Role of miRNAs and their potential to be useful as diagnostic and prognostic biomarkers in gastric cancer

Kelly Cristina da Silva Oliveira, Taíssa Maíra Thomaz Araújo, Camila Inagaki Albuquerque, Gabriela Alcantara Barata, Carolina Oliveira Gigek, Mariana Ferreira Leal, Fernanda Wisnieski, Fernando Augusto Rodrigues Mello Junior, André Salim Khayat, Paulo Pimentel de Assumpção, Rommel Mário Rodrigues Burbano, Marília Cardoso Smith, Danielle Queiroz Calcagno

Kelly Cristina da Silva Oliveira, Taíssa Maíra Thomaz Araújo, Camila Inagaki Albuquerque, Gabriela Alcantara Barata, Fernando Augusto Rodrigues Mello Junior, André Salim Khayat, Paulo Pimentel de Assumpção, Danielle Queiroz Calcagno, Núcleo de Pesquisas em Oncologia, Universidade Federal do Pará, Hospital Universitário João de Barros Barreto, Belém, PA 66073-000, Brazil

Carolina Oliveira Gigek, Mariana Ferreira Leal, Fernanda Wisnieski, Marília Cardoso Smith, Disciplina de Genética, Departamento de Morfologia e Genética, Universidade Federal de São Paulo, São Paulo 04021-001, Brazil

Rommel Mário Rodrigues Burbano, Laboratório de Citogenética Humana, Instituto de Ciências Biológicas, Universidade Federal do Pará, Belém, PA 66073-000, Brazil

Author contributions: da Silva Oliveira KC and Calcagno DQ performed the review design; da Silva Oliveira KC, Thomaz Araújo TM, Albuquerque CI and Calcagno DQ collected the data; Thomaz Araújo TM, Albuquerque GA, Rodrigues Mello Junior FA and Calcagno DQ wrote the paper; Gigek CO performed corrections and suggestions; de Assumpção PP, Rodriguez Burbano RM and Smith MC revised the paper critically; all the authors contributed to this manuscript.

Supported by: Fundação de Amparo à Pesquisa do Estado de São Paulo; the Conselho Nacional de Desenvolvimento Científico e Tecnológico; and the Coordenação de Aperfeiçoamento de Pessoal de Nível Superior.

Conflict-of-interest statement: Authors declare no conflict of interests for this article.

Open-Access: This article is an open-access article which was selected by an in-house editor and fully peer-reviewed by external reviewers. It is distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: http://creativecommons.org/licenses/by-nc/4.0/

Manuscript source: Unsolicited manuscript

Correspondence to: Danielle Queiroz Calcagno, PhD, Núcleo de Pesquisas em Oncologia, Universidade Federal do Pará, Hospital Universitário João de Barros Barreto, 2º Piso da UNACON, Av. Mundurucus, Belém, PA 66073-000, Brazil. danicalcagno@gmail.com

Telephone: +55-91-32016776

Received: March 12, 2016
Peer-review started: March 12, 2016
First decision: April 14, 2016
Revised: June 14, 2016
Accepted: August 1, 2016
Article in press: August 1, 2016
Published online: September 21, 2016

Abstract

Alterations in epigenetic control of gene expression play an important role in many diseases, including gastric cancer. Many studies have identified a large number of upregulated oncogenic miRNAs and downregulated tumour-suppressor miRNAs in this type of cancer. In this review, we provide an overview of the role of miRNAs, pointing to their potential to be useful as diagnostic and/or prognostic biomarkers in gastric cancer. Moreover, we discuss the influence of polymorphisms and epigenetic modifications on miRNA activity.

Key words: Gastric cancer; Epigenetic; Diagnostic biomarkers; miRNAs; Prognostic biomarkers
Core tip: Accumulating evidence indicates that dysregulated miRNAs play important roles in gastric cancer pathogenesis. In this context, we provide an overview of the role of miRNAs, pointing to their potential to be used as diagnostic and prognostic biomarkers in gastric cancer. Moreover, we discuss the influence of polymorphisms and epigenetic modifications on miRNA activity.

da Silva Oliveira KC, Thomaz Araújo TM, Albuquerque CI, Barata GA, Gigeck CO, Leal MF, Wisnieski F, Rodrigues Mello Junior FA, Khayat AS, de Assumpção PP, Rodriguez Burbano RM, Smith MC, Calcagno DQ. Role of miRNAs and their potential to be useful as diagnostic and prognostic biomarkers in gastric cancer. World J Gastroenterol 2016; 22(35): 7951-7962 Available from: URL: http://www.wjgnet.com/1007-9327/full/v22/i35/7951. htm DOI: http://dx.doi.org/10.3748/wjg.v22.i35.7951

INTRODUCTION

Gastric cancer (GC) is the fifth most frequent cancer, besides being the third leading cause of cancer-related death worldwide[1]. According to Laurén, GC is classified into intestinal and diffuse types[2], which are a consequence of an accumulation of genetic and epigenetic modifications[3].

Epigenetic events refer to alterations that promote gene expression variation without changing the DNA sequence yet leading to transcriptional activation or silencing of the gene[4].

Epigenetic alterations, mainly aberrant DNA methylation, histone modifications and microRNA (miRNA) expression play a central role in many diseases, including GC[5,6].

miRNAs are a class of small non-coding RNAs (19–25 nucleotides) that act as important epigenetic players in many cellular processes, such as differentiation, proliferation and apoptosis, exerting a great influence in cancer pathogenesis[5,6].

In general, miRNA genes are located in intergenic regions, suggesting that most miRNA genes are transcribed as autonomous transcription units[9,10]. Moreover, these molecules are usually transcribed by RNA polymerase II, generating long primary transcripts (pri-miRNAs). The pri-miRNAs are processed to premiRNAs (70 nucleotides) by Drosha. Then, these premiRNAs are processed by Dicer and generate a double-stranded RNA, which includes the mature miRNA[8].

The mature miRNAs repress protein translation through binding to the target protein-coding mRNAs by base-pairing to partially complementary regions frequently located at the 3’-untranslated regions (3’-UTR) of the target transcript[11,12].

A large number of miRNAs with different biological functions have been found altered in correlation with clinico-pathological features and/or prognosis in GC[5,7]. Ribeiro-dos-Santos et al[13] and Moreira et al[14] suggested the existence of gastric tissue and organ miRNA expression signatures. Accordingly, Gomes et al[15] observed a specific expression signature of let-7b, miR-21, miR-29c, miR-31, miR-192, miR-141, miR-148c and miR-451 in GC.

In this review, we describe the role and clinical significance of miRNAs, highlighting their use as potential prognostic and/or diagnostic biomarkers in GC. Moreover, we discuss the influence of polymorphisms and epigenetic modifications on miRNA activity.

ROLES AND CLINICAL SIGNIFICANCE OF miRNAs IN GASTRIC CANCER

In cancer, miRNAs can function as oncogenes and/or tumour suppressor genes depending on the outcome of the target mRNA (oncomiRNA or tsmiRNA, respectively). Increased activity of an oncomiRNA leads to inhibition of apoptosis and cell proliferation. In contrast, decreased activity of a tsmiRNA leads to increased tumour formation[16].

