**Name of journal:** **World Journal of Gastroenterology**

**ESPS Manuscript No: 6682**

**Columns: TOPIC HIGHLIGHTS**

WJG 20th Anniversary Special Issues (8): Gastric cancer

**Role of microRNAs in gastric cancer**

Ishiguro H *et al*. MicroRNAs in gastric cancer

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**Received:** October26, 2013  **Revised:** December11, 2013

**Accepted:** January 19, 2014

**Published online:**

**Abstract**

Although gastric cancer (GC) is one of the leading causes of cancer-related death, major therapeutic advances have not been made, and patients with GC still face poor outcomes. The prognosis of GC also remains poor because the molecular mechanisms of GC progression are incompletely understood. MicroRNAs (miRNAs) are noncoding RNAs that are associated with gastric carcinogenesis. Studies investigating the regulation of gene expression by miRNAs have made considerable progress in recent years, and abnormalities in miRNA expression have been shown to be associated with the occurrence and progression of GC. miRNAs contribute to gastric carcinogenesis by altering the expression of oncogenes and tumor suppressors, affecting cell proliferation, apoptosis, motility, and invasion. Moreover, a number of miRNAs have been shown to be associated with tumor type, tumor stage, and patient survival and therefore may be developed as novel diagnostic or prognostic markers. In this review, we discuss the involvement of miRNAs in GC and the mechanisms through which they regulate gene expression and biological functions. Then, we review recent research on the involvement of miRNAs in GC prognosis, their potential use in chemotherapy, and their effects on *Helicobacter pylori* infections in GC. A greater understanding of the roles of miRNAs in gastric carcinogenesis could provide insights into the mechanisms of tumor development and could help to identify novel therapeutic targets.

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**Key words:** microRNA; gastric cancer; Reverse transcription-polymerase chain reaction; chemosensitivity; *Helicobacter pylori*; circulating miRNA

**Core tip:** In this review, we discuss the involvement of miRNAs in gastric cancer (GC) and the mechanisms through which they regulate gene expression and biological functions. Then, we review recent research on the involvement of miRNAs in GC prognosis, their potential use in chemotherapy, and their effects on *Helicobacter pylori* infections in GC. A greater understanding of the roles of miRNAs in gastric carcinogenesis could provide insights into the mechanisms of tumor development and could help to identify novel therapeutic targets.

Ishiguro H, Kimura M, Takeyama H. Role of microRNAs in gastric cancer. World J Gastroenterol 2014;

**Available from:**

**DOI:**

**Introduction**

Despite the decreasing incidence of gastric cancer (GC) in developed countries, GC remains the second leading cause of cancer-related deaths worldwide[[1](#_ENREF_1),[2](#_ENREF_2)], with 700000 deaths attributed to this malignancy annually[[3](#_ENREF_3)]. Therefore, the development of novel therapies to improve the prognosis of patients with GC is critical.

MicroRNAs (miRNAs) are a subset of small noncoding RNA molecules, typically 21–23 nucleotides in length, that are believed to regulate the expression of several genes[[4](#_ENREF_4)]. Mature miRNAs are cleaved from 70- to 100-nucleotide hairpin pre-miRNA precursors[[4](#_ENREF_4)]. The precursor is cleaved by cytoplasmic RNase III Dicer into a miRNA duplex[[5-7](#_ENREF_5)]. One strand of the short-lived duplex is degraded, whereas the other strand serves as the mature miRNA[[8](#_ENREF_8)]. Mature miRNAs associate with a cellular complex that is similar to the RNA-induced silencing complex that participates in RNA interference[[9](#_ENREF_9),[10](#_ENREF_10)]. Recent studies have reported miRNA-mediated regulation of cell growth and apoptosis[[11](#_ENREF_11),[12](#_ENREF_12)]. Moreover, the measurement of miRNA expression has shown that certain miRNAs are specifically involved in cancer[[12-15](#_ENREF_12)]. In the context of GC, the number of publications investigating the relationship between miRNAs and GC has been increasing each year. miRNAs have the unique ability to negatively regulate gene expression, thereby resulting in changes in cell development, proliferation, and apoptosis[[16](#_ENREF_16)]. These biological properties of miRNAs may provide the ability to regulate a variety of human diseases, including cancer[[17](#_ENREF_17)]. According to recent findings, miRNAs may play important roles in human cancer by acting as potential oncogenes or tumor-suppressor genes[[18-20](#_ENREF_18)].

In this review, we introduce and discuss the newest knowledge on the relationship between GC and miRNAs.

***Aberrant expression of miRNAs in GC***

Although more than 1000 miRNAs are thought to exist, no comprehensive analysis of miRNA expression in GC has been performed to date. Each miRNA modulates the expression of hundreds of genes, and we speculate that miRNAs act in a network-type fashion to mediate the expression of genes.

While several reports have published comprehensive expression analysis of miRNAs[[21](#_ENREF_21),[22](#_ENREF_22)], more data, including expression profile analysis by high-throughput real-time reverse transcription-polymerase chain reaction (RT-PCR) or miRNA microarrays, are required. A summary of reported miRNA expression abnormalities in GC is presented in Table 1.

