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**MiRNA as potential biomarkers and therapeutic targets for gastric cancer**

# Shin VY *et al*. MiRNA and gastric cancer

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# Abstract

Gastric cancer is one of the leading causes of cancer mortality in the world. Aberrant expression of microRNAs (miRNAs) is the hallmarks of this disease. MiRNAs are endogenous non-coding RNA that involved in many biological processes (*e.g.,* cell proliferation, differentiation, apoptosis, invasion and development) through gene repression. Deregulation of miRNA expression in gastric tumors and cancer cell lines have been documented to contribute in tumorigenesis, and the expression signature may correlate with different cancer types and clinicopathological features. Here, we summarized the updated gastric cancer-associated miRNAs and the downstream targets in the process of tumorigenesis. Recently, many researchers make use of the miRNA microarray platform to profile miRNA expression in gastric cancer and correlated with different clinical parameters. Its application on cancer diagnosis, prognosis and predictive treatment response rate are still underway and needs further investigation. Emerging roles of miRNAs with oncogenic or tumor suppressive properties in gastric tumorigenesis were discussed. Epigenetic silencing of miRNA by hypermethylation of promoter CpG island was also observed in gastric cancer. However, detailed mechanisms of how miRNAs regulate gene expression in gastric cancer has not been well studied. In this review, we highlight the up-to-date findings on the deregulated miRNAs in gastric cancer, and the potential use of miRNA in the clinical settings, such as diagnostic/prognostic markers and chemotherapeutic tools.

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**Key words**: miRNA; Gastric cancer; Biomarker; Diagnosis; Prognosis; Clinical application

**Core tip:** This minireview summarized the most up-to-date important microRNAs (miRNAs) involved in tumor progression and development in gastric cancer. The potential use of miRNAs in the different areas of clinical settings is discussed.

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# Introduction

Gastric cancer is the second leading cause of cancer mortality in the world, and has a particularly high incidence in Asian countries including China and Japan. Despite the declining incidence of gastric cancer, there are still over 1 million cases newly diagnosed and 850000 deaths globally each year[[1](#_ENREF_1)]. The high mortality rate is mainly due to late presentation, since early stage of gastric cancer is either asymptomatic or presents with non-specific symptoms. The survival rate depends on the stage of gastric cancer at the time of diagnosis[[2](#_ENREF_2)]. In Western countries, the 5-year survival ranged from 5%-20%, whereas in Japan, the survival rate was about 50% due to early diagnosis[[3](#_ENREF_3)]. Today, surgery remains the mainstay of potentially curative treatment for gastric cancer. Nevertheless, over 50% of the patients may still develop recurrence after curative resection. A good screening method for early detection is the best way to reduce gastric cancer mortality. Due to the associated side effects with endoscopy, including perforation, aspiration pneumonia or bleeding, thus making endoscopic screening not a common practice in the community. Hence there is an urge for the discovery of biomarkers for non-invasive early detection in gastric cancer patients.

 MicroRNAs (miRNAs) are endogenous noncoding regulatory RNAs with 17-25 nucleotides, which play important roles in post-transcriptional gene regulation. The ability to bind complementary sequences in 3’-untranslated regions (3’-UTR) of various target mRNAs leading to direct mRNA degradation or translational repression. MiRNAs regulate gene expression and contribute to development, differentiation, inflammation, and carcinogenesis. At present, over 24500 entries have been listed in the miR Registry Database (release 20, <http://www.mirbase.org/>), implicating more than 30,000 mature miRNA products, and the number of miRNAs is expected to increase exponentially in the future. Studies have shown that over 30% of human genes are regulated by miRNAs, in which a single miRNA controls over hundreds of RNA.

 MiRNA plays pivotal role in biological processes including cell proliferation, metastasis, differentiation, development and apoptosis[[4](#_ENREF_4),[5](#_ENREF_5)]. Accumulating evidence showed that the miRNA profiles were differentially expressed in cancerous tissues and normal counterparts[[6](#_ENREF_6),[7](#_ENREF_7)]. The fact that miRNAs are very specific for different types of tissues and even for types of cells within those tissues,many studies profiled the miRNA patterns in various cancer types, which put forward the diagnostic and prognostic values of miRNAs in clinical applications. To date, there are many different platforms to study the expressions of miRNA, for example, northern blots, real-time PCR, primer extension and microarrays. Microarray has been the most widely used for miRNA research, not only it is a more user-friendly platform, its high throughput property makes possible to profile the whole genome of miRNA.

 Deregulation of miRNA in human cancers was a result of impaired miRNA-biogenesis, genomic or epigenetic alterations, leading to the proto-oncogenic or tumor suppressive role of miRNA in tumorigenesis. For oncogenic miRNA, inhibitor of miRNA blocks the function of miRNA; while tumor suppressive miRNA, reconstitute miRNA precursor produce an anti-tumor effect. Hence targeting specific miRNA could be a possible alternative for treating gastric cancer patients.

## **Biogenesis of miRNA**

The biogenesis of miRNA involves the transcription of miRNA by RNA polymerase II to form large double-stranded precursor (Pri-miRNA) in the nucleus. It appeared in a hairpin structure which was then cleaved by RNase III endonuclease Drosha to produce a 60-70 nucleotides hairpin precursor (Pre-miRNA) and exported to the cytoplasm by a nuclear membrane export receptor Expotin-5. Pre-miRNA is then cleaved by another RNase III enzyme Dicer to form a mature double-stranded miRNA (about 22 nucleotides) which comprises a mature miRNA guide strand and passenger strand. The guide strand (mature miRNA) is incorporated into RNA-induced silencing complex (RISC) to target mRNA via 2 mechanisms: (1) cleavage of mRNA at the miRNA binding site; and (2) repression of translation. Due to the fact that miRNAs are present in the genomic regions that involved in cancers, miRNAs become increasingly recognized as potential marker for diagnosis and prognosis.

### GASTRIC CANCER RELATED MIRNAS IN CELL PROLIFERATION AND APOPTOSIS

Microarray is a useful and convenient platform to profile the miRNA expression in human cancers. By comparing the expression in gastric cancerous tissue with non-tumor tissue, the distinct miRNA signatures are associated with progression and perhaps prognosis of gastric cancer[[8](#_ENREF_8)]. The miRNA signatures have a higher accuracy and reproducibility than mRNA expression profiles, over 80% of the paired gastric samples were classified correctly by the miRNA signatures. Prediction and validation of downstream targets become increasingly important in miRNA research, here; we listed the targets of upregulated and downregulated miRNAs in gastric cancer (Table 1).