Because in vitro and in vivo introduction of tsmiRNAs promotes antitumoural activity by restoring lost tumour suppressor activity[18,19] and the use of antagonirs inhibits the pro-tumourigenic activity of oncomiRNAs[20], improved understanding of miRNAs’ role in cancer could be helpful for providing novel insights into the role of miRNAs as molecular targets, whose modulation might hold therapeutic promise.

Both the overexpression of oncomiRNAs and the decreased expression of tsmiRNAs play pivotal roles in GC, and many studies in the literature have identified a large number of upregulated and downregulated miRNAs and their potential targets in this type of cancer. Therefore, aberrant expression of miRNAs has been significantly related to clinico-pathological features such as tumour stage, size, differentiation, metastasis and H. pylori status (Table 1)[21-28].

In GC, studies have consistently reported that miR-106a has oncogenic activity through suppressing the expression of TIMP2, PTEN, FAS and RUNX3 genes[45-50]. Zhu et al[50] demonstrated that miR-106a is frequently upregulated in human GC and is closely associated with local tumour invasion and distant spreading by directly regulating its functional target TIMP2, a metastasis associated gene. Similarly, Xiao et al[48] stated that the level of miR-106a in GC tissues was significantly higher than that in non-tumour tissues, with an average increase of 1.625-fold and was significantly associated with tumour stage, size and differentiation, lymphatic and distant metastasis and invasion.

On the other hand, let-7a is one of the most important tsmiRNAs involved in gastric carcinogenesis,
| miRNA/role | Targets | Clinicopathological features | Ref. |
|------------|---------|-----------------------------|------|
| **OncomiRNAs** | | | |
| miR-17 | UBE2C | Tumor size | [21-24] |
| | FBXO31 | Tumor infiltration | |
| | | Clinical grade | |
| | | Prognosis | |
| mir-19a | MXD1 | Migration | [25-28] |
| | SOCS1 | Invasion | |
| | PTEN | Metastasis | |
| | | Proliferation | |
| | | Multidrug resistance | |
| miR-20a | EGR2 | Overall survival | [29-31] |
| | E2F1 | Relapse-free survival | |
| | | Self-renewal and proliferation of GC stem cells | |
| | | Chemoresistance of GC cells to cisplatin and docetaxel | |
| miR-21 | PTEN | Differentiation | [29,32-37] |
| | PDCD4 | Lymph node metastasis | |
| | RECK | H. pylori infection | |
| | SERPIN1 | Tumor stage | |
| | | Tumor size | |
| miR-25 | FBXW7 | Proliferation | [38-41] |
| | TOB1 | Invasion | |
| | RECK | Migration | |
| | | Metastasis | |
| | | Aggressive phenotype | |
| | | Poor long-term survival | |
| miR-27a | P21 | Lymph node metastasis | [42-44] |
| | ZBTB10 | Proliferation | |
| | HOXA10 | Drug resistance | |
| | CCND1 | H. pylori infection | |
| miR-106a | TIMP2 | Invasion | [45-50] |
| | PTEN | Differentiation | |
| | FAS | Distant metastasis | |
| | RINX3 | Lymph node metastasis | |
| | | Tumor stage | |
| | | Tumor size | |
| miR-106b | P21 | Lymph node metastasis | [29,46,51-54] |
| | E2F5 | Depth of infiltration | |
| | E2F1 | | |
| miR-206b | ZEB1 | Diffuse-type | [55-58] |
| | ZEB2 | Poor overall survival | |
| | SUZ12 | H. pylori infection | |
| | DNMT3A | Metastasis | |
| | DNMT3B | Tumor size | |
| | SP1 | | |
| | WNT-1 | | |
| miR-215 | RB1 | Tumor stage | [59-61] |
| | RINX1 | | |
| miR-222 | PTEN | Shorter metastasis-free survival | [38,62-65] |
| | RECK | Proliferation | |
| | | | |
| **tmiRNAs** | | | |
| let-7a | RAB40C | Differentiation | [66-71] |
| | CDXN1 | Lymph node metastasis | |
| | SPHK2 | Cell cycle arrest | |
| | F1 | Growth suppression | |
| | | Overall survival | |
| | | Relapse-free survival | |

Table 1: Deregulated miRNA in gastric cancer tumor

miR-143: COX-2, Invasion, Haematogenous metastasis, Lymph node metastasis, Tumor stage

miR-148a: ROCK1, MMP7, p27, Poor overall survival, DNMT1, Epithelial-mesenchymal transition

miR-200c: RND3, DNMT3A, DNMT3B, Sensitivity of chemotherapy to cisplatin, SP1, Invasion

miR-204: SIRT1, Epithelial-mesenchymal transition, BCL-2, Anoikis resistance, EZR, Migration, Invasion, Colony forming ability

miR-218: VOPP1, ROBO1, Proliferation, Migration, Metastasis

miR-433: RAB34, Tumor stage, KRAS, Overall survival, Proliferation, Migration, Invasion

miR-9: CCND1, Proliferation, Invasion, Metastasis

miR-107: FOXO1, VICER1, CDK6, Lymph node metastasis, Tumor size, Tumor stage, Overall survival

miR-146a: EGFR, IRAK1, Poor differentiation, LICAM, CARD10, LYAPT1, Poor differentiation

miR-155: SMAD2, Invasion, Lymph node metastasis, CDC73, CYCLIN D1, H. pylori infection, Cell viability, Apoptosis

miR-181b: CREB1, Proliferation, BCL2, Migration, Invasion, Colony formation, Apoptosis, Multidrug resistance

miR-223: EPB41L3, Poor metastasis-free survival, STN1, Apoptosis, FBXW7, Proliferation, Invasion, HMGA2, Poor clinical prognosis

da Silva Oliveira KC et al. miRNA and gastric cancer
and studies in the literature have reported RAB40C, CDKN1, SPHK2 and FN1 as its targets\(^66-71\). Yang et al\(^48\) demonstrated that GC tumour and cell lines with lower expression of let-7a tended to have poor differentiation. Furthermore, they demonstrated that induced overexpression of let-7a resulted in a decrease in cell proliferation, G1 arrest and significant suppression of anchorage-dependent growth in vitro and tumourigenicity of GC cells in a nude mouse xenograft model.

Several studies have reported on miRNAs with a controversial role in gastric carcinogenesis such as miR-107 and mir-181b. For example, Guo et al\(^114\) stated that the proliferation, migration and invasion of GC cells significantly increased after miR-181b transfection, probably due to downregulation of protein levels of TIMP3. Conversely, Chen et al\(^115\) showed that mir-181b is downregulated in human GC cell lines in comparison with gastric epithelial cells. They observed that overexpression of mir-181b suppressed the proliferation and colony formation rate of GC cells, suggesting that miR-181b may function as a tumour suppressor in gastric adenocarcinoma cells through negatively regulating the CREB1 gene.

The dual role of this and other miRNAs could be explained by the fact that a single miRNA is capable of targeting multiple genes, repressing the production of hundreds of proteins, directly or indirectly. Additionally, each gene can be regulated by multiple miRNAs, so the final effect will depend on these complex interactions\(^119,120\).

Because miRNAs have thousands of predict targets in a complex regulatory cell signalling network, it is important to study multiple target genes simultaneously. Thus, a research group at Federal University of Pará (UFPA) developed the web tool TargetCompare (http://lghm.ufpa.br/targetcompare) to analyse multiple gene targets of pre-selected miRNAs. The described tool is useful for reducing arbitrariness and increasing the chances of selecting target genes having an important role in the analysis\(^121\).  