**Upregulated miRNAs (oncomirs)**: Aberrant expression of miRNAs has been observed in many cancers[[19](#_ENREF_19),[23](#_ENREF_23)]. Oncomirs are oncogenic miRNAs that are up-regulated in cancer cells and have been shown to act as oncogenes in GC. One such oncomir is *miR-21*, which has been widely reported as an oncomir in GC[[24-26](#_ENREF_24)].

Overexpression of *miR-21* has been reported in various cancers, such as esophageal cancer[[27](#_ENREF_27)], breast cancer[[28](#_ENREF_28)], and glioblastoma[[29](#_ENREF_29)]. In GC, the expression of *miR-21* is upregulated compared with normal tissues[[22](#_ENREF_22),[30](#_ENREF_30),[31](#_ENREF_31)]. Motoyama *et al*[[31](#_ENREF_31)] and Cao *et al*[[32](#_ENREF_32)] reported an inverse correlation between *miR-21* and *PDCD4* expression in GC. *PDCD4*, a direct target gene of *miR-21*, encodes a protein that inhibits cell growth and invasion[[33](#_ENREF_33),[34](#_ENREF_34)]. Moreover, Zhang *et al*[[26](#_ENREF_26)] reported that *PTEN*, a well-known tumor-suppressor gene, is a target of *miR-21*. Thus, these data support the idea that *miR-21* acts as a key oncomir in GC by inhibiting the tumor-suppressor genes *PDCD4* and *PTEN*.

In addition to *miR-21*, *miR-106a* expression is also upregulated in GC (Table 1), as well as in several other human tumors, compared with adjacent normal tissues[[35](#_ENREF_35)]. *miR-106a* mimics the function of positive regulators of the G1-to-S transition[[35](#_ENREF_35)]. In several human hematopoietic cell lines, *miR-106a* has been shown to target interleukin (IL) 10[[36](#_ENREF_36)], downregulating the expression of this critical cytokine by binding to the 3′ untranslated region (UTR)[[36](#_ENREF_36)]. As a further regulatory element, SP1 and EGR1 indirectly downregulate IL10 expression by inducing *miR-106a* expression[[36](#_ENREF_36)].

**Downregulated miRNAs (tumor-suppressor miRNAs):** Down-regulated miRNAs in cancer tissue are referred to as tumor-suppressor miRNAs[[37-39](#_ENREF_37)]. The important target gene of a tumor-suppressor miRNA is usually an oncogene. Therefore, decreased expression of the tumor-suppressive miRNA induces the expression of the oncogene. The genomic loss of *miR-101* in cancer leads to overexpression of EZH2 and concomitant dysregulation of epigenetic pathways, resulting in cancer progression[[40](#_ENREF_40),[41](#_ENREF_41)]. Because *miR-101* targets cyclooxygenase (COX) 2 in GC, downregulation of *miR-101* induces COX2 expression[[42](#_ENREF_42)]. COX2 activates the arachidonic acid/prostaglandin E2 (PGE2) pathway following cell proliferation[[42](#_ENREF_42)]. Oncogenic targets of *miR-101* induce cell proliferation in GC. Therefore, *miR-101* may be useful for gene therapy in GC.

Another miRNA that has been suggested to have a role in cancer is *let-7*. Expression of *let-7* reduces the expression of 3 human *RAS* genes, *HRAS*, *KRAS*, and *NRAS*. Moreover, *let-7* expression is lower in lung tumors than in normal lung tissue, whereas expression of the RAS proteins is significantly higher in lung tumors, suggesting a possible role of *let-7* in cancer[[43](#_ENREF_43)]. The expression of *let-7* miRNA is also reduced in human lung cancer[[44](#_ENREF_44)], breast cancer[[45](#_ENREF_45)], and hepatocellular carcinomas (HCCs)[[46](#_ENREF_46)]. In addition, overexpression of *let-7* inhibits the growth of lung cancer cells *in vitro*[[44](#_ENREF_44)]. In GC, RAB40C, a target of *let-7a*, has been reported to play an essential role in gastric tumorigenesis[[47](#_ENREF_47)].

*miR-148a* has been shown to act as a tumor suppressor in prostate cancer, and its expression is lower in prostate cancer cells compared with normal prostate epithelial cells[[48](#_ENREF_48)]. In GC, *miR-148a* is inactivated by hypermethylation of the promoter region[[49](#_ENREF_49)]. This may result in the upregulation of DNA methyltransferase (DNMT1), which is a target of *miR-148a*[[49](#_ENREF_49)]. Moreover, *miR-148a* suppresses tumor cell invasion by downregulating ROCK1[[50](#_ENREF_50)]. In a report from our laboratory, we found that *miR-148a* expression is downregulated in undifferentiated GC[[51](#_ENREF_51)].

