Hence, their results suggested that loss of *miR-129* is linked to progression in CRC. Additionally, they identified *miR-129* as a novel regulator of *Bcl-2* expression. The expression of *miR-129* promoted apoptosis, inhibited cell proliferation and caused cell-cycle arrest in CRC cells. *miR-129*-based therapies could help to achieve a multi-targeted anti-cancer therapeutic strategy. 5-FU-based chemotherapy still remains the main option for advanced mCRC treatment, but the possibility of *miR-129* restoration may lead to a new strategy in reducing resistance to chemotherapeutic drugs. Furthermore, Karaayvaz *et al.*^[63] showed that *miR-129* is a suppressor of the 5-FU target protein TYMS and therefore enhances chemosensitivity to 5-FU. In their *in vivo* tumor xenografts, they demonstrated that increasing *miR-129* expression to normal levels using synthetic miRNAs made tumors more sensitive to 5-FU-based drugs.

MiR-19b

MiR-19b is one of the 6 miRNAs which are encoded by the *miR-17-92* cluster. The activation of this cluster is mediated by the transcription factor E2F1 which accumulates early in the G1 phase of the cell cycle, suggesting that miRNAs generated from this cluster might play a role in the G1 phase. Kurokawa and colleagues found that *miR-19b* expression is upregulated in the DLD-1/R colon cancer cell line, but they did not observe any changes in the cell cycle profile after 5-FU treatment. In addition, they demonstrated that *miR-19b* expression correlated with response to the widely-used anti-cancer drug 5-FU^[64]. Likewise, a recent study showed that *miR-19a*, a paralogue of *miR-19b*, is upregulated in HCT-119 and HT29 cells in response to 5-FU-based treatment^[65].

MiR-34a

MiR-34a is a member of the *miR-34* family which also includes *miR-34b* and *miR-34c*. Low expression levels of *miR-34a* have been identified in various types of tumors,

including CRC^[66]. Moreover, *miR-34a* was observed as one of the most downregulated miRNAs in the 5-FU-resistant DLD-1 CRC cell line. Akao *et al.*^[67] showed that exposure to 5-FU activated the PI3K/Akt signaling pathway in the resistant DLD-1 cell line in comparison to the parental cells and led to an apparent increase in growth. In addition, *miR-34a* expression in the 5-FU-resistant cell line was prolonged at a low level, whereas it showed an upregulation in the parental cells after treatment with a 5-FU-based drug. They observed an upregulation of Sirt-1, a target gene of *miR-34a* which is associated with drug resistance, in the 5-FU-resistant cells and also that silencing of Sirt-1 significantly increased the sensitivity to 5-FU in the 5-FU-resistant cells. This suggested that *miR-34a* is a negative regulator of 5-FU resistance in the CRC cell line DLD-1.

MiR-143

A few studies showed that *miR-143* expression is low in tumors compared to their normal counterparts, both at adenomatous and cancer stages of colorectal neoplasia, as well as in CRC cell lines^[68]. In addition, *miR-143* has been identified to directly target the *KRAS* mRNA^[69]. Borralho *et al.*^[70] investigated the role of *miR-143* in the HCT116 CRC cell line. They showed that transient overexpression of *miR-143* led to a 60% reduction in cell viability and stable overexpression of *miR-143* resulted in decreased viability and increased cell death after treatment with 5-FU. These changes were linked to increased nuclear fragmentation and caspase -3, -8 and -9 activities. Furthermore, they demonstrated that exposure of *miR-143*-overexpressing cells to 5-FU resulted in downregulation of the extracellular-regulated protein kinase 5 and Bcl-2 protein expression. In addition, *miR-143* led to increased sensitivity to 5-FU-based drugs, suggesting that *miR-143* is involved in CRC development and plays a role as a chemosensitizer to 5-FU.

MiR-203

Zhou *et al.*^[71] recently showed that *miR-203* is upregulated in three oxaliplatin-resistant CRC cell lines. They demonstrated that exogenous expression of *miR-203* in chemo-naïve CRC cells reduced sensitivity of cells to oxaliplatin treatment. Silencing of *miR-203* expression led to increased sensitivity of CRC cells to oxaliplatin. Furthermore, they performed an *in-silico* analysis and identified ataxia telangiectasia mutated (*ATM*), a primary mediator of the DNA damage response, as a potential target of *miR-203*. Their study showed that mutation of the putative *miR-203* target region in the 3' untranslated region of *ATM* mRNA eliminated the inhibitory effect of *miR-203* on *ATM*. In addition, they demonstrated that stable knockdown of *ATM* led to resistance to oxaliplatin in chemo-naïve CRC cells.

MiR-200c

Hur *et al.*^[72] reported that *miR-200c* expression modulates EMT in colorectal metastasis. In their study, they demonstrated for the first time that the *miR-200c/429*

cluster was significantly overexpressed in liver metastasis in comparison to primary CRC and that the expression of these miRNAs was specifically regulated by aberrant methylation of their promoter regions. A recent study by Toiyama *et al.*^[73] revealed that the serum levels of *miR-200c* might serve as potential prognostic and metastatic-predictive biomarkers in CRC patients. They showed that *miR-200c* expression in serum is strongly associated with a metastatic phenotype in CRC; in particular, expression of *miR-200c* in serum was a good predictive marker for lymph node metastasis. Moreover, they demonstrated that *miR-200c* expression in serum can be used as a prognostic and predictive marker of tumor recurrence in patients undergoing curative surgery.

CONCLUSION

Currently, therapeutic agents including 5-FU, oxaliplatin, irinotecan, bevacizumab cetuximab, panitumumab, aflibercept and regorafenib are widely used in clinical practice for CRC treatment. However, many patients are resistant or develop secondary resistance to these agents, highlighting the necessity for the development of novel prognostic markers for drug resistance. As important regulators of gene expression, miRNAs possess high potential as predictive markers for therapeutic response to chemotherapeutic drugs. On the other hand, targeting miRNAs that are involved in the resistance mechanism may improve the therapeutic efficacy in chemo-resistant patients. We foresee that in the near future, miRNA-based prognostic tools could be developed to aid in patient selection for certain treatments, and miRNA-based therapeutics may finally reach the clinical stages.

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