### CIRCULATING miRNAs AS POTENTIAL GASTRIC CANCER BIOMARKERS

In cancer, it has been shown that primary tumour cells can release specific cancer miRNAs into the tumour microenvironment as well as into the circulation\(^112,123\). In recent years, studies have reported that miRNAs detectable in plasma or serum are more stable among individuals of the same species in comparison with other circulating nucleic acids\(^124\).

This finding could be explained by the fact that circulating miRNAs exhibit resistance to endogenous ribonuclease activity by binding certain proteins such as Argonaute2 and high-density lipoproteins, besides being packaged in secretory particles including apoptotic bodies and exosomes, which allow them to be protected from existing ribonucleases\(^125-127\). Thus, it is plausible to use circulating miRNAs as biomarkers for early detection of various diseases, including GC.

Several studies have described circulating miRNAs as reproducible and reliable potential biomarkers as well as therapeutic targets in GC (Table 2)\(^128-137\). Tsujiura et al\(^130\) suggested that miR-18a, which is a component of the miR-17-92 cluster, could be considered a novel plasma biomarker in GC patients. In addition to observing that the plasma miR-18a concentrations were significantly higher in GC patients than in healthy controls, they also stated that the plasma miR-18a levels were significantly reduced in postoperative samples compared to preoperative samples.

Recently, Wang et al\(^138\) assessed the diagnostic performance of circulating miRNAs for the detection of gastrointestinal cancer in a meta-analysis including 21 GC studies. The majority of the GC studies were of Asian ethnicity, and the most frequent miRNAs found in plasma or serum were miR-106b and miR-21. In Caucasian patients with GC, they described miR-203, miR-146b-5p, miR-192 and miR-200c as potential biomarkers in plasma. However, many of these biomarkers have been tested in very restricted parameters and are highly influenced by ethnic and environmental factors, thus making it even more difficult to find specific biomarkers for GC.

### EPIGENETIC FACTORS INFLUENCING miRNA EXPRESSION IN GASTRIC CANCER

Many molecular mechanisms lead to miRNA deregulation such as genetic mutation and epigenetic aberration. Approximately half of miRNA genes are located next to CpG islands, and the expression of these miRNAs is regulated by alterations in DNA methylation and histone modification\(^139-143\).

DNA methylation is involved in silencing expression of tumour suppressor genes by establishing and maintaining a repressive status at gene promoters\(^5,7,144\). The basic transcription mechanism of miRNAs is fundamentally similar to that of classical protein-coding genes, and aberrant DNA hypermethylation has been shown to silence tsmiRNAs in cancer.

Many miRNAs have been reported to be downregulated due to hypermethylation of the CpG islands in GC, such as miR-9, miR-34b/c, miR-129, miR-137, miR-181c, miR-199a, miR-212, miR-338, miR-512, miR-516, miR-941 and miR-1247\(^142,143,145-150\).

Several studies have shown that the miRNA methylation level was positively associated with the clinicopathological features of GC\(^147\). Low expression levels of miR-34b and miR-129-3p are associated with a poor clinical outcome in GC patients, and hypermethylation of miR-129-2 and miR-34b CpG islands tends to correlate with poor clinicopathological features\(^149\).

miRNAs can also be decontrolled as a consequence...
of aberrant expression of specific epigenetic regulators such as polycomb repressor complexes and histone deacetylases (HDACs). Wisnieski et al. demonstrated HDAC1 downregulation in gastric tumours compared with adjacent non-tumour samples. According to Scott et al., inhibition of HDACs results in transcriptional changes in approximately 40% of miRNAs expressed in a breast cancer cell line (SKBr3).

In 2009, Saito et al. analysed the miRNA expression profile in human GC cells treated with 5-aza-2′-deoxycytidine (5-Aza-CdR) and 4-phenylbutyric acid (PBA), and they suggested that chromatin remodelling at Alu repeats by DNA demethylation and HDAC inhibition can induce expression of silenced miR-512-5p. Moreover, activation of miR-512-5p can lead to suppression of Mcl-1, resulting in apoptosis of gastric cancer cells. Thus, epigenetic treatment, by using synthetic miRNAs, can serve as an “endogenous silencer” of target oncogenes in GC cells, blocking their activity as tumour enhancers.

### SINGLE-NUCLEOTIDE miRNA POLYMORPHISMS IN GASTRIC CANCER

Single-nucleotide polymorphisms (SNPs) in miRNA have also been associated with alteration of GC susceptibility.
and modification of target gene expression. However, the role of these genetic variants in GC susceptibility remains essentially unidentified. Table 3 summarizes described SNPs in miRNA in GC.

One of the most described miRNA SNPs associated with elevated risk in GC is SNP rs2910164 of miR-146a. Ahn et al. demonstrated that the C/G polymorphism in miR-146a decreases miR-146a expression and subsequently leads to reduced regulation of the target genes TRAF6, IRAK1 and PTC1 by the C allele. Moreover, some studies reported that miR-146a rs2910164 also affects susceptibility to gastric lesions. Song et al. found that the G/C polymorphism in miR-146a rs2910164 may play a role in the evolution of H. pylori-associated gastric lesions. Thus, SNP rs2910164 may be used as a genetic biomarker to predict GC risk.

SNPs in pri-miRNAs and pre-miRNAs could affect the maturation process and function of the miRNA, which may affect the expression of many proteins in the interaction pathway. Recently, Xu et al. found that upregulation of pri-let-7a-2 expression by the rs629367 C/C genotype was associated with increased risk and low survival in GC, probably by affecting the expression of mature let-7a.

The binding capacity of a miRNA with its target can be modified by SNPs affecting the miRNA TAG sequence. Additionally, a SNP in an mRNA sequence could influence the complementarity between the miRNA and the target mRNA. This could result in alteration of susceptibility to tumorigenesis. Wang et al. described that a SNP in the PDL1 (rs4143815) could affect its protein expression by interfering with miR-570 negative regulation. Furthermore, this SNP was significantly related to the risk of GC and depth of tumour infiltration, differentiation grade, lymph node metastasis, tumour size and staging.

Hence, SNP data could be useful to improve our understanding of the contribution of individual susceptibility to GC pathogenesis.

**FUTURE PERSPECTIVES**

Accumulating evidence indicates that the dysregulation of miRNAs plays important roles in GC pathogenesis. In this context, miRNA expression profiles have been shown to correlate with GC development, progression and response to therapy, suggesting their possible use as diagnostic, prognostic and predictive biomarkers.

Moreover, miRNA-based anticancer therapies have recently been explored, either alone or in combination with current targeted therapies. However, a big challenge in using miRNAs in cancer therapeutics is the considerable number of genes that a single miRNA can target, leading to a pleiotropic effect that may limit their manipulation at the systemic level. Nevertheless, the increasing capability of producing synthetic interfering miRNAs with higher affinity to the desired target is minimizing this barrier.