***Roles of miRNAs as prognostic factors***

Because many factors affect the prognosis of cancer patients, it is difficult to clarify how miRNAs are involved in the prognosis of patients with GC. However, advances in research on the potential role of miRNAs in patient prognosis may lead to the use of miRNAs as tools in medical treatment or diagnosis in the future. The detection of miRNAs involved in the prognosis of GC patients will not only be useful for predicting prognosis but helpful for developing therapeutic targets in the future. In Table 2, we have summarized the current knowledge on the relationship between miRNAs and prognosis. In particular, *miR-21*, *-93*, and *-125* have been well studied in this context. While we mentioned the usefulness of *miR-21* previously, overexpression of *miR-93* in GC cells has been shown to reduce the cellular response to transforming growth factor (TGF)-β (*TGFB1*) by interfering with the synthesis of p21 (*CDKN1A*) and BIM (*BCL2L11*), the 2 most important downstream effectors of TGF-β-dependent cell cycle arrest and apoptosis, respectively[[52](#_ENREF_52)]. High expression of *miR-98* was found to predict poor survival[[53](#_ENREF_53),[54](#_ENREF_54)]. Interestingly, low expression of *miR-125* in GC has been shown to be an independent prognostic factor for survival[[55](#_ENREF_55),[56](#_ENREF_56)]. One target gene of *miR-125a-5p* is ERBB2 (*HER2*), which is an important molecular target in chemotherapy[[56](#_ENREF_56)].

Notably, many genes act as prognostic factors for patients with GC; miRNAs may regulate these genes, thereby affecting prognosis. Thus, further analysis of candidate miRNAs is necessary.

***miRNAs involved in chemosensitivity***

Chemotherapy is an important tool for the treatment of GC. However, with currently available tools, it is impossible to predict whether GC patients will respond to chemotherapeutic approaches. The ability to predict the effects of chemotherapy may help reduce the unnecessary use of chemotherapeutics in GC. Current chemotherapeutic agents used in the treatment of GC include 5FU, CDDP, taxan, and irinotecan. Many studies have reported that miRNAs may affect the efficacy of chemotherapy. Wang *et al*[[57](#_ENREF_57)] identified 9 upregulated miRNAs and 18 downregulated miRNAs involved in 5FU sensitivity by microarray and RT-PCR (Table 3). Moreover, *miR-143*, *miR-145*, and *miR-144* have been reported to be involved in 5FU sensitivity[[58](#_ENREF_58),[59](#_ENREF_59)]. In Tables 3, we summarize the involvement of miRNAs in CPT, CDDP, and CF sensitivity. In the near future, we will be able to use miRNA expression as a predictor of chemotherapeutic efficacy. Additionally, gene therapy with miRNAs may be able to induce chemosensitivity in patients with GC.

***miRNAs involved in Helicobacter pylori infection***

*Helicobacter pylori* (*H. pylori*) selectively colonize the gastric epithelium and typically persist for the lifetime of the host. Among colonized individuals, however, only a fraction develop gastric adenocarcinoma, emphasizing the importance of understanding the pathogenic mechanisms through which *H. pylori* promote chronic inflammation and the progression to GC[[60](#_ENREF_60)]. miRNAs involved in *H. pylori* infections have been reported in several papers. *Let-7* expression has been shown to be downregulated by Cag A after *H. pylori* infection, and Ras, a target of *let-7*, is overexpressed in GC[[61](#_ENREF_61)]. Additionally, *miR-17/92*, the *miR-106b-93-25* cluster, *miR-21*, *miR-194*, *miR-196*, *miR155*, *miR-222*, and *miR-223* are upregulated in gastric mucosa infected by *H. pylori*[[62-64](#_ENREF_62)]. Among these miRNAs, Li et al. revealed that *miR-222* targets RECK, which inhibits the tumorigenicity of GC[[64-66](#_ENREF_64)]. Further analysis of miRNAs and target genes may clarify the complicated mechanism of GC that occurs in the context of *H. pylori* infections.

***Circulating miRNAs as biomarkers***

Presently, circulating miRNAs found in the blood of patients constitute the most promising type of miRNA for clinical use, because these are concise for blood collecting. We summarized the circulating miRNAs in the blood of GC patients in Table 4.

There are a number of reports describing the use of miR-106[[67-69](#_ENREF_67)], miR-17[[67](#_ENREF_67),[70](#_ENREF_70)], miR-21[[67](#_ENREF_67),[71](#_ENREF_71)], and miR-221 as potential biomarkers[[72](#_ENREF_72)]. The detection of miRNA in peripheral blood may be a novel tool for monitoring circulating tumor cells in patients with gastric cancers. Moreover, circulating miRNA may be a promising, non-invasive molecular marker for tracking pathological progression, predicting prognosis and monitoring chemotherapeutic effects in gastric cancer.

Finally, the precise mechanism of each miRNA is not well known. Further reports about miRNA are expected to help us better understand cancer mechanisms. This research will be useful for clinical diagnosis or treatment for GC patients.

**Conclusion**

In this review, we presented and discussed the newest knowledge on miRNAs in gastric cancer and their potential usefulness as future medical treatments and diagnostic tools. Although the molecular biology of GC has been well characterized, research on miRNAs in GC is still in its infancy. Thus, in the near future, we anticipate that advances in miRNA research in GC may help to develop novel medical treatments or diagnostic tools, thereby improving the prognosis of GC patients.