Over 92% of the gastric cancer patients demonstrated an upregulation of miR-21 in solid human tumors, including gastric cancer[[9](#_ENREF_9)]. Currently, it has been reported that miR-21 was upregulated not only in cancerous tissues but also in *Helicobacter pylori (H. pylori)*-infected gastric mucosa[[10](#_ENREF_10)]. Gastric cancer is a result of multistep and long-term interactions between genetic and environmental factors which process from chronic gastritis, atrophic gastritis, intestinal metaplasia, glandular atrophy and dysplasia[[11](#_ENREF_11)]. The miRNA that was associated with *H. pylori*-induced inflammation was miR-218, overexpression of this miR abrogated nuclear factor-kappa B (NF-κB) activation[[12](#_ENREF_12)]. It was hypothesized that miR-21 might augment the progression of infected normal mucosa to chronic gastritis with unknown mechanisms. The signal transducer and activator of transcription 3 (STAT3) activated the induction of miR-21[[13](#_ENREF_13)]. Activation of nuclear factor-kappa B (NF-κB) and interleukin (IL-6) stimulated STAT3 signaling, which may explain the *H. pylori*-mediated upregulation of miR21. Interestingly, there is a transcription binding site of NF-κB located in miR-21 transcriptional elements, suggesting that miR-21 upregulation is a result of NF-κB activation in gastric cancer[[14](#_ENREF_14)].

Numerous evidence revealed that miR-21 attributed to gastric cancer through enhanced cell proliferation and inhibited apoptosis. On top of that, miR-21 also has the ability to incite cell invasion and migration. It has been reported that RECK, a tumor suppressor gene, is the target of miR-21. It involves in the process of metastasis and angiogenesis through regulating metalloproteases (MMPs)[[10](#_ENREF_10)]. MiR-125b, miR-199a and miR-100 have been shown to be the most important progression-related miRNA in gastric cancer and pancreatic adenocarcinoma[[12](#_ENREF_12),[15](#_ENREF_15)], implicating that miRNA may have different functions depends upon the tumor site. There are some miRs (miR-32, miR-182 and miR-143) that are found to be associated with intestinal-type gastric cancer, this study implicated the usefulness of miRNA expression profiles may serve as diagnostic biomarkers for different subtypes of gastric cancers[[16](#_ENREF_16)]. Expressions of miR-143, miR-145, miR-9, miR-443, miR-31, and miR-34 have been reported to downregulate in gastric cancer[[17-19](#_ENREF_17)]. The roles of miR-143 and miR-145 on cell proliferation have also been demonstrated in other gastrointestinal cancers[[20](#_ENREF_20)]. Ectopic expression of miR-143 and miR-145 showed significant growth retardation and sensitized to 5-fluorouracil treatment in gastric cancer cells[[17](#_ENREF_17)].

**GASTRIC CANCER RELATED MIRNAS IN CELL INVASION AND METASTASIS**

There is a strong correlation of elevated expression of high mobility group AT-hook 2 (HMGA2), a nonhistone chromosomal protein that modulate translation, with tumor invasiveness in gastric cancer. HMGA2 was inversely regulated by the let-7 miRNA family. High expression of HMGA2 correlated with tumor invasion and was an independent prognostic factor in gastric cancer[[21](#_ENREF_21)]. In addition, miR-214 was reported to modulate hedgehog signaling, where activation of hedgehog contributes to gastric cancer[[8](#_ENREF_8)]. High expression of miR-214 was identified to correlate with unfavorable outcome in gastric cancer. In ovarian cancer, miR-214 regulated the downstream target PTEN to induce cell survival[[22](#_ENREF_22)]. Furthermore, miR-196b expression has been shown to be significantly higher in gastric cancer tissues than normal counterparts[[23](#_ENREF_23)]. Silence of ETS2 (a transcriptional modulator) enhanced miR-196b expression which promoted gastric cancer cell migration and invasion by increased vimentin, MMP-2 and MMP-9 expressions and suppressed E-cadherin expression.

### *Epigenetic alteration of miRNAs*

Gastric carcinogenesis is a multistep process with genetic alterations including mutation, activation of oncogenes and suppression of tumor suppressor genes, and overexpression of growth factors. Genetic instability, DNA methylation and mutations are known to participate in the early development of gastric cancer. Epigenetic changes become important areas in gastric cancer research. DNA methylation altered gene expression by methylation of gene promoters at CpG islands which lead to silencing of tumor suppressor genes in cancer cells. Accumulating evidence revealed that abnormal methylation pattern was observed in human diseases, as well as cancer. MiR-9-1, miR-34b/c, miR-148, miR-137, miR-193a, miR-203 and miR-342 were hypermethylated in various human cancers[[24](#_ENREF_24),[25](#_ENREF_25)].

Aberrant expression of miRNAs has been observed in relation to gastric tumor progression, which may partially be explained by epigenetic modulation. Expressions of miR-34b, miR-127-3p, miR-129-3p and miR-409 have been found to correlate with the methylation status in human gastric cancer tissues, as well as in gastric cancer cell lines[[26](#_ENREF_26)]. Methylation status of the CpG islands in miR-34b and miR-129 promoters was higher in gastric cancer tissues than normal counterparts. In addition, treatment with 5-aza-2’-deoxycytidine (demethylating agent) and trichostatin A (histone deacetylase inhibitor) significantly restored the expression of these miRNAs in a time-dependent fashion, suggesting low expression of these two miRNAs was due to hypermethylation of CpG islands. In consistent with the findings in gastric cancer, hypermethylation of miR-34b has been implicated in other cancers like ovarian, non-small cell lung and colorectal cancers[[24](#_ENREF_24),[27](#_ENREF_27),[28](#_ENREF_28)]. A recent study revealed that methyl-CpG-binding protein (MeCP2) level was highly expressed in gastric cancer cell lines and primary gastric cancer[[29](#_ENREF_29)]. Ectopic expression of miR-212 abrogated MeCP2 protein through binding at the MECP2 3’-UTR region leading to cell growth retardation. Notably, there were allelic loss at 3p, 4p, 5q, 8p, 9p, 13q, 17p and 18q in gastric carcinoma, and miR-212 is located at chromosome 17p13.3, which could partly explain the downregulation of miR-212.