Thus, the strategy of using miRNAs for targeted therapy in the near future is probably over-optimistic, considering that the studies of miRNA-based the-

### Table 3 miRNA related to the risk of gastric cancer

| miRNA    | SNP       | Country       | Population | Number of cases/controls | Ref. |
|----------|-----------|---------------|------------|--------------------------|------|
| miR-27a  | rs895819  | China         | Asian      | 304/304                  | [43] |
|          |           |               | China      | 295/413                  | [154]|
|          |           |               | China      | 278/278                  | [135]|
|          |           |               | Japan      | 892/978                  | [156]|
|          |           |               | Japan      | 278/278                  | [155]|
|          |           |               | Japan      | 304/304                  | [157]|
|          |           |               | Japan      | 583/1637                 | [158]|
|          |           |               | Japan      | 90/90                    | [101]|
|          |           |               | China      | 1686/1895                | [159]|
| miR-146a | rs11671784| China         | Asian      | 304/304                  | [157]|
|          |           | Japan         | Asian      | 552/697                  | [161]|
|          |           | South Korea   | Asian      | 1686/1895                | [159]|
| miR-196a | rs11614913| Japan         | Asian      | 552/697                  | [161]|
|          |           | China         | Asian      | 233/213                  | [162]|
|          |           | South Korea   | Asian      | 461/447                  | [160]|
|          |           | Greece        | Greek      | 163/480                  | [163]|
| miR-499  | rs3746444 | Japan         | Asian      | 697/552                  | [161]|
|          |           | South Korea   | Asian      | 461/447                  | [160]|
| miR-149  | rs2292832 | China         | Asian      | 274/269                  | [165]|
|          |           | South Korea   | Asian      | 461/447                  | [160]|
|          |           | Greece        | Greek      | 163/480                  | [163]|
| miR-24   | rs4819388 | China         | Asian      | 183/348                  | [166]|
| miR-570  | rs4143815 | China         | Asian      | 205/393                  | [167]|
| miR-200c | rs12904   | China         | Asian      | 522/501                  | [168]|
| miR-505  | rs111638916| China         | Asian      | 877/748                  | [169]|
| Pre-miR-30c | rs928508 | China         | Asian      | 240/240                  | [170]|
| Pri-let-7a-2 | rs629367 | China         | Asian      | 107/124                  | [171]|

---

da Silva Oliveira KC et al. miRNA and gastric cancer
miRNAs and cancer: an epigenetics view. 

Modulation of miRNA activity in cancer. 

Expression Profile in Gastric Cancer Using Self-Organizing Maps. 

Identification of miRNAs for the human gastric cancer. 

Ultra-deep sequencing reveals the microRNA expression pattern of the human stomach. 

MiRNA expression profile for the human gastric cancer. 

interpretation of core miRNA pathway mutants. 

Gastric cancer-molecular and clinical dimensions. 

miR-21 plays a pivotal role in gastric cancer pathogenesis and miR-19a-b/20a/92a regulates the self-renewal and proliferation of gastric cancer stem cells. 

miR-20a in promoting gastric cancer progression by targeting SOCS1 in gastric cancer. 

Cancer Lett 2009; 285: 116-126 [PMID: 19464788 DOI: 10.1016/j.canlet.2009.04.031]

Tong AW, Nemunaitis J. Modulation of miRNA activity in human cancer: a new paradigm for cancer gene therapy? Cancer Gene Ther 2008; 15: 341-355 [PMID: 18369380 DOI: 10.1038/cgt.2008.8]

Kota J, Chivukula RR, O'Donnell KA, Wentzel EA, Montgomery CL, Hwang HW, Chang TC, Vivekanandan P, Tornborg M, Clark KR, Mendell JR, Mendell JT. Therapeutic microRNA delivery suppresses tumorigenesis in a murine liver cancer model. Cell 2009; 137: 1005-1017 [PMID: 19524505 DOI: 10.1016/j.cell.2009.04.021]

Krützfeldt J, Rajewsky N, Braich R, Rajeev KG, Tuschi T, Manoharan M, Stoffel M. Silencing of microRNAs in vivo with ‘antagomirs’. Nature 2005; 438: 685-689 [PMID: 16258535 DOI: 10.1038/nature04030]

Zhang X, Kong Y, Xu X, Xing H, Zhang Y, Han F, Li W, Yang Q, Zeng J, Jia L, Liu Z. F-box protein FBXO31 is down-regulated in gastric cancer and negatively regulated by miR-17 and miR-20a. Oncotarget 2014; 5: 6178-6190 [PMID: 25115392]

Zhang Y, Han T, Wei G, Wang Y. Inhibition of microRNA-17/20a suppresses cell proliferation in gastric cancer by modulatingUBE2C expression. Oncol Rep 2015; 33: 2529-2536 [PMID: 25760688 DOI: 10.3892/or.2015.3835]

Park D, Lee SC, Park JW, Cho SY, Kim HK. Overexpression of miR-17 in gastric cancer is correlated with proliferation-associated oncogene amplification. Pathol Int 2014; 64: 309-314 [PMID: 25047501 DOI: 10.1111/pat.12178]

Chen S, Zhu J, Yu F, Tian Y, Ma S, Liu X. Combination of miRNA and RNA functions as potential biomarkers for gastric cancer. Tumour Biol 2015; 36: 9909-9918 [PMID: 26168960 DOI: 10.1007/s13277-015-3756-9]

Wu Q, Yang Z, An Y, Hu H, Yin J, Zhang P, Nie Y, Wu K, Shi Y, Fan D. MiR-19a/b modulate the metastasis of gastric cancer cells by targeting the tumour suppressor MXD1. Cell Death Dis 2014; 5: e1144 [PMID: 24675462 DOI: 10.1038/cddis.2014.110]

Qin S, Ai F, Ji WF, Rao W, Zhang HC, Yao WJ. miR-19a promotes cell growth and tumorigenesis through targeting SOCS1 in gastric cancer. Asian Pac J Cancer Prev 2013; 14: 835-840 [PMID: 23621248 DOI: 10.7314/APJCP.2013.14.2.835]

Wang F, Li T, Zhang B, Li H, Wu Q, Yang L, Nie Y, Wu K, Shi Y, Fan D. MicroRNA-19a/b regulates multidrug resistance in human gastric cancer cells by targeting the tumour suppressor RFX3. Mol Cell Oncol 2014; 5: e103683 [PMID: 24040625 DOI: 10.1016/j.mco.2014.04.010]

Guo J, Miao Y, Xiao B, Huan R, Jiang Z, Meng D, Wang Y. Differential expression of microRNA species in human gastric cancer versus non-tumorous tissues. J Gastroenterol Hepatol 2009; 24: 652-657 [PMID: 19175831 DOI: 10.1111/j.1440-1746.2008.05666]

Wang JI, Hu Y, Kong X, Wang ZH, Chen HY, Xu J, Fang JY. Candidate microRNA biomarkers in human gastric cancer: a systematic review and validation study. PLoS One 2013; 8: e73683 [PMID: 24040625 DOI: 10.1371/journal.pone.0073683]

Xu L, Zhang Z, Yu M, Li L, Du G, Xiao W, Yang H. Involvement of miR-20a in promoting gastric cancer progression by targeting early growth response 2 (EGFR2). Int J Mol Sci 2013; 14: 16226-16239 [PMID: 23924943 DOI: 10.3390/ijms140816226]

Wu Q, Yang Z, Wang F, Hu S, Yang L, Shi Y, Fan D. MiR-19b/20a/92a regulates the self-renewal and proliferation of gastric cancer stem cells. J Cell Sci 2013; 126: 4220-4229 [PMID: 23868977 DOI: 10.1242/jcs.127944]