**References**

1 **Jemal A**, Siegel R, Ward E, Hao Y, Xu J, Murray T, Thun MJ. Cancer statistics, 2008. *CA Cancer J Clin* 2008; **58**: 71-96 [PMID: 18287387 DOI: 10.3322/CA.2007.0010]

2 **Jemal A**, Bray F, Center MM, Ferlay J, Ward E, Forman D. Global cancer statistics. *CA Cancer J Clin* 2011; **61**: 69-90 [PMID: 21296855 DOI: 10.3322/caac.20107]

3 **Parkin DM**, Bray F, Ferlay J, Pisani P. Global cancer statistics, 2002. *CA Cancer J Clin* 2005; **55**: 74-108 [PMID: 15761078 DOI: 10.3322/canjclin.55.2.74]

4 **Bartel DP**. MicroRNAs: genomics, biogenesis, mechanism, and function. *Cell* 2004; **116**: 281-297 [PMID: 14744438 DOI: 10.1016/S0092-8674(04)00045-5]

5 **Rossbach M**. Small non-coding RNAs as novel therapeutics. *Curr Mol Med* 2010; **10**: 361-368 [PMID: 20455856 DOI: 10.2174/156652410791317048]

6 **Nelson KM**, Weiss GJ. MicroRNAs and cancer: past, present, and potential future. *Mol Cancer Ther* 2008; **7**: 3655-3660 [PMID: 19074842 DOI: 10.1158/1535-7163.MCT-08-0586]

7 **Wiemer EA**. The role of microRNAs in cancer: no small matter. *Eur J Cancer* 2007; **43**: 1529-1544 [PMID: 17531469 DOI: 10.1016/j.ejca.2007.04.002]

8 **Liu W**, Mao SY, Zhu WY. Impact of tiny miRNAs on cancers. *World J Gastroenterol* 2007; **13**: 497-502 [PMID: 17278213]

9 **Hutvágner G**, Zamore PD. A microRNA in a multiple-turnover RNAi enzyme complex. *Science* 2002; **297**: 2056-2060 [PMID: 12154197 DOI: 10.1126/science.1073827]

10 **Lin SL**, Kim H, Ying SY. Intron-mediated RNA interference and microRNA (miRNA). *Front Biosci* 2008; **13**: 2216-2230 [PMID: 17981704 DOI: 10.2741/2836]

11 **Cheng AM**, Byrom MW, Shelton J, Ford LP. Antisense inhibition of human miRNAs and indications for an involvement of miRNA in cell growth and apoptosis. *Nucleic Acids Res* 2005; **33**: 1290-1297 [PMID: 15741182 DOI: 10.1093/nar/gki200]

12 **Matsubara H**, Takeuchi T, Nishikawa E, Yanagisawa K, Hayashita Y, Ebi H, Yamada H, Suzuki M, Nagino M, Nimura Y, Osada H, Takahashi T. Apoptosis induction by antisense oligonucleotides against miR-17-5p and miR-20a in lung cancers overexpressing miR-17-92. *Oncogene* 2007; **26**: 6099-6105 [PMID: 17384677 DOI: 10.1038/sj.onc.1210425]

13 **Akao Y**, Nakagawa Y, Naoe T. let-7 microRNA functions as a potential growth suppressor in human colon cancer cells. *Biol Pharm Bull* 2006; **29**: 903-906 [PMID: 16651716 DOI: 10.1248/bpb.29.903]

14 **Cahill S**, Smyth P, Finn SP, Denning K, Flavin R, O'Regan EM, Li J, Potratz A, Guenther SM, Henfrey R, O'Leary JJ, Sheils O. Effect of ret/PTC 1 rearrangement on transcription and post-transcriptional regulation in a papillary thyroid carcinoma model. *Mol Cancer* 2006; **5**: 70 [PMID: 17156473 DOI: 10.1186/1476-4598-5-70]

15 **Iorio MV**, Ferracin M, Liu CG, Veronese A, Spizzo R, Sabbioni S, Magri E, Pedriali M, Fabbri M, Campiglio M, Ménard S, Palazzo JP, Rosenberg A, Musiani P, Volinia S, Nenci I, Calin GA, Querzoli P, Negrini M, Croce CM. MicroRNA gene expression deregulation in human breast cancer. *Cancer Res* 2005; **65**: 7065-7070 [PMID: 16103053 DOI: 10.1158/0008-5472.CAN-05-1783]

16 **Ambros V**. The functions of animal microRNAs. *Nature* 2004; **431**: 350-355 [PMID: 15372042 DOI: 10.1038/nature02871]

17 **Alvarez-Garcia I**, Miska EA. MicroRNA functions in animal development and human disease. *Development* 2005; **132**: 4653-4662 [PMID: 16224045 DOI: 10.1242/dev.02073]