In another report, miRNA microarray data showed that miR-181c was upregulated in 5’aza-2”-deoxycitidine-treated cells when compare with untreated gastric cancer cells, and yet the expression was downregulated in primary gastric carcinoma[[30](#_ENREF_30)]. With the use of cDNA microarray analysis, it revealed that Notch4 and K-ras were the downstream targets of miR-181c. Recent data showed that low expression of miR-181c also involved in the pathogenesis of glioblastoma[[31](#_ENREF_31)]. Reduced miR-181c expression was observed in a panel of high-grade glioblastoma tumors and cell lines. A highly positively correlated transcript p300/CBP-associated factor modulated by miR-181c inhibited cell growth and increase apoptosis. However, in squamous cell carcinoma, miR-181c expression was found to be upregulated when compare with the normal tissues[[32](#_ENREF_32)].

Epigenetic modifications plays a crucial role in the control of miR expression and linked to cancer phenotype or potentially serve as early detection, disease progression marker for gastric cancer, hence, further mechanistic studies on miR methylation would be an important area to the development of therapeutic strategy in treating against this disease.

**CLINICAL APPLICATIONS**

***Potential mirna as biomarker***

It was found that the expression levels of miRNA correlated with clinical outcome. MiR-421 was overexpressed in 73% (44/60) of gastric cancer tissues when compared with the adjacent normal counterparts, and there is no correlation with poor prognosis of patients, suggesting that miR-421 upregulation could be an early diagnostic marker for gastric cancer[[33](#_ENREF_33)]. In another study, miR-31 was found to be downregulated in gastric cancer tissues by real-time RT-PCR[[19](#_ENREF_19)] however, the molecular mechanism is yet to be elucidated. MiR-106a expression was correlated with some clinic pathological features including tumor stage, size and differentiation, metastasis and invasion[[34](#_ENREF_34)]. Higher level of miR-106a was observed in gastric carcinoma when compared with non-tumor tissues. Recently, a five-miRNA signature (miR-1, miR-20, miR-27a, miR-34 and miR-423-5p) was identified as a diagnostic marker for gastric cancer with the receiver operating characteristic (ROC) curve over 0.85% in serum samples, which demonstrated a higher sensitivity than conventional marker (CEA or CA19-9)[[35](#_ENREF_35)].

It was hypothesized that miRNA-derived from tumors would be shredded into the circulation. Indeed, several studies have shown that miRNAs have differential expression in the plasma of gastric cancer patients when compare with the normal controls[36,37]. Most of the studies demonstrated an improved sensitivity and specificity than conventional tumor markers (CEA, CA12-5, CA19-9 and CA72-4)[35,37,38]. These mark a new era for the potential use of circulating miRNA in diagnosis of gastric cancer. Taken together, the deregulated miRNAs could serve as a diagnostic biomarker for gastric cancer, and hopefully detection of miRNA deregulation in plasma might help in early diagnosis of gastric cancer, so that designing individualized treatment to antagonize the action of miR could be done in the early stage to improve survival.

**MiRNA as prognostic marker**

Recently, many researchers are looking into the potential use of miRNAs as prognostic tools other than diagnostic application , however, this specific marker needs to correlate closely with clinical outcomes and metastatic potential. Profiling of miRNAs seems to be advantageous over mRNAs in terms of cancer phenotypes differentiation. A current report suggested a prognostic signature for gastric cancer which consist of four risk miRs (miR-10b, miR-21, miR-223 and miR-338; with hazard ratio > 1) and three protective miRs (miR-30a-5p, miR-126 and let-7a; hazard ratio < 1), and was associated with clinical outcomes[[39](#_ENREF_36)]. Another study showed that low expressions of miR-21 and miR-181b are associated with overall survival in patients treated with S-1 and doxifluridine[[40](#_ENREF_37)]. Low expression of miR-125a-3p is correlated with tumor size, invasion, metastasis and advanced clinical stage, and an independent prognostic marker for gastric cancer[[41](#_ENREF_38)]. Ectopic expression of miR-125a-3p showed remarkable retardation of gastric cancer growth in vitro, illustrating the tumor suppressive property and potential clinical use of miR-125a-3p. On the other hand, the other strand of miR-125a, miR-125-5p also showed similar tumor suppressive effect in gastric cancer, and low expression was associated with poor prognosis[[42](#_ENREF_39)]. Other study showed that HMGA2 expression was directly correlated with tumor invasiveness and prognosis, which is modulated by let-7 family[[21](#_ENREF_21)]. A similar observation was also seen in pituitary adenomas, in which low expression of let-7 induced HGMA2 and related to tumor proliferation and invasion[43].

### MiRNA and chemotherapy

Though surgery is a promising treatment for gastric cancer, however, over 50% of patients will have recurrence or systemic metastasis. Chemotherapy has been widely used in the management of patients with advanced disease to prolong survival. However, multidrug resistance (MDR) often hinders successful chemotherapeutic treatment. And there are the two mechanisms exist in tumor cells towards cytostatic drugs: intrinsic or acquired drug resistance.

MiR-138 was found to be highly expressed in MDR variant when compared with its parental leukemia cells[4[4](#_ENREF_41)]. Increased accumulation of adriamycin inside the cells resulted in apoptosis through the repression of P-gylcoprotein (P-gp) and Bcl2 expressions. Multidrug resistance-associated protein (MRP-1) is another transporter, other than P-gp, that expels cytostatic drugs out of the cell. Transfection with miR-326 reduced expression of MRP-1 and sensitized the cells to VP-16 and doxorubicin in resistance cells[4[5](#_ENREF_42)]. Similar approach by using miR-27a and miR-451 antagomirs decreased P-gp and multidrug resistance-1(MDR1) mRNA expression which increased the intracellular concentration of cytotoxic drugs in the cells[[46](#_ENREF_43)]. When the miRNA expression profiles in MDR variant were compared with its parental gastric cell line, a small subset of miRs has been excavated. Downregulation of miR-15b and miR-16 in MDR cells restrained the cells from apoptosis by modulation of Bcl2[[47](#_ENREF_44)]. Ectopic expression of miR-15b and miR-16 sensitized MDR cells to chemotherapeutic agent, which lead to cell apoptosis[48]. These findings are of great impact on the functions of miRs, and notably improve/sensitize the efficacy of chemotherapeutic agent in gastric cancer.