Zhang X, Li Z, Guo 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]

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 Onkol 2010; 36: 1089-1095 [PMID: 20372781 DOI: 10.3892/
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]

Yamanaka S, Owaru AN, Fu An, Luvsanjav D, Jin Z, Agarwal R, Tomuleasa C, Popescu I, Alexandrescu S, Dima S, Chivu-Economescu M, Montgomery EA, Torbenson M, Meltzer SJ, Selaru FM. MicroRNA-21 inhibits SerpinH1, a gene with novel tumour suppressive effects in gastric cancer. Dig Liver Dis 2012; 44: 589-596 [PMID: 22446562 DOI: 10.1016/j.dld.2012.06.020]

Cao Z, Yoon JH, Nam SW, Lee JY, Park WS. FDCD4 expression inversely correlated with mir-21 levels in gastric cancers. J Cancer Res Clin Oncol 2012; 138: 611-619 [DOI: 10.1007/s00231-011-1408-0]

Xu Y, Sun J, Xu J, Li Q, Guo Y, Zhang Q. miR-21 Is A Promising Novel Biomarker for Lymph Node Metastasis in Patients with Gastric Cancer. Gastroenterol Res Pract 2012; 2012: 640168 [PMID: 22729026 DOI: 10.1155/2012/640168]

Kim BH, Hong SW, Kim A, Choi SH, Yoon SO. Prognostic implications for high expression of oncospecific microRNAs in advanced gastric cancer. J Surg Oncol 2013; 107: 505-510 [PMID: 22994633 DOI: 10.1002/jso.23271]

Zhao H, Wang Y, Yang L, Jiang R, Li W. MiR-25 promotes gastric cancer cells growth and motility by targeting RECK. Mol Cell Biochem 2014: 385: 207-213 [PMID: 24078004 DOI: 10.1007/s11010-013-1829-x]

Gong J, Cui Z, Li L, Mu Q, Wang Q, Guo Y, Sun H. MicroRNA-25 promotes gastric cancer proliferation, invasion, and migration by directly targeting F-box and WD-40 Domain Protein 7, FBXW7. Tumour Biol 2015; 36: 7831-7840 [PMID: 25944166 DOI: 10.1007/s13277-015-3510-3]

Li BS, Zuo QF, Zhao YL, Xiao B, Zhuang Y, Mao XD, Wu C, Yang SM, Zeng H, Zou QM, Guo G. MicroRNA-25 promotes gastric cancer migration, invasion and proliferation by directly targeting transducer of ERBB2, 1 and correlates with poor survival. Oncogene 2015; 34: 2556-2565 [PMID: 25043310 DOI: 10.1038/onc.2014.214]

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.clet.2008.08.003]

Sun Q, Gu H, Zeng Y, Xia Y, Wang Y, Jing Y, Yang L, Wang B. Hsa-mir-27a genetic variant contributes to gastric cancer susceptibility through affecting miR-27a and target gene expression. Cancer Sci 2010; 101: 2241-2247 [PMID: 20667779 DOI: 10.1111/j.1440-1695.2010.01667]

Zhao X, Yang L, Hu J. Down-regulation of miR-27a might inhibit proliferation and drug resistance of gastric cancer cells. J Exp Clin Cancer Res 2011; 30: 55 [PMID: 21256941 DOI: 10.1186/1756-9966-30-55]

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]

Tsujirua A, Ichikawa D, Komatsu S, Shiozaki A, Takeshita H, Kosuga T, Konishi H, Morimura R, Deguchi K, Fujiwara T, Tsujiura M. MicroRNA-106a induces multidrug resistance in gastric cancer by targeting RUNX3. FEBS Lett 2013; 587: 3069-3075 [PMID: 23932924 DOI: 10.1016/j.febslet.2013.06.058]

Zhu M, Zhang N, He S, Liu Y, Lu G, Zhao L. MicroRNA-106a targets TIMP2 to regulate invasion and metastasis of gastric cancer. FEBS Lett 2014; 588: 600-607 [PMID: 24440352 DOI: 10.1016/j.febslet.2013.12.028]

Petrucha F, Visone R, Onelli MR, Shah MH, Nicoloso MS, de Martino I, Iliopoulos D, Pilozzi E, Liu CG, Negrini M, Cazavani V, 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]

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]

Teeranritsa O, Kasajima A, Schafer R, Kuban RJ, Ungethüm U, Györffy B, Neumann U, Simon E, Weichert W, Ebert MP, Röcken C. Systematic evaluation of the miRNA-ome and its downstream effects on miRNA expression identifies gastric cancer progression. J Pathol 2010; 222: 310-319 [PMID: 20726036 DOI: 10.1002/path.2759]

Yao YL, Wu XY, Wu JH, Gu T, Chen L, Gu JH, Liu Y, Zhang QH. Effects of microRNA-106 on proliferation of gastric cancer cell through regulating p21 and E2F5. Asian Pac J Cancer Prev 2013; 14: 2839-2843 [PMID: 23803041 DOI: 10.7314/APJCP.2013.14.5.2389]

Kurashige J, Kamohara H, Watanabe M, Hiyoshi Y, Iwatsuki H, Ichikawa D, Komatsu S, Shiozaki A, Takeshita J, Kuban RJ, Ungethüm U, Kasajima A, Schäfer R, Kuban RJ, Ungethüm U, Kasajima A, Schäfer R. Novel Biomarker for Lymph Node Metastasis in Patients with Thigh Node Metastasis in Patients with Gastric Cancer. J. Detection of miR-106a in gastric carcinoma and its clinical significance. Clin Cancer Res 2010; 1672-1681 [PMID: 19153141 DOI: 10.1093/nar/gkp002]

Tchernitsa O, Kasajima A, Schafer R, Kuban RJ, Ungethüm U, Györffy B, Neumann U, Simon E, Weichert W, Ebert MP, Röcken C. Systematic evaluation of the miRNA-ome and its downstream effects on miRNA expression identifies gastric cancer progression. J Pathol 2010; 222: 310-319 [PMID: 20726036 DOI: 10.1002/path.2759]
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]

46 Wang M, Zhao C, Shi H, Zhang B, Zhang L, Xiang Z, Wang S, Wu X, Yang T, Huang F, Cai J, Zhu Q, Zhu W, Qian H, Xu W. Deregulated microRNAs in gastric cancer tissue-derived mesenchymal stem cells: novel biomarkers and a mechanism for gastric cancer. Br J Cancer 2014; 110: 1199-1210 [PMID: 24473397 DOI: 10.1038/bjc.2014.14]

47 Liu W, Song N, Yao H, Zhao L, Liu H, Li G. miR-221 and miR-222 Simultaneously Target RECK and Regulate Growth and Invasion of Gastric Cancer Cells. Med Sci Monit 2015; 21: 2718-2725 [PMID: 26364844 DOI: 10.1265/sdm.894332]

48 Zhu YM, Zhong ZX, Liu ZM. Relationship between let-7-a and gastric mucosa carcinization and its significance. World J Gastroenterol 2010; 16: 3325-3329 [PMID: 20614490 DOI: 10.3748/wjg.v16.i26.3325]

49 Zhu Y, Zhong Z, Liu Z. Lentiviral vector-mediated upregulation of let-7a inhibits gastric carcinoid cell growth in vitro and in vivo. Scand J Gastroenterol 2011; 46: 53-59 [PMID: 20809749 DOI: 10.3109/00365521.2010.510566]