18 **Zhang B**, Pan X, Cobb GP, Anderson TA. microRNAs as oncogenes and tumor suppressors. *Dev Biol* 2007; **302**: 1-12 [PMID: 16989803 DOI: 10.1016/j.ydbio.2006.08.028]

19 **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 USA* 2006; **103**: 2257-2261 [PMID: 16461460 DOI: 10.1073/pnas.0510565103]

20 **He L**, Thomson JM, Hemann MT, Hernando-Monge E, Mu D, Goodson S, Powers S, Cordon-Cardo C, Lowe SW, Hannon GJ, Hammond SM. A microRNA polycistron as a potential human oncogene. *Nature* 2005; **435**: 828-833 [PMID: 15944707 DOI: 10.1038/nature03552]

21 **Yao Y**, Suo AL, Li ZF, Liu LY, Tian T, Ni L, Zhang WG, Nan KJ, Song TS, Huang C. MicroRNA profiling of human gastric cancer. *Mol Med Rep* 2009; **2**: 963-970 [PMID: 21475928 DOI: 10.3892/mmr\_00000199]

22 **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]

23 **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]

24 **Zeng Z**, Wang J, Zhao L, Hu P, Zhang H, Tang X, He D, Tang S, Zeng Z. Potential role of microRNA-21 in the diagnosis of gastric cancer: a meta-analysis. *PLoS One* 2013; **8**: e73278 [PMID: 24023850 DOI: 10.1371/journal.pone.0073278]

25 **Osawa S,** Shimada Y, Sekine S, Okumura T, Nagata T, Fukuoka J, Tsukada K. MicroRNA profiling of gastric cancer patients from formalin-fixed paraffin-embedded samples. *Oncol Lett* 2011; **2**: 613-619 [PMID: 22848236 DOI: 10.3892/ol.2011.313]

26 **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]

27 **Mori Y**, Ishiguro H, Kuwabara Y, Kimura M, Mitsui A, Ogawa R, Katada T, Harata K, Tanaka T, Shiozaki M, Fujii Y. MicroRNA-21 induces cell proliferation and invasion in esophageal squamous cell carcinoma. *Mol Med Rep* 2009; **2**: 235-239 [PMID: 21475818 DOI: 10.3892/mmr\_00000089]

28 **Si ML**, Zhu S, Wu H, Lu Z, Wu F, Mo YY. miR-21-mediated tumor growth. *Oncogene* 2007; **26**: 2799-2803 [PMID: 17072344 DOI: 10.1038/sj.onc.1210083]

29 **Chan JA**, Krichevsky AM, Kosik KS. MicroRNA-21 is an antiapoptotic factor in human glioblastoma cells. *Cancer Res* 2005; **65**: 6029-6033 [PMID: 16024602 DOI: 10.1158/0008-5472.CAN-05-0137]

30 **Inoue T**, Iinuma H, Ogawa E, Inaba T, Fukushima R. Clinicopathological and prognostic significance of microRNA-107 and its relationship to DICER1 mRNA expression in gastric cancer. *Oncol Rep* 2012; **27**: 1759-1764 [PMID: 22407237 DOI: 10.3892/or.2012.1709]

31 **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]

32 **Cao Z**, Yoon JH, Nam SW, Lee JY, Park WS. PDCD4 expression inversely correlated with miR-21 levels in gastric cancers. *J Cancer Res Clin Oncol* 2012; **138**: 611-619 [PMID: 22212233 DOI: 10.1007/s00432-011-1140-8]

33 **Hiyoshi Y**, Kamohara H, Karashima R, Sato N, Imamura Y, Nagai Y, Yoshida N, Toyama E, Hayashi N, Watanabe M, Baba H. MicroRNA-21 regulates the proliferation and invasion in esophageal squamous cell carcinoma. *Clin Cancer Res* 2009; **15**: 1915-1922 [PMID: 19276261 DOI: 10.1158/1078-0432.CCR-08-2545]

34 **Lu Z**, Liu M, Stribinskis V, Klinge CM, Ramos KS, Colburn NH, Li Y. MicroRNA-21 promotes cell transformation by targeting the programmed cell death 4 gene. *Oncogene* 2008; **27**: 4373-4379 [PMID: 18372920 DOI: 10.1038/onc.2008.72]

35 **Ivanovska I**, Ball AS, Diaz RL, Magnus JF, Kibukawa M, Schelter JM, Kobayashi SV, Lim L, Burchard J, Jackson AL, Linsley PS, Cleary MA. MicroRNAs in the miR-106b family regulate p21/CDKN1A and promote cell cycle progression. *Mol Cell Biol* 2008; **28**: 2167-2174 [PMID: 18212054 DOI: 10.1128/MCB.01977-07]

36 **Sharma A**, Kumar M, Aich J, Hariharan M, Brahmachari SK, Agrawal A, Ghosh B. Posttranscriptional regulation of interleukin-10 expression by hsa-miR-106a. *Proc Natl Acad Sci USA* 2009; **106**: 5761-5766 [PMID: 19307576 DOI: 10.1073/pnas.0808743106]