# CONCLUSION

The important roles of miRNAs in cancer biology have been extensively studied in recent years. Ideally, miRNA could be a better therapeutic tool over single gene therapy, due to its ability to target multiple genes. However, several problems were encountered when translated into clinical applications. Firstly, as agreed by most of the researchers, identification of the downstream targets of miRNA is intricating. Despite several target prediction algorithms (*e.g.,* TargetScan, miRTar and miRecords etc) currently available to envisage miRNA targets, however, the complication is that various miRNA could target the same mRNA, hence, justification from results algorithms are inevitable. Microarray and real-time RT-PCR are the analyzing techniques that are commonly used for screening and validation. With the use of locked nucleic acid (LNA) oligos for *in situ* hybridization, knockdown or PCR studies, these enhance the sensitivity and specificity for the analysis of miRNAs. Detailed studies on the mechanism of miRNA biogenesis and interaction with RISC in gastric carcinogenesis would favor the manipulation of miRNA expression which might help in designing a more specific chemotherapeutic agent.

There are increasing demand on miRNA profiling with the expansion of its application into differentiating subtypes and predict treatment response in gastric cancers. The stability of miRNAs in the circulation makes it suitable as diagnostic and prognostic markers in various cancers. Also, it is likely to acquire a miRNA signature, instead of a single miRNA, to provide useful information for the clinicians to make decision on personalized management of the disease. With a better understanding of these miRNAs and their target genes, it would open up new perspectives for more sophisticated and effective therapeutic agents for treating gastric cancer.

**References**

1 **Bertuccio P**, Chatenoud L, Levi F, Praud D, Ferlay J, Negri E, Malvezzi M, La Vecchia C. Recent patterns in gastric cancer: a global overview. *Int J Cancer* 2009; **125**: 666-673 [PMID: 19382179 DOI: 10.1002/ijc.24290]

2 **Hundahl SA**, Phillips JL, Menck HR. The National Cancer Data Base Report on poor survival of U.S. gastric carcinoma patients treated with gastrectomy: Fifth Edition American Joint Committee on Cancer staging, proximal disease, and the "different disease" hypothesis. *Cancer* 2000; **88**: 921-932 [PMID: 10679663]

3 **Hochwald SN**, Kim S, Klimstra DS, Brennan MF, Karpeh MS. Analysis of 154 actual five-year survivors of gastric cancer. *J Gastrointest Surg* 2000; **4**: 520-525 [PMID: 11077328 DOI: 10.1016/S1091-255X(00)80095-5]

4 **He L**, Hannon GJ. MicroRNAs: small RNAs with a big role in gene regulation. *Nat Rev Genet* 2004; **5**: 522-531 [PMID: 15211354 DOI: 10.1038/nrg1379]

5 **Bushati N**, Cohen SM. microRNA functions. *Annu Rev Cell Dev Biol* 2007; **23**: 175-205 [PMID: 17506695 DOI: 10.1146/annurev.cellbio.23.090506.123406]

6 **Lu J**, Getz G, Miska EA, Alvarez-Saavedra E, Lamb J, Peck D, Sweet-Cordero A, Ebert BL, Mak RH, Ferrando AA, Downing JR, Jacks T, Horvitz HR, Golub TR. MicroRNA expression profiles classify human cancers. *Nature* 2005; **435**: 834-838 [PMID: 15944708 DOI: 10.1038/nature03702]

7 **Volinia S**, Calin GA, Liu CG, Ambs S, Cimmino A, Petrocca F, Visone R, Iorio M, Roldo C, Ferracin M, Prueitt RL, Yanaihara N, Lanza G, Scarpa A, Vecchione A, Negrini M, Harris CC, Croce CM. A microRNA expression signature of human solid tumors defines cancer gene targets. *Proc Natl Acad Sci U S A* 2006; **103**: 2257-2261 [PMID: 16461460 DOI: 10.1073/pnas.0510565103]

8 **Ueda T**, Volinia S, Okumura H, Shimizu M, Taccioli C, Rossi S, Alder H, Liu CG, Oue N, Yasui W, Yoshida K, Sasaki H, Nomura S, Seto Y, Kaminishi M, Calin GA, Croce CM. Relation between microRNA expression and progression and prognosis of gastric cancer: a microRNA expression analysis. *Lancet Oncol* 2010; **11**: 136-146 [PMID: 20022810 DOI: 10.1016/S1470-2045(09)70343-2]

9 **Chan SH**, Wu CW, Li AF, Chi CW, Lin WC. miR-21 microRNA expression in human gastric carcinomas and its clinical association. *Anticancer Res* 2008; **28**: 907-911 [PMID: 18507035]

10 **Zhang Z**, Li Z, Gao C, Chen P, Chen J, Liu W, Xiao S, Lu H. miR-21 plays a pivotal role in gastric cancer pathogenesis and progression. *Lab Invest* 2008; **88**: 1358-1366 [PMID: 18794849 DOI: 10.1038/labinvest.2008.94]

11 **Correa P**. Human gastric carcinogenesis: a multistep and multifactorial process--First American Cancer Society Award Lecture on Cancer Epidemiology and Prevention. *Cancer Res* 1992; **52**: 6735-6740 [PMID: 1458460]

12 **Gao C**, Zhang Z, Liu W, Xiao S, Gu W, Lu H. Reduced microRNA-218 expression is associated with high nuclear factor kappa B activation in gastric cancer. *Cancer* 2010; **116**: 41-49 [PMID: 19890957]

13 **Löffler D**, Brocke-Heidrich K, Pfeifer G, Stocsits C, Hackermüller J, Kretzschmar AK, Burger R, Gramatzki M, Blumert C, Bauer K, Cvijic H, Ullmann AK, Stadler PF, Horn F. Interleukin-6 dependent survival of multiple myeloma cells involves the Stat3-mediated induction of microRNA-21 through a highly conserved enhancer. *Blood* 2007; **110**: 1330-1333 [PMID: 17496199 DOI: 10.1182/blood-2007-03-081133]

14 **Shin VY**, Jin H, Ng EK, Cheng AS, Chong WW, Wong CY, Leung WK, Sung JJ, Chu KM. NF-κB targets miR-16 and miR-21 in gastric cancer: involvement of prostaglandin E receptors. *Carcinogenesis* 2011; **32**: 240-245 [PMID: 21081469 DOI: 10.1093/carcin/bgq240]

15 **Bloomston M**, Frankel WL, Petrocca F, Volinia S, Alder H, Hagan JP, Liu CG, Bhatt D, Taccioli C, Croce CM. MicroRNA expression patterns to differentiate pancreatic adenocarcinoma from normal pancreas and chronic pancreatitis. *JAMA* 2007; **297**: 1901-1908 [PMID: 17473300 DOI: 0.1001/jama.297.17.1901]