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

51 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: 1451-1459 [PMID: 21874264 DOI: 10.3892/or.2011.1437]

52 Zhu Y, Xiao O, Dong L, Liu Z. Investigation and identification of let-7-a related functional proteins in gastric carcinoma by proteomics. Anal Cell Pathol (Amst) 2012; 35: 285-295 [PMID: 22596182 DOI: 10.3233/ACP-2012-0063]

53 Golestanian AF, Atashia A, Langrodli L, Shafiee A, Ghaemi N, Soleimani M. miRNAs expressed differently in cancer stem cells and cancer cells of human gastric cancer cell line MKN-45. Cell Biochem Funct 2012; 30: 411-418 [PMID: 22374783 DOI: 10.1002/cbf.2815]

54 Takagi T, Iio A, Nakagawa Y, Naoe T, Tanigawa N, Aoyagi K, Sasaki H, Yasui W. MicroRNA-148a regulates MEG3 in gastric cancer by targeting DNA methyltransferase 1. J Cancer Res Clin Oncol 2011; 137: 261-270 [PMID: 21460602 DOI: 10.1588/1578-7445.AMO2011-133]

55 Sacconi A, Biagioni F, Canu V, Mori F, Di Benedetto A, Lorenzon L, Ercolani C, Di Agostino S, Cambria AM, Gernoni S, Grasso G, Blandino R, Panebianco V, Ziparo V, Federici O, Muti P, Strano S, Carboni F, Mottolene M, Diodoro M, Pescarmona E, Garafalo A, Blandino G. miR-204 targets Bcl-2 expression and enhances responsiveness of gastric cancer. Cell Death Dis 2012; 3: e423 [PMID: 23152059 DOI: 10.1038/cddis.2012.160]

56 Zhang L, Wang X, Chen P. MiR-204 down regulates SIRT1 and reverses SIRT1-induced epithelial-mesenchymal transition, anokis resistance and invasion in gastric cancer cells. BMC Cancer 2013; 13: 290 [PMID: 23768087 DOI: 10.1186/1471-2407-13-290]

57 Tie J, Pan Y, Zhu 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: 20300857 DOI: 10.1371/journal.pgen.1000879]

58 Gao C, Zhang Z, Liu W, Xiao S, Gu W, Hu L. Reduced microRNA-218 expression is associated with high nuclear factor kappa B activation in gastric cancer. Cancer 2010; 116: 41-49 [PMID: 19890957 DOI: 10.1002/cncr.24743]

59 Gao CP, Zhang ZY, Cai GH, Liu WZ, Xiao SD, Hu L. [Reduced expression of miR-218 and its significance in gastric cancer]. Zhonghua Zhong Liu Za Zhi 2010; 32: 249-252 [PMID: 20510672]

60 Gao C, Pang M, Yu J, Long S, Dong Y, Yang J, Cao M, Zhang C, Han S, Li L. Epidermal growth factor receptor-complified and overexpressed protein (VOPP1) is a putative oncoogene in gastric cancer. Clin Exp Med 2015; 15: 469-475 [PMID: 25398664 DOI: 10.1007/s10238-014-0320-7]

61 Luo H, Zhang H, Zhang Z, Zhang X, Bing 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]

62 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. Relationship 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)70343-5]

63 Wu LH, Li H, Wang F, Yu J, He JS. The Tumor Suppressor Roles of miR-433 and miR-127 in Gastric Cancer. Int J Mol Sci 2013; 14: 14171-14184 [PMID: 23880861 DOI: 10.3390/ijms140714171]

64 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]

65 Rotkrua P, Akiyama Y, Hashimoto Y, Otsubo T, Yaasa Y. MiR-9 downregulates CDX2 expression in gastric cancer cells. Int J}
da Silva Oliveira KC et al. miRNA and gastric cancer

Cancer 2011; 129: 2611-2620 [PMID: 21225631 DOI: 10.1002/jpc.25923]

Zheng L, Qi T, Yang D, Qi M, Li D, Xiang X, Huang K, Tong Q. microRNA-9 suppresses the proliferation, invasion and metastasis of gastric cancer cells through targeting cyclin D1 and Ets1. PLoS One 2013; 8: e55719 [PMID: 23383271 DOI: 10.1371/journal.pone.0055719]

Deng J, Lei W, Xiang Z, Xiang L, Lei J, Gong Y, Song M, Wang Y, Fang Z, Yu F, Feng M, Sun Z, Chen J, Zhan X, Zong J. Cullin 4A (CUL4A), a direct target of miR-9 and miR-137, promotes gastric cancer proliferation and invasion by regulating the Hippo signaling pathway. Oncotarget 2016; 7: 10037-10050 [PMID: 26840256 DOI: 10.18632/oncotarget.7048]

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 oncogenic 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.1582-4932.2010.01194.x]

Feng L, Xie Y, Zhang H, Wu Y. miR-107 targets cyclin-dependent kinase 6 expression, induces cell cycle G1 arrest and inhibits invasion in gastric cancer cells. Med Oncol 2012; 29: 856-863 [PMID: 21264532 DOI: 10.1007/s12032-011-9823-1]

Inoue T, Inumaru H, Ogawa E, Inaba T, Fukushima R. Clinicopathological and prognostic significance of microRNA-107 and its relationship to Dicer1 miRNA expression in gastric cancer. Oncol Rep 2012; 27: 1759-1764 [PMID: 22407237 DOI: 10.3892/or.2012.1709]

Li F, Liu B, Gao Y, Liu Y, Xu Y, Tong W, Zhang A. Upregulation of microRNA-107 induces proliferation in human gastric cancer cells by targeting the transcription factor FOXO1. FEBS Lett 2014; 588: 538-544 [PMID: 24374340 DOI: 10.1016/j.febslet.2013.12.009]

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: 10.1186/1078-0432.CCR-10-2866]

Hou Z, Zou Q, Chen Q, Lai R, Wu X, Wu X, Liu F, Xu G, Ji Y. Elevated microRNA-107 induces proliferation in human gastric cancer cells through targeting cyclin D1 and Ets1. PLoS One 2013; 8: 22929343 DOI: 10.1371/journal.pone.0033919

Hou Z, Yin H, Chen C, Dai X, Li X, Liu B, Fang X. microRNA-146a targets the L1 cell adhesion molecule and suppresses the metastatic potential of gastric cancer. Mol Med Rep 2012; 6: 501-506 [PMID: 22711666 DOI: 10.3892/mmr.2012.946]

Crone SG, Jacobsen A, Federspiel B, Bardram L, Krogh A, Lund AH, Friis-Hansen L. microRNA-146a inhibits G protein-coupled receptor-mediated activation of NF-kB by targeting CARD10 and COP9S in gastric cancer. Mol Med Rep 2012; 11: 71 [PMID: 22992343 DOI: 10.1186/1746-4811-11-71]

Xiao B, Zou ED, Li N, Lu DS, Li W, Li BS, Zhao YL, Mao XH, Guo G, Yu PW, Zou QM. Increased miR-146a in gastric cancer directly targets SMAD4 and is involved in modulating cell proliferation and apoptosis. Med Oncol 2012; 29: 886-892 [PMID: 21347720 DOI: 10.1007/s12032-011-9862-7]