37 **Grammatikakis I**, Gorospe M, Abdelmohsen K. Modulation of Cancer Traits by Tumor Suppressor microRNAs. *Int J Mol Sci* 2013; **14**: 1822-1842 [PMID: 23325049 DOI: 10.3390/ijms14011822]

38 **Yim RL**, Kwong YL, Wong KY, Chim CS. DNA Methylation of Tumor Suppressive miRNAs in Non-Hodgkin's Lymphomas. *Front Genet* 2012; **3**: 233 [PMID: 23162567 DOI: 10.3389/fgene.2012.00233]

39 **Wang LQ**, Liang R, Chim CS. Methylation of tumor suppressor microRNAs: lessons from lymphoid malignancies. *Expert Rev Mol Diagn* 2012; **12**: 755-765 [PMID: 23153241 DOI: 10.1586/erm.12.64]

40 **Varambally S**, Cao Q, Mani RS, Shankar S, Wang X, Ateeq B, Laxman B, Cao X, Jing X, Ramnarayanan K, Brenner JC, Yu J, Kim JH, Han B, Tan P, Kumar-Sinha C, Lonigro RJ, Palanisamy N, Maher CA, Chinnaiyan AM. Genomic loss of microRNA-101 leads to overexpression of histone methyltransferase EZH2 in cancer. *Science* 2008; **322**: 1695-1699 [PMID: 19008416 DOI: 10.1126/science.1165395]

41 **Carvalho J**, van Grieken NC, Pereira PM, Sousa S, Tijssen M, Buffart TE, Diosdado B, Grabsch H, Santos MA, Meijer G, Seruca R, Carvalho B, Oliveira C. Lack of microRNA-101 causes E-cadherin functional deregulation through EZH2 up-regulation in intestinal gastric cancer. *J Pathol* 2012; **228**: 31-44 [PMID: 22450781 DOI: 10.1002/path.4032]

42 **He XP**, Shao Y, Li XL, Xu W, Chen GS, Sun HH, Xu HC, Xu X, Tang D, Zheng XF, Xue YP, Huang GC, Sun WH. Downregulation of miR-101 in gastric cancer correlates with cyclooxygenase-2 overexpression and tumor growth. *FEBS J* 2012; **279**: 4201-4212 [PMID: 23013439 DOI: 10.1111/febs.12013]

43 **Johnson SM**, Grosshans H, Shingara J, Byrom M, Jarvis R, Cheng A, Labourier E, Reinert KL, Brown D, Slack FJ. RAS is regulated by the let-7 microRNA family. *Cell* 2005; **120**: 635-647 [PMID: 15766527 DOI: 10.1016/j.cell.2005.01.014]

44 **Takamizawa J**, Konishi H, Yanagisawa K, Tomida S, Osada H, Endoh H, Harano T, Yatabe Y, Nagino M, Nimura Y, Mitsudomi T, Takahashi T. Reduced expression of the let-7 microRNAs in human lung cancers in association with shortened postoperative survival. *Cancer Res* 2004; **64**: 3753-3756 [PMID: 15172979 DOI: 10.1158/0008-5472.CAN-04-0637]

45 **Yu F**, Yao H, Zhu P, Zhang X, Pan Q, Gong C, Huang Y, Hu X, Su F, Lieberman J, Song E. let-7 regulates self renewal and tumorigenicity of breast cancer cells. *Cell* 2007; **131**: 1109-1123 [PMID: 18083101 DOI: 10.1016/j.cell.2007.10.054]

46 **Gramantieri L**, Ferracin M, Fornari F, Veronese A, Sabbioni S, Liu CG, Calin GA, Giovannini C, Ferrazzi E, Grazi GL, Croce CM, Bolondi L, Negrini M. Cyclin G1 is a target of miR-122a, a microRNA frequently down-regulated in human hepatocellular carcinoma. *Cancer Res* 2007; **67**: 6092-6099 [PMID: 17616664 DOI: 10.1158/0008-5472.CAN-06-4607]

47 **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]

48 **Fujita Y**, Kojima K, Ohhashi R, Hamada N, Nozawa Y, Kitamoto A, Sato A, Kondo S, Kojima T, Deguchi T, Ito M. MiR-148a attenuates paclitaxel resistance of hormone-refractory, drug-resistant prostate cancer PC3 cells by regulating MSK1 expression. *J Biol Chem* 2010; **285**: 19076-19084 [PMID: 20406806 DOI: 10.1074/jbc.M109.079525]

49 **Zhu A**, Xia J, Zuo J, Jin S, Zhou H, Yao L, Huang H, Han Z. MicroRNA-148a is silenced by hypermethylation and interacts with DNA methyltransferase 1 in gastric cancer. *Med Oncol* 2012; **29**: 2701-2709 [PMID: 22167392 DOI: 10.1007/s12032-011-0134-3]