16 **Li X**, Luo F, Li Q, Xu M, Feng D, Zhang G, Wu W. Identification of new aberrantly expressed miRNAs in intestinal-type gastric cancer and its clinical significance. *Oncol Rep* 2011; **26**: 1431-1439 [PMID: 21874264 DOI: 10.3892/or.2011.1437]

17 **Takagi T**, Iio A, Nakagawa Y, Naoe T, Tanigawa N, Akao Y. Decreased expression of microRNA-143 and -145 in human gastric cancers. *Oncology* 2009; **77**: 12-21 [PMID: 19439999 DOI: 10.1159/000218166]

18 **Luo H**, Zhang H, Zhang Z, Zhang X, Ning B, Guo J, Nie N, Liu B, Wu X. Down-regulated miR-9 and miR-433 in human gastric carcinoma. *J Exp Clin Cancer Res* 2009; **28**: 82 [PMID: 19531230 DOI: 10.1186/1756-9966-28-82]

19 **Zhang Y**, Guo J, Li D, Xiao B, Miao Y, Jiang Z, Zhuo H. Down-regulation of miR-31 expression in gastric cancer tissues and its clinical significance. *Med Oncol* 2010; **27**: 685-689 [PMID: 19598010 DOI: 10.1007/s12032-009-9269-x]

20 **Michael MZ**, O' Connor SM, van Holst Pellekaan NG, Young GP, James RJ. Reduced accumulation of specific microRNAs in colorectal neoplasia. *Mol Cancer Res* 2003; **1**: 882-891 [PMID: 14573789]

21 **Motoyama K**, Inoue H, Nakamura Y, Uetake H, Sugihara K, Mori M. Clinical significance of high mobility group A2 in human gastric cancer and its relationship to let-7 microRNA family. *Clin Cancer Res* 2008; **14**: 2334-2340 [PMID: 18413822 DOI: 10.1158/1078-0432]

22 **Yang H**, Kong W, He L, Zhao JJ, O'Donnell JD, Wang J, Wenham RM, Coppola D, Kruk PA, Nicosia SV, Cheng JQ. MicroRNA expression profiling in human ovarian cancer: miR-214 induces cell survival and cisplatin resistance by targeting PTEN. *Cancer Res* 2008; **68**: 425-433 [PMID: 18199536 DOI: 10.1158/0008-5472.CAN-07-2488]

23 **Liao YL**, Hu LY, Tsai KW, Wu CW, Chan WC, Li SC, Lai CH, Ho MR, Fang WL, Huang KH, Lin WC. Transcriptional regulation of miR-196b by ETS2 in gastric cancer cells. *Carcinogenesis* 2012; **33**: 760-769 [PMID: 22298639 DOI: 10.1093/carcin/bgs023]

24 **Lujambio A**, Calin GA, Villanueva A, Ropero S, Sánchez-Céspedes M, Blanco D, Montuenga LM, Rossi S, Nicoloso MS, Faller WJ, Gallagher WM, Eccles SA, Croce CM, Esteller M. A microRNA DNA methylation signature for human cancer metastasis. *Proc Natl Acad Sci U S A* 2008; **105**: 13556-13561 [PMID: 18768788 DOI: 10.1073/pnas.0803055105]

25 **Bandres E**, Agirre X, Bitarte N, Ramirez N, Zarate R, Roman-Gomez J, Prosper F, Garcia-Foncillas J. Epigenetic regulation of microRNA expression in colorectal cancer. *Int J Cancer* 2009; **125**: 2737-2743 [PMID: 19521961 DOI: 10.1002/ijc.24638]

26 **Tsai KW**, Wu CW, Hu LY, Li SC, Liao YL, Lai CH, Kao HW, Fang WL, Huang KH, Chan WC, Lin WC. Epigenetic regulation of miR-34b and miR-129 expression in gastric cancer. *Int J Cancer* 2011; **129**: 2600-2610 [PMID: 21960261 DOI: 10.1002/ijc.25919]

27 **Corney DC**, Hwang CI, Matoso A, Vogt M, Flesken-Nikitin A, Godwin AK, Kamat AA, Sood AK, Ellenson LH, Hermeking H, Nikitin AY. Frequent downregulation of miR-34 family in human ovarian cancers. *Clin Cancer Res* 2010; **16**: 1119-1128 [PMID: 20145172 DOI: 10.1158/1078-0432.CCR-09-2642]

28 **Gallardo E**, Navarro A, Viñolas N, Marrades RM, Diaz T, Gel B, Quera A, Bandres E, Garcia-Foncillas J, Ramirez J, Monzo M. miR-34a as a prognostic marker of relapse in surgically resected non-small-cell lung cancer. *Carcinogenesis* 2009; **30**: 1903-1909 [PMID: 19736307 DOI: 10.1093/carcin/bgp219]

29 **Wada R**, Akiyama Y, Hashimoto Y, Fukamachi H, Yuasa Y. miR-212 is downregulated and suppresses methyl-CpG-binding protein MeCP2 in human gastric cancer. *Int J Cancer* 2010; **127**: 1106-1114 [PMID: 20020497 DOI: 10.1002/ijc.25126]

30 **Hashimoto Y**, Akiyama Y, Otsubo T, Shimada S, Yuasa Y. Involvement of epigenetically silenced microRNA-181c in gastric carcinogenesis. *Carcinogenesis* 2010; **31**: 777-784 [PMID: 20080834 DOI: 10.1093/carcin/bgq013]

31 **Liu T**, Papagiannakopoulos T, Puskar K, Qi S, Santiago F, Clay W, Lao K, Lee Y, Nelson SF, Kornblum HI, Doyle F, Petzold L, Shraiman B, Kosik KS. Detection of a microRNA signal in an in vivo expression set of mRNAs. *PLoS One* 2007; **2**: e804 [PMID: 17726534 DOI: 10.1371/journal.pone.0000804]

32 **Wong TS**, Liu XB, Wong BY, Ng RW, Yuen AP, Wei WI. Mature miR-184 as Potential Oncogenic microRNA of Squamous Cell Carcinoma of Tongue. *Clin Cancer Res* 2008; **14**: 2588-2592 [PMID: 18451220 DOI: 10.1158/1078-0432.CCR-07-0666]