Hou Z, Zou Q, Chen H, Chen C, Dai X, Li X, Liu B, Fang X. microRNA-146a targets the L1 cell adhesion molecule and suppresses the metastatic potential of gastric cancer. Mol Med Rep 2012; 6: 501-506 [PMID: 22711666 DOI: 10.3892/mmr.2012.946]

Chen L, Yang Q, Kong QW, Liu T, Liu M, Li X, Tang H. microRNA-181B targets cAMP responsive element binding protein 1 in gastric adenocarcinomas. IUBMB Life 2012; 64: 628-635 [PMID: 22539488 DOI: 10.1002/iub.1030]

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, Daming F. microRNA-223 promotes gastric cancer invasion and metastasis by targeting tumor suppressor EPB41L3. Mol Cancer 2011; 11: 824-833 [PMID: 21628394 DOI: 10.1186/1557-4172-MCR-10-0529]

Kang W, Tong JH, Chan AW, Lung RW, Chau SL, Wong QW, Wong N, Yu J, Cheng AS, To KF. Stathmin I plays oncogenic role and is a target of microRNA-223 in gastric cancer. PLoS One 2012; 7: e33919 [PMID: 22470493 DOI: 10.1371/journal.pone.0033919]

Li J, Guo Y, Liang X, Sun M, Wang G, De W, Wu W. microRNA-223 functions as an oncogene in human gastric cancer by targeting FBXW7/cdk6. J Cancer Res Clin Oncol 2012; 138: 763-774 [PMID: 22279066 DOI: 10.1007/s00432-011-1154-x]

Back D, Villen J, Shiri C, Camargo ED, Gygi SP, Bartel DP. The impact of microRNAs on protein output. Nature 2008; 455: 64-71 [PMID: 18668037 DOI: 10.1038/nature07242]

Selbach M, Schwahn-Hausser B, Thierfelder N, Fang Z, Khanin R, Rajewsky N. Widespread changes in protein synthesis induced by microRNAs. Nature 2008; 455: 58-63 [PMID: 18668040 DOI: 10.1038/nature07228]

Moreira FC, Dustan B, Hamuy IG, Ribeiro-Dos-Santos AM, Dos Santos AR. TargetCompare: A web interface to compare simultaneous miRNAs targets. Bioinformation 2014; 10: 602-605 [PMID: 25352731 DOI: 10.60207320630010602]

Zhu C, Ren C, Han J, Ding Y, Du J, Dai N, Dai J, Ma H, Hu Z, Shen H, Xu Y, Jin A. A five-microRNA panel in plasma was identified as potential biomarker for early detection of gastric cancer. Br J Cancer 2014; 110: 2291-2299 [PMID: 24595006 DOI: 10.1038/bjc.2014.119]

Schisterman EF, Sana J, Slaby O. Circulating miRNAs as new blood-based biomarkers for solid cancers. Future Oncol 2013; 9: 387-402 [PMID: 23469974 DOI: 10.2217/fon.12.192]

Arroyo JD, Chevillet JR, Kroh EM, Ruf IK, Pritchard CC, Gibson DF, Mitchell PS, Bennett CF, Pogosova-Agadjanyan EL, Stirewalt DF, Tait JF, Tewari M. Argonaute2 complexes carry a population
of circulating microRNAs independent of vesicles in human plasma. Proc Natl Acad Sci USA 2011; 108: 5003-5008 [PMID: 21383914 DOI: 10.1073/pnas.1009551108]

126 Vickers KC, Palmisano BT, Shoouri BM, Shamburek RD, Remaley AT. MicroRNAs are transported in plasma and delivered to recipient cells by high-density lipoproteins. Nat Cell Biol 2011; 13: 423-433 [PMID: 21423718 DOI: 10.1038/ncll2010]

127 Turchinovich A, Weiz L, Langheinz A, Burwinkel B. Characterization of extracellular circulating microRNA. Nucleic Acids Res 2011; 39: 7223-7233 [PMID: 21609964 DOI: 10.1093/nar/gkq254]

128 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.2010.02.025]

129 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: 22406925 DOI: 10.3892/mmr.2012.828]

130 Tsujura M, Komatsu S, Ichikawa D, Shiozaki A, Konishi H, Takeshita H, Morimura R, Nagata H, Kawaguchi T, Hirajima S, Arita T, Fujiwara H, Okamoto K, Osugi E. Circulating miR-18a contributes to plasma cancer detection and monitoring in patients with gastric cancer. Gastric Cancer 2015; 18: 271-279 [PMID: 24626859 DOI: 10.1007/s10120-014-0363-1]

131 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]

132 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, Osugi E. Prognostic impact of circulating miR-21 in the plasma of patients with gastric carcinoma. Anticancer Res 2013; 33: 271-276 [PMID: 23267156]

133 Kim SY, Jeon T, Choi CI, Kim DH, Kim DH, Kim GH, Ryu DY, Lee BE, Kim HH. Validation of circulating miRNA biomarkers for predicting lymph node metastasis in gastric cancer. J Mol Diagn 2013; 15: 661-669 [PMID: 23806809 DOI: 10.1016/j.jmldx.2013.04.004]

134 Li BS, Zhao YL, Guo G, Li W, Zhu ED, Luo X, Mao XH, Zou QM, Yu PW, Zuo QF, Li N, Tan B, Liu KY, Xiao B. Plasma microRNAs, miR-223, miR-21 and miR-218, as novel potential biomarkers for gastric cancer detection. Mol Carcinog 2010; 49: 716-723 [PMID: 22428419 DOI: 10.1002/mc.22293]

135 Tsai KW, Wu CW, Hu LY, Li SC, Liao CH, Lai CH, Kao HW, Fang WL, Huang KH, Chan WC, Lin WC. Epigenetic regulation of miR-34b and miR-129 expression in gastric cancer. Biochem Biophys Res Commun 2011; 409: 1047-1052 [PMID: 20351975 DOI: 10.1016/j.bbrc.2010.03.121]

136 Ma J, Hong L, Chen Z, Nie Y, Fan D. Epigenetic regulation of miR-9 and miR-195 as potential biomarkers for early diagnosis of gastric cancer. World J Gastroenterol 2013; 19: 536-547 [PMID: 25159093 DOI: 10.1007/s13277-013-0742-y]

137 Zhang XJ. Association analysis of genetic variants in microRNA genes in gastric cancer and their modulation by trichostatin A. J Cancer Res Clin Oncol 2010; 136: 2738-2744 [PMID: 19503096 DOI: 10.1007/s00432-009-1409-3]

138 Zhou Y, Du WD, Chen G, Ruan J, Xu S, Zhou FS, Zuo XB, Lv ZJ, Zhang XJ. Association analysis of genetic variants in microRNA networks and gastric cancer risk in a Chinese Han population. J Cancer Res Clin Oncol 2012; 138: 939-945 [PMID: 22350505 DOI: 10.1007/s00432-012-1164-8]

139 Song B, Yan G, Hao H, Yang B. rs11671784 G/A and rs895819 A/G polymorphisms inversely affect gastric cancer susceptibility and miR-27a expression in a Chinese population. Med Sci Monit 2014; 20: 2318-2326 [PMID: 25399405 DOI: 10.12659/MSM.892499]
Yang Q, Jie Z, Ye S, Li Z, Han Z, Wu J, Yang C, Jiang Y. Genetic variations in miR-27a gene decrease mature miR-27a level and reduce gastric cancer susceptibility. *Onogene* 2014; 33: 193-202 [PMID: 23246964 DOI: 10.1038/onc.2012.569]