50 **Zheng B**, Liang L, Wang C, Huang S, Cao X, Zha R, Liu L, Jia D, Tian Q, Wu J, Ye Y, Wang Q, Long Z, Zhou Y, Du C, He X, Shi Y. MicroRNA-148a suppresses tumor cell invasion and metastasis by downregulating ROCK1 in gastric cancer. *Clin Cancer Res* 2011; **17**: 7574-7583 [PMID: 21994419 DOI: 10.1158/1078-0432.CCR-11-1714]

51 **Katada T**, Ishiguro H, Kuwabara Y, Kimura M, Mitui A, Mori Y, Ogawa R, Harata K, Fujii Y. microRNA expression profile in undifferentiated gastric cancer. *Int J Oncol* 2009; **34**: 537-542 [PMID: 19148490]

52 **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]

53 **Yu BQ**, Su LP, Li JF, Cai Q, Yan M, Chen XH, Yu YY, Gu QL, Zhu ZG, Liu BY. microrna expression signature of gastric cancer cells relative to normal gastric mucosa. *Mol Med Rep* 2012; **6**: 821-826 [PMID: 22842726 DOI: 10.3892/mmr.2012.1006]

54 **Chen L**, Jiang M, Yuan W, Tang H. Prognostic value of miR-93 overexpression in resectable gastric adenocarcinomas. *Acta Gastroenterol Belg* 2012; **75**: 22-27 [PMID: 22567743]

55 **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]

56 **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]

57 **Wang Y**, Gu X, Li Z, Xiang J, Jiang J, Chen Z. microRNA expression profiling in multidrug resistance of the 5‑Fu‑induced SGC‑7901 human gastric cancer cell line. *Mol Med Rep* 2013; **7**: 1506-1510 [PMID: 23525256 DOI: 10.3892/mmr.2013.1384]

58 **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]

59 **Akiyoshi S**, Fukagawa T, Ueo H, Ishibashi M, Takahashi Y, Fabbri M, Sasako M, Maehara Y, Mimori K, Mori M. Clinical significance of miR-144-ZFX axis in disseminated tumour cells in bone marrow in gastric cancer cases. *Br J Cancer* 2012; **107**: 1345-1353 [PMID: 22955854 DOI: 10.1038/bjc.2012.326]

60 **Noto JM**, Peek RM. The role of microRNAs in Helicobacter pylori pathogenesis and gastric carcinogenesis. *Front Cell Infect Microbiol* 2011; **1**: 21 [PMID: 22919587 DOI: 10.3389/fcimb.2011.00021]

61 **Hayashi Y**, Tsujii M, Wang J, Kondo J, Akasaka T, Jin Y, Li W, Nakamura T, Nishida T, Iijima H, Tsuji S, Kawano S, Hayashi N, Takehara T. CagA mediates epigenetic regulation to attenuate let-7 expression in Helicobacter pylori-related carcinogenesis. *Gut* 2013; **62**: 1536-1546 [PMID: 22936674 DOI: 10.1136/gutjnl-2011-301625]

62 **Shiotani A**, Uedo N, Iishi H, Murao T, Kanzaki T, Kimura Y, Kamada T, Kusunoki H, Inoue K, Haruma K. H. pylori eradication did not improve dysregulation of specific oncogenic miRNAs in intestinal metaplastic glands. *J Gastroenterol* 2012; **47**: 988-998 [PMID: 22382634 DOI: 10.1007/s00535-012-0562-7]

63 **Oertli M**, Engler DB, Kohler E, Koch M, Meyer TF, Müller A. MicroRNA-155 is essential for the T cell-mediated control of Helicobacter pylori infection and for the induction of chronic Gastritis and Colitis. *J Immunol* 2011; **187**: 3578-3586 [PMID: 21880981 DOI: 10.4049/jimmunol.1101772]

64 **Li N**, Tang B, Zhu ED, Li BS, Zhuang Y, Yu S, Lu DS, Zou QM, Xiao B, Mao XH. Increased miR-222 in H. pylori-associated gastric cancer correlated with tumor progression by promoting cancer cell proliferation and targeting RECK. *FEBS Lett* 2012; **586**: 722-728 [PMID: 22321642 DOI: 10.1016/j.febslet.2012.01.025]

65 **Hong KJ**, Wu DC, Cheng KH, Chen LT, Hung WC. RECK inhibits stemness gene expression and tumorigenicity of gastric cancer cells by suppressing ADAM-mediated Notch1 activation. *J Cell Physiol* 2014; **229**: 191-201 [PMID: 23881612 DOI: 10.1002/jcp.24434]

66 **Du YY**, Dai DQ, Yang Z. Role of RECK methylation in gastric cancer and its clinical significance. *World J Gastroenterol* 2010; **16**: 904-908 [PMID: 20143471]

67 **Komatsu S**, Ichikawa D, Tsujiura M, Konishi H, Takeshita H, Nagata H, Kawaguchi T, Hirajima S, Arita T, Shiozaki A, Kubota T, Fujiwara H, Okamoto K, Otsuji E. Prognostic impact of circulating miR-21 in the plasma of patients with gastric carcinoma. *Anticancer Res* 2013; **33**: 271-276 [PMID: 23267156]