33 **Jiang Z**, Guo J, Xiao B, Miao Y, Huang R, Li D, Zhang Y. Increased expression of miR-421 in human gastric carcinoma and its clinical association. *J Gastroenterol* 2010; **45**: 17-23 [PMID: 19802518 DOI: 10.1007/s00535-009-0135-6]

34 **Xiao B**, Guo J, Miao Y, Jiang Z, Huan R, Zhang Y, Li D, Zhong J. Detection of miR-106a in gastric carcinoma and its clinical significance. *Clin Chim Acta* 2009; **400**: 97-102 [PMID: 18996365 DOI: 10.1016/j.cca.2008.10.021]

35 **Liu R**, Zhang C, Hu Z, Li G, Wang C, Yang C, Huang D, Chen X, Zhang H, Zhuang R, Deng T, Liu H, Yin J, Wang S, Zen K, Ba Y, Zhang CY. A five-microRNA signature identified from genome-wide serum microRNA expression profiling serves as a fingerprint for gastric cancer diagnosis. *Eur J Cancer* 2011; **47**: 784-791 [PMID: 21112772 DOI: 10.1016/j.ejca.2010.10.025]

36 **Ng EK**, Chong WW, Jin H, Lam EK, Shin VY, Yu J, Poon TC, Ng SS, Sung JJ. Differential expression of microRNAs in plasma of patients with colorectal cancer: a potential marker for colorectal cancer screening. *Gut* 2009; **58**: 1375-1381 [PMID: 19201770 DOI: 10.1136/gut.2008.167817]

37 **Tsujiura M**, Ichikawa D, Komatsu S, Shiozaki A, Takeshita H, Kosuga T, Konishi H, Morimura R, Deguchi K, Fujiwara H, Okamoto K, Otsuji E. Circulating microRNAs in plasma of patients with gastric cancers. *Br J Cancer* 2010; **102**: 1174-1179 [PMID: 20234369 DOI: 10.1038/sj.bjc.6605608]

38 **Li C**, Li JF, Cai Q, Qiu QQ, Yan M, Liu BY, Zhu ZG. MiRNA-199a-3p: A potential circulating diagnostic biomarker for early gastric cancer. *J Surg Oncol* 2013; **108**: 89-92 [PMID: 23733518 DOI: 10.1002/jso.23358]

39 **Li X**, Zhang Y, Zhang Y, Ding J, Wu K, Fan D. Survival prediction of gastric cancer by a seven-microRNA signature. *Gut* 2010; **59**: 579-585 [PMID: 19951901 DOI: 10.1136/gut.2008.175497]

40 **Jiang J**, Zheng X, Xu X, Zhou Q, Yan H, Zhang X, Lu B, Wu C, Ju J. Prognostic significance of miR-181b and miR-21 in gastric cancer patients treated with S-1/Oxaliplatin or Doxifluridine/Oxaliplatin. *PLoS One* 2011; **6**: e23271 [PMID: 21876743 DOI: 10.1371/journal.pone.0023271]

41 **Hashiguchi Y**, Nishida N, Mimori K, Sudo T, Tanaka F, Shibata K, Ishii H, Mochizuki H, Hase K, Doki Y, Mori M. Down-regulation of miR-125a-3p in human gastric cancer and its clinicopathological significance. *Int J Oncol* 2012; **40**: 1477-1482 [PMID: 22322911 DOI: 10.3892/ijo.2012.1363]

42 **Nishida N**, Mimori K, Fabbri M, Yokobori T, Sudo T, Tanaka F, Shibata K, Ishii H, Doki Y, Mori M. MicroRNA-125a-5p is an independent prognostic factor in gastric cancer and inhibits the proliferation of human gastric cancer cells in combination with trastuzumab. *Clin Cancer Res* 2011; **17**: 2725-2733 [PMID: 21220473 DOI: 10.1158/1078-0432.CCR-10-2132]

43 **Qian ZR**, Asa SL, Siomi H, Siomi MC, Yoshimoto K, Yamada S, Wang EL, Rahman MM, Inoue H, Itakura M, Kudo E, Sano T. Overexpression of HMGA2 relates to reduction of the let-7 and its relationship to clinicopathological features in pituitary adenomas. *Mod Pathol* 2009; **22**: 431-441 [PMID: 19136928 DOI: 10.1038/modpathol.2008.202]

44 **Zhao X**, Yang L, Hu J, Ruan J. miR-138 might reverse multidrug resistance of leukemia cells. *Leuk Res* 2010; **34**: 1078-1082 [PMID: 19896708 DOI: 10.1016/j.leukres.2009]

45 **Liang Z**, Wu H, Xia J, Li Y, Zhang Y, Huang K, Wagar N, Yoon Y, Cho HT, Scala S, Shim H. Involvement of miR-326 in chemotherapy resistance of breast cancer through modulating expression of multidrug resistance-associated protein 1. *Biochem Pharmacol* 2010; **79**: 817-824 [PMID: 19883630 DOI: 10.1016/j.bcp.2009.10.017]

46 **Zhu H**, Wu H, Liu X, Evans BR, Medina DJ, Liu CG, Yang JM. Role of MicroRNA miR-27a and miR-451 in the regulation of MDR1/P-glycoprotein expression in human cancer cells. *Biochem Pharmacol* 2008; **76**: 582-588 [PMID: 18619946 DOI: 10.1016/j.bcp.2008.06.007]

47 **Cimmino A**, Calin GA, Fabbri M, Iorio MV, Ferracin M, Shimizu M, Wojcik SE, Aqeilan RI, Zupo S, Dono M, Rassenti L, Alder H, Volinia S, Liu CG, Kipps TJ, Negrini M, Croce CM. miR-15 and miR-16 induce apoptosis by targeting BCL2. *Proc Natl Acad Sci U S A* 2005; **102**: 13944-13949 [PMID: 16166262 DOI: 10.1073/pnas.0506654102]

48 **Xia L**, Zhang D, Du R, Pan Y, Zhao L, Sun S, Hong L, Liu J, Fan D. miR-15b and miR-16 modulate multidrug resistance by targeting BCL2 in human gastric cancer cells. *Int J Cancer* 2008; **123**: 372-379 [PMID: 18449891 DOI: 10.1002/ijc.23501]

49 **Zhang BG**, Li JF, Yu BQ, Zhu ZG, Liu BY, Yan M. microRNA-21 promotes tumor proliferation and invasion in gastric cancer by targeting PTEN. *Oncol Rep* 2012; **27**: 1019-1026 [PMID: 22267008 DOI: 10.3892/or.2012.1645]