Zeng Y, Suo QM, Liu NN, Dong GH, Chen J, Yang L, Wang B. Correlation between pre-miR-146a C/G polymorphism and gastric cancer risk in Chinese population. *World J Gastroenterol* 2010; 16: 3578-3583 [PMID: 20653068 DOI: 10.3748/wjg.v16.i28.3578]

Hishida A, Matsuoka K, Goto Y, Naito M, Wakai K, Tajima K, Hamajima N. Combined effect of miR-146a rs2910164 G/C polymorphism and Toll-like receptor 4 +3725 C/G polymorphism on the risk of severe gastric atrophy in Japanese. *Dig Dis Sci* 2011; 56: 1131-1137 [PMID: 20721625 DOI: 10.1007/s10620-010-1376-1]

Zhou F, Zha H, Luo D, Wang M, Dong X, Hong Y, Lu B, Zhou Y, Zhou J, Zhang Z, Gong W. A functional polymorphism in Pre-miR-146a is associated with susceptibility to gastric cancer in a Chinese population. *DNA Cell Biol* 2012; 31: 1290-1295 [PMID: 22455393 DOI: 10.1089/dna.2011.1596]

Ahn DH, Rah H, Choi YK, Jeon YJ, Min KT, Kwaak K, Hong SP, Hwang SG, Kim NK. Association of the miR-146a C>G, miR-149 T>C, miR-196a2 T>C, and miR-499 A>G polymorphisms with gastric cancer risk and survival in the Korean population. *Mol Carcinog* 2013; 52 Suppl 1: E39-E51 [PMID: 23001871 DOI: 10.1002/mc.21962]

Okubo M, Tahara T, Shibata T, Yamashita H, Nakamura M, Yoshioka D, Yonemura J, Ishizuka T, Arisawa T, Hirata I. Association between common genetic variants in pre-microRNAs and gastric cancer risk in Japanese population. *Helicobacter* 2010; 15: 524-531 [PMID: 20173609 DOI: 10.1111/j.1523-5378.2010.00806.x]

Peng S, Kuang Z, Sheng C, Zhang Y, Xu H, Cheng Q. Association of microRNA-196a-2 gene polymorphism with gastric cancer risk in a Chinese population. *Dig Dis Sci* 2010; 55: 2288-2293 [PMID: 19934808 DOI: 10.1007/s10620-009-1007-x]

Dikeakos P, Theodoropolous G, Rizos S, Tzanakis N, Zografos G, Gazouli M. Association of the miR-146a C>G, miR-149 T>C, and miR-196a2 T>C polymorphisms with gastric cancer risk and survival in the Greek population. *Mol Biol Rep* 2014; 41: 1075-1080 [PMID: 24379078 DOI: 10.1007/s11033-013-2953-0]

Cai M, Zhang Y, Ma Y, Li W, Min P, Qiu J, Xu W, Zhang M, Li M, Li L, Liu Y, Yang D, Zhang J, Cheng F. Association between microRNA-499 polymorphism and gastric cancer risk in Chinese population. *Bull Cancer* 2015; 102: 973-978 [PMID: 26597478 DOI: 10.1016/j.bulcan.2015.09.012]

Zhang MW, Jin MJ, Yu YX, Zhang SC, Liu B, Jiang X, Pan YF, Li QI, Ma SY, Chen K. Associations of lifestyle-related factors, hsa-miR-149 and hsa-miR-605 gene polymorphisms with gastrointestinal cancer risk. *Mol Carcinog* 2012; 51 Suppl 1: E21-E31 [PMID: 21976437 DOI: 10.1002/mc.20863]

Yang P, Tang R, Zhu J, Zou L, Wu R, Zhou H, Mao Y, Li R, Hua D, Wang W, Zhang H. A functional variant at miR-24 binding site in B7-H1 alters susceptibility to gastric cancer in a Chinese Han population. *Mol Immunol* 2013; 56: 98-103 [PMID: 23688438 DOI: 10.1016/j.molimm.2013.04.010]

Wang W, Li F, Mao Y, Zhou H, Sun J, Li R, Liu C, Chen W, Hua D, Zhang X. A miR-57b binding site polymorphism in the B7-H1 gene is associated with the risk of gastric adenocarcinoma. *Hum Genet* 2013; 132: 641-648 [PMID: 23430453 DOI: 10.1007/s00439-013-1275-6]

Li Y, Nie Y, Cao J, Tu S, Lin Y, Du Y, Li Y. G-A variant in miR-200c binding site of EFNAB1 alters susceptibility to gastric cancer. *Mol Carcinog* 2014; 53: 219-229 [PMID: 23605816 DOI: 10.1002/mc.21966]

Liu Y, Xu J, Jiang M, Ni L, Chen Y, Ling Y. Association between functional PSMD10 rs111638916 variant regulated by MiR-505 and gastric cancer risk in a Chinese population. *Cell Physiol Biochem* 2015; 37: 1010-1017 [PMID: 26394032 DOI: 10.1159/000430227]

Mu YP, Su XL. Polymorphism in pre-miR-30c contributes to gastric cancer risk in a Chinese population. *Med Oncol* 2012; 29: 1723-1732 [PMID: 22108846 DOI: 10.1007/s12032-011-0115-6]

Xu Q, Dong Q, He C, Liu W, Sun L, Liu J, Xing C, Li X, Wang B, Yuan Y. A new polymorphism biomarker rs629367 associated with increased risk and poor survival of gastric cancer in chinese by up-regulated miRNA-let-7a expression. *PloS One* 2014; 9: e95249 [PMID: 24760009 DOI: 10.1371/journal.pone.0095249]

Song MY, Su HJ, Zhang L, Ma JL, Li JY, Pan KY, You WC. Genetic polymorphisms of miR-146a and miR-27a, H. pylori infection, and risk of gastric lesions in a Chinese population. *PloS One* 2013; 8: e61250 [PMID: 23613822 DOI: 10.1371/journal.pone.0061250]

Tang GH, Tang M, Xie YJ. The Role of miRNAs in Gastric Cancer. *J Gastroint Dig Syst* 2013; 3: 129 [DOI: 10.4172/2161-069X.1000129]

Xu X, Yang X, Xing C, Zhang S, Cao J. miRNA: The nemesis of gastric cancer (Review). *OncoLett* 2013; 6: 631-641 [PMID: 24137382 DOI: 10.3982/ol.2013.1428]

Kim CH, Kim HK, Retting RL, Kim J, Lee ET, Aprelikova O, Choi JJ, Munroe DJ, Green JE. miRNA signature associated with outcome of gastric cancer patients following chemotherapy. *BMC Med Genomics* 2011; 4: 79 [PMID: 22112324 DOI: 10.1186/1755-7894-7-79]

Iorio MV, Croce CM. MicroRNA dysregulation in cancer: diagnostics, monitoring and therapeutics. A comprehensive review. *EMBO Mol Med* 2012; 4: 143-159 [PMID: 22351564 DOI: 10.1002/emmm.201100209]

P-Reviewer: Umemura A S-Editor: Qi Y L-Editor: A E-Editor: Wang CH