68 **Zhou H**, Guo JM, Lou YR, Zhang XJ, Zhong FD, Jiang Z, Cheng J, Xiao BX. Detection of circulating tumor cells in peripheral blood from patients with gastric cancer using microRNA as a marker. *J Mol Med* (Berl) 2010; **88**: 709-717 [PMID: 20349219 DOI: 10.1007/s00109-010-0617-2]

69 **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]

70 **Wang M**, Gu H, Wang S, Qian H, Zhu W, Zhang L, Zhao C, Tao Y, Xu W. Circulating miR-17-5p and miR-20a: molecular markers for gastric cancer. *Mol Med Rep* 2012; **5**: 1514-1520 [PMID: 22406928 DOI: 10.3892/mmr.2012.828]

71 **Zheng Y**, Cui L, Sun W, Zhou H, Yuan X, Huo M, Chen J, Lou Y, Guo J. MicroRNA-21 is a new marker of circulating tumor cells in gastric cancer patients. *Cancer Biomark* 2011; **10**: 71-77 [PMID: 22430134 DOI: 10.3233/CBM-2011-0231]

72 **Cai H**, Yuan Y, Hao YF, Guo TK, Wei X, Zhang YM. Plasma microRNAs serve as novel potential biomarkers for early detection of gastric cancer. *Med Oncol* 2013; **30**: 452 [PMID: 23307259 DOI: 10.1007/s12032-012-0452-0]

**P-Reviewers:** de Franciscis V,Poltronieri P, Ren T **S-Editor:** Ma YJ **L-Editor:** **E-Editor:**

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| **Table 1 Aberrant expression of miRNAs in gastric cancer** |
| Up-regulated miRNAs |
| let-7a, miR-9, -10a, -10b, -17, -17-5p, -18a, -18b, -19a, -19b, -20a, -20b, -21, -23a, -23b |
| miR-25, -26b, -27, -29b-1, -30b, -31, -34a, -34b, -34c, -92, -98, -99a, -100, -103, -106a |
| miR-106b, -107, -125b, -126, -128a, -130b, -138, -142-3p, -146a, -147, -150, -151-5p |
| miR-155, 181a, -181a-2, -181b, -181c, -185, -191, -192, -194, -196a, -196b, -199a |
| miR-199a-3p, -200b, -210, -214, -215, -221, -222, -223, -296-5p |
| miR-301a, -302f, -337-3p, -340, -370, -421, -520c-3p, -575, -601, -616, -658, -1259 |
| Down-regulated miRNAs |
| let-7a, -7f, miR-7, -9, -22, -29c, -30a-5p, -31, -34a, -34b, -34c |
| miR-101, -126, -128b, -129, -129-2, -129-3p, -130b, -133b, -135a, -137, -141, -145 |
| miR-146a, -148, -148b, -149, -152, -155, -181b, -181c, -182, -193b, -195, -195-5p, -197 |
| miR-200, -204, -206, -210, -212, -218, -219-2-3p, -302b, -331-3p, -375 |
| miR-378, -408-3p, -429, -433, -486, -495, -551a, -574-3p, -610, -622, -638, -663, -874 |

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| --- |
| **Table 2 miRNAs associated with prognosis in gastric cancer patients** |
| let-7a ,-7i |
| miR-10b, -20a, -20b, -21, -22, -25, -27a, -30a-5p, -34a, -93 |
| miR-103, -106a, -106b, -107, -125a-5p, -126, -130, -142-5p, -144, -146a, -150 |
| miR-155, -181c, -195, -196a, -199a-3p, -200c, -206, -221, -222, -223 |
| miR-335, -338, -372, -375, -451 |

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| --- | --- | --- | --- | --- |
| **Table 3 miRNAs involved in chemosensitivity** | | |  |  |
| 5FU sensitivity |  | | | |
| let-7g |  | | | | | |
| miR-10b, -22, -30c, -31, -32, | |  | | | |
| miR-133b, -143, -144, -145, -181b, -190, -197, -200c, -204, -210 | | |  |  |
| miR-335, -501, -501-5p, -532, -615, -615-5p, -766, -877 |  | | | | | |
| miR-1224-3p, -1229, -3131, -3149, -3162-3p, -4763-3p |  | | | | | |
| CPT sensitivity |  | | | | | |
| let-7g |  | | | | | |
| miR-7, -31, -98, -126, -196a, -200, -338 |  | | | | | |
| CDDP, CF sensitivity | |  | | | |
| let-7g |  | | | | | |
| miR-1, -16, -21, -34, -181, -181b, -342, -497 |  | | | | | |

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| --- | --- | --- | --- | --- | --- |
| **Table 4 Circulating miRNAs as biomarkers** | | | |  | |
| Up-regulated miRNAs | |  |  |  | |
| miR-1, -17, -17-5p, -20a, -21, -27a, -31, -34, -103, -106a, -106b, -107,-194, -200c | | | | | |
| miR-210, -221, -223, -370, -376a, -378, 421, 423-5p, 451, -486, 744 | | | | |  |
| Down-regulated miRNAs | | | | |  |
| miR-218, -375 |  | | | | |