50 **Motoyama K**, Inoue H, Mimori K, Tanaka F, Kojima K, Uetake H, Sugihara K, Mori M. Clinicopathological and prognostic significance of PDCD4 and microRNA-21 in human gastric cancer. *Int J Oncol* 2010; **36**: 1089-1095 [PMID: 20372781]

51 **Liu X**, Ru J, Zhang J, Zhu LH, Liu M, Li X, Tang H. miR-23a targets interferon regulatory factor 1 and modulates cellular proliferation and paclitaxel-induced apoptosis in gastric adenocarcinoma cells. *PLoS One* 2013; **8**: e64707 [PMID: 23785404 DOI: 10.1371/journal.pone.0064707]

52 **Liu T**, Tang H, Lang Y, Liu M, Li X. MicroRNA-27a functions as an oncogene in gastric adenocarcinoma by targeting prohibitin. *Cancer Lett* 2009; **273**: 233-242 [PMID: 18789835 DOI: 10.1016/j.canlet.2008.08.003]

53 **Guo X**, Jing C, Li L, Zhang L, Shi Y, Wang J, Liu J, Li C. Down-regulation of VEZT gene expression in human gastric cancer involves promoter methylation and miR-43c. *Biochem Biophys Res Commun* 2011; **404**: 622-627 [PMID: 21156161 DOI: 10.1016/j.bbrc.2010.12.026]

54 **Petrocca F**, Visone R, Onelli MR, Shah MH, Nicoloso MS, de Martino I, Iliopoulos D, Pilozzi E, Liu CG, Negrini M, Cavazzini L, Volinia S, Alder H, Ruco LP, Baldassarre G, Croce CM, Vecchione A. E2F1-regulated microRNAs impair TGFbeta-dependent cell-cycle arrest and apoptosis in gastric cancer. *Cancer Cell* 2008; **13**: 272-286 [PMID: 18328430 DOI: 10.1016/j.ccr.2008.02.013]

55 **Kim YK**, Yu J, Han TS, Park SY, Namkoong B, Kim DH, Hur K, Yoo MW, Lee HJ, Yang HK, Kim VN. Functional links between clustered microRNAs: suppression of cell-cycle inhibitors by microRNA clusters in gastric cancer. *Nucleic Acids Res* 2009; **37**: 1672-1681 [PMID: 19153141 DOI: 10.1093/nar/gkp002]

56 **Li X**, Zhang Y, Shi Y, Dong G, Liang J, Han Y, Wang X, Zhao Q, Ding J, Wu K, Fan D. MicroRNA-107, an oncogene microRNA that regulates tumour invasion and metastasis by targeting DICER1 in gastric cancer. *J Cell Mol Med* 2011; **15**: 1887-1895 [PMID: 21029372 DOI: 10.1111/j.1582-4934.2010.01194.x]

57 **Lai KW**, Koh KX, Loh M, Tada K, Subramaniam MM, Lim XY, Vaithilingam A, Salto-Tellez M, Iacopetta B, Ito Y, Soong R. MicroRNA-130b regulates the tumour suppressor RUNX3 in gastric cancer. *Eur J Cancer* 2010; **46**: 1456-1463 [PMID: 20176475 DOI: 10.1016/j.ejca.2010.01.036]

58 **Wu Q**, Jin H, Yang Z, Luo G, Lu Y, Li K, Ren G, Su T, Pan Y, Feng B, Xue Z, Wang X, Fan D. MiR-150 promotes gastric cancer proliferation by negatively regulating the pro-apoptotic gene EGR2. *Biochem Biophys Res Commun* 2010; **392**: 340-345 [PMID: 20067763 DOI: 10.1016/j.bbrc.2009.12.182]

59 **Li X**, Zhang Y, Zhang H, Liu X, Gong T, Li M, Sun L, Ji G, Shi Y, Han Z, Han S, Nie Y, Chen X, Zhao Q, Ding J, Wu K, Daiming F. miRNA-223 promotes gastric cancer invasion and metastasis by targeting tumor suppressor EPB41L3. *Mol Cancer Res* 2011; **9**: 824-833 [PMID: 21628394 DOI: 10.1158/1541-7786.MCR-10-0529]

60 **Yang Q**, Jie Z, Cao H, Greenlee AR, Yang C, Zou F, Jiang Y. Low-level expression of let-7a in gastric cancer and its involvement in tumorigenesis by targeting RAB40C. *Carcinogenesis* 2011; **32**: 713-722 [PMID: 21349817 DOI: 10.1093/carcin/bgr035]

61 **Wan HY**, Guo LM, Liu T, Liu M, Li X, Tang H. Regulation of the transcription factor NF-kappaB1 by microRNA-9 in human gastric adenocarcinoma. *Mol Cancer* 2010; **9**: 16 [PMID: 20102618 DOI: 10.1186/1476-4598-9-16]

62 **Rotkrua P**, Akiyama Y, Hashimoto Y, Otsubo T, Yuasa Y. MiR-9 downregulates CDX2 expression in gastric cancer cells. *Int J Cancer* 2011; **129**: 2611-2620 [PMID: 21225631 DOI: 10.1002/ijc.25923]

63 **Ji Q**, Hao X, Meng Y, Zhang M, Desano J, Fan D, Xu L. Restoration of tumor suppressor miR-34 inhibits human p53-mutant gastric cancer tumorspheres. *BMC Cancer* 2008; **8**: 266 [PMID: 18803879 DOI: 10.1186/1471-2407-8-266]

64 **Pei L**, Xia JZ, Huang HY, Zhang RR, Yao LB, Zheng L, Hong B. [Role of miR-124a methylation in patients with gastric cancer]. *Zhonghua Wei Chang Wai Ke Za Zhi* 2011; **14**: 136-139 [PMID: 21365509]

65 **Feng R**, Chen X, Yu Y, Su L, Yu B, Li J, Cai Q, Yan M, Liu B, Zhu Z. miR-126 functions as a tumour suppressor in human gastric cancer. *Cancer Lett* 2010; **298**: 50-63 [PMID: 20619534 DOI: 10.1016/j.canlet.2010.06.004]

66 **Shen R,** Pan S, Qi S, Lin X, Cheng S. Epigenetic repression of microRNA-129-2 leads to overexpression of SOX4 in gastric cancer. *Biochem Biophys Res Commun* 2010; **394**: 1047-1052 [PMID: 20331975 DOI: 10.1016/j.bbrc.2010.03.121]

67 **Kogo R**, Mimori K, Tanaka F, Komune S, Mori M. Clinical significance of miR-146a in gastric cancer cases. *Clin Cancer Res* 2011; **17**: 4277-4284 [PMID: 21632853 DOI: 10.1158/1078-0432.CCR-10-2866]

68 **Song YX**, Yue ZY, Wang ZN, Xu YY, Luo Y, Xu HM, Zhang X, Jiang L, Xing CZ, Zhang Y. MicroRNA-148b is frequently down-regulated in gastric cancer and acts as a tumor suppressor by inhibiting cell proliferation. *Mol Cancer* 2011; **10**: 1 [PMID: 21205300 DOI: 10.1186/1476-4598-10-1]

69 **Shinozaki A**, Sakatani T, Ushiku T, Hino R, Isogai M, Ishikawa S, Uozaki H, Takada K, Fukayama M. Downregulation of microRNA-200 in EBV-associated gastric carcinoma. *Cancer Res* 2010; **70**: 4719-4727 [PMID: 20484038 DOI: 10.1158/0008-5472.CAN-09-4620]

70 **Tie J**, Pan Y, Zhao L, Wu K, Liu J, Sun S, Guo X, Wang B, Gang Y, Zhang Y, Li Q, Qiao T, Zhao Q, Nie Y, Fan D. MiR-218 inhibits invasion and metastasis of gastric cancer by targeting the Robo1 receptor. *PLoS Genet* 2010; **6**: e1000879 [PMID: 20300657 DOI: 10.1371/journal.pgen.1000879]

71 **Tsukamoto Y**, Nakada C, Noguchi T, Tanigawa M, Nguyen LT, Uchida T, Hijiya N, Matsuura K, Fujioka T, Seto M, Moriyama M. MicroRNA-375 is downregulated in gastric carcinomas and regulates cell survival by targeting PDK1 and 14-3-3zeta. *Cancer Res* 2010; **70**: 2339-2349 [PMID: 20215506 DOI: 10.1158/0008-5472.CAN-09-2777]

72 **Ding L**, Xu Y, Zhang W, Deng Y, Si M, Du Y, Yao H, Liu X, Ke Y, Si J, Zhou T. MiR-375 frequently downregulated in gastric cancer inhibits cell proliferation by targeting JAK2. *Cell Res* 2010; **20**: 784-793 [PMID: 20548334 DOI: 10.1038/cr.2010.79]

73 **Bandres E**, Bitarte N, Arias F, Agorreta J, Fortes P, Agirre X, Zarate R, Diaz-Gonzalez JA, Ramirez N, Sola JJ, Jimenez P, Rodriguez J, Garcia-Foncillas J. microRNA-451 regulates macrophage migration inhibitory factor production and proliferation of gastrointestinal cancer cells. *Clin Cancer Res* 2009; **15**: 2281-2290 [PMID: 19318487 DOI: 10.1158/1078-0432.CCR-08-1818]

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**Table 1 Gastric cancer-associated miRNAs**

|  |  |  |  |
| --- | --- | --- | --- |
|  | **Functions** | **Targets** | **Ref.** |
| ***Upregulated miRNAs*** |  |  |  |
| miR-15b, miR-16 | Cell survival | BCL2 | [47] |
|  |  |  |  |
| miR-21 | Cell proliferation, invasion | PTEN | [49] |
|  |  | PDCD4 | [50] |
|  |  |  |  |
| miR-23a | Cell proliferation | IRF1, IL6R | [51] |
|  |  |  |  |
| miR-27a | Cell proliferation | PROHIBITIN | [52] |
|  |  |  |  |
| miR-43c | Epigenetic regulation | VEZT | [53] |
|  |  |  |  |
| miR-106a | Cell cycle regulation | RB1 | [34] |
|  |  |  |  |
| miR-106b-25 cluster | Cell cycle arrest, apoptosis | E2F1 | [54] |
|  |  | p57, p21, p27 | [55] |
|  |  |  |  |
| miR-107 | Invasion, metastasis | DICER1 | [56] |
|  |  |  |  |
| miR-130b | Apoptosis, epigenetic regulation | BIM, RUNX3 | [57] |
|  |  |  |  |
| miR-150 | Cell proliferation | EGR2 | [58] |
|  |  |  |  |
| miR-223 | Invasion, metastasis | EPB41L3 | [59] |
|  |  |  |  |
| *Downregulated miRNAs* |  |  |  |
| let-7a | Cell proliferation | RAB40C | [60] |
|  |  |  |  |
| miR-9 | Cell proliferation | NFkB | [61] |
|  | Cell proliferation, cell cycle regulation | CDX2 | [62] |
|  |  |  |  |
| miR-34b | Cell proliferation, transcription, | NOTCH1, c-Myc | [63] |
|  | epigenetic regulation | BCL2, SIRT1 |  |
|  |  |  |  |
| miR-124a | Cell cycle arrest | CDK6 | [64] |
|  |  |  |  |
| miR-126 | Cell cycle arrest | CRK | [65] |
|  |  |  |  |
| miR-129-2 | Cell proliferation, differentiation, | SOX4 | [66] |
|  | epigenetic regulation |  |  |
|  |  |  |  |
| miR-143 | Cell proliferation | AKT | [17] |
|  |  |  |  |
| miR-145 | Cell proliferation | IRS-1 | [17] |
|  |  |  |  |
| miR-146a | Invasion, migration | EGFR, IRAK1 | [67] |
|  |  |  |  |
| miR-148b | Cell proliferation | CCKBR | [68] |
|  |  |  |  |
| miR-181c | Transcriptional activation | NOTCH4, K-ras | [30] |
|  |  |  |  |
| mir-200 family | Cell proliferation, invasion, migration | ZEB2, E-cadherin | [69] |
|  |  |  |  |
| miR-212 | Cell proliferation | MeCP2 | [29] |
|  |  |  |  |
| miR-218 | Invasion, metastasis | ROBO1 receptor | [70] |
|  |  |  |  |
|  | Transcriptional activation | NFkB | [12] |
|  |  |  |  |
| miR-375 | Cell survival | PDK1 , 14-3-3zeta | [71] |
|  |  |  |  |
|  | Cell proliferation | JAK2 | [72] |
|  |  |  |  |
| miR-451 | Cell proliferation | MIF | [73] |
|   |   |   |   |
|  |  |  |  |