Komatsu *et al. J Cancer Metastasis Treat* 2018;4:36
DOI: 10.20517/2394-4722.2017.58

Journal of Cancer Metastasis and Treatment

Review

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Circulating microRNAs as a liquid biopsy: a next-generation clinical biomarker for diagnosis of gastric cancer

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How to cite this article: Komatsu S, Kiuchi J, Imamura T, Ichikawa D, Otsuji E. Circulating microRNAs as a liquid biopsy: a next-generation clinical biomarker and treatment target in gastric cancer. *J Cancer Metastasis Treat* 2018;4:36. http://dx.doi.org/10.20517/2394-4722.2017.58

Received: 18 Oct 2017 **Accepted**: 14 Jul 2018 **Published**: 18 Jul 2018

Science Editors: Lucio Miele, Masayuki Watanabe **Copy Editor**: Jun-Yao Li **Production Editor**: Cai-Hong Wang

Abstract

Accumulating evidence has suggested the potential clinical utility of novel body fluid biomarkers, or "liquid biopsy", using circulating tumor cells and cell-free nucleic acids from cancer patients. Noninvasive and reproducible, liquid biopsy could provide the basis for individualized therapeutic strategies by identifying genetic and epigenetic aberrations that are closely associated with cancer initiation and progression. MicroRNAs (miRNAs) are short noncoding RNAs that post-transcriptionally regulate gene expression. They also play important roles in various physiological and developmental processes as oncogenic or tumor-suppressive regulators. Specific miRNA expression signatures have been identified in a number of human cancers. Circulating miRNAs have been detected in plasma and serum, and this in blood has attracted the attention of researchers for their potential as noninvasive biomarkers. Circulating miRNAs have emerged as tumor-associated biomarkers that reflect not only the existence of cancer, but also the dynamics, malignant potential, and drug resistance of tumors. Herein, we review the recent biological and clinical research on the circulating miRNAs of gastric cancer and discuss future perspectives for their clinical applications as a liquid biopsy.

Keywords: Liquid biopsy, circulating nucleic acids, circulating microRNA, biomarker, gastric cancer

INTRODUCTION

Gastric cancer is third-leading cause of death among all cancers worldwide[1]. While improved perioperative management and diagnostic techniques have boosted early detection and decreased mortality in recent years,

gastric cancer continues to constitute a global health problem as a prevalent form of cancer[1]. Gastric cancer patients at advanced stages of the disease have a very poor prognosis[2]. Despite these continued difficulties, no biomarker molecule has been employed for the early diagnosis of gastric cancer in clinical settings, and researchers have validated only a scant number of molecules as therapeutic targets[3-7]. Therefore, for gastric cancer, identifying novel molecular targets and clinical biomarkers remain vital clinical challenges.

Recently, the concept of a "liquid biopsy" has become widely accepted in the clinical setting. Liquid biopsy is a less approaches for obtaining genetic and epigenetic aberrations that are closely associated with cancer initiation and progression[8]. Moreover, liquid approaches allows for repeated sampling and this makes it possible to evaluate the longitudinal evolution of a tumor and its heterogeneous characteristics, which single sampling may fail to capture[9-13]. Understanding circulating tumor cells and cell-free nucleic acids in cancer patients may bring new insights into prognostic and predictive value of liquid biopsy. In this article, we review recent research on the circulating miRNAs of gastric cancers, and discuss future perspectives on next-generation clinical biomarkers and treatment targets in gastric cancer.

THE MOLECULAR FEATURES AND BIOLOGICAL SIGNIFICANCE OF MICRORNAS

Small noncoding RNAs known as microRNAs (miRNAs) regulate how specific protein-coding genes are translated. After miRNAs were discovered in 1993[14], researchers have correlated changes in miRNA expression with diseases progression in multiple forms of cancer[15-18]. Numerous recent studies have detailed how miRNAs can be detected in plasma/serum while keeping their impressive stability[16,19-22]. Plasma/serum miRNAs resist endogenous ribonuclease activity through binding with plasma proteins such as Argonaute 2 and high-density lipoprotein (HDL)[23,24] or being surrounded by different secretory vesicles, including plasma/serum exosomes and apoptotic bodies[19,25-27]. Thus, miRNAs in peripheral blood are not digested by RNase or damaged by other conditions such as low or high pH, extended storage, boiling, and multiple freeze-thaw cycles. In addition, numerous extracellular miRNAs are made present by active secretion in addition to cell lysis[10,28,29]; such miRNAs are able to play a role as intercellular transmitters[22,28,30,31]. As one possible mechanism, the extracellular miRNAs involved in exosome vesicles has been reported to be released through ceramide-dependent secretory systems and function in recipient cells[29].

CIRCULATING MICRORNAS ARE A PROMISING SOURCE OF DIAGNOSTIC AND PROGNOSITC INFORMATION IN SOLID TUMORS

Mitchell *et al.*[19] first reported that circulating miRNAs had potential utility as new biomarkers in patients with solid cancers. As noninvasive and reproducible biomarkers in cancer patients, circulating miRNAs have since attracted the attention of researchers. As indicated by the usefulness of cell-free DNA and circulating tumor cells, the concept of "liquid biopsy" through circulating miRNAs may also provide ideal individualized therapeutic strategies for cancer patients and contribute to the development of precision medicine. Indeed, previous studies, including our own, have identified various blood-based miRNA biomarker candidates, which are useful for cancer detection, monitoring tumor dynamics, and predicting malignant potential, prognosis, and chemoresistance in cancer patients[32-45].

HIGH LEVELS OF CIRCULATING MICRORNAS IN PLASMA/SERUM IN GASTRIC CANCER

Various studies have identified circulating miRNAs for use in the diagnosis and prognosis of gastric cancer patients [Table 1]. In 2010, we reported the usefulness of circulating miRNAs and demonstrated their feasibility as biomarkers in the plasma of patients with gastric cancer. We selected four miRNAs (miR-17-5p, 21, 106a, and 106b) that has been previously reported as upregulated in gastric cancer tissues, analyzed their levels in plasma using RT-qPCR, and confirmed their utility as diagnostic biomarkers[32]. We then identified plasma miR-451 and miR-486 as novel cancer screening markers using the Toray® 3D-Gene microRNA

Table 1. High level of circulating microRNAs in plasma/serum in gastric cancer

miR	Sample	Ethnicity	Gastric cancer patietns	Controls	Value	Ref.
miR-16	Plasma	China	200	200	D	Zhu *et al*. 2014[55]
		China	50	47	D	Wang *et al*. 2014[69]
		China	155	111	D	Zhang *et al*. 2015[58]
miR-17-5p	Plasma	Japan	69	30	D	Tsujiura *et al*. 2010[32]
		China	65	NA	P, M	Wang *et al*. 2012[70]
	All blood	China	90	27	D	Zhou *et al*. 2010[71]
miR-18a	Plasma	Japan	104	65	D, M	Tsujiura *et al*. 2015[40]
miR-19b	Plasma	China	155	111	D	Zhang *et al*. 2015[58]
miR-20a	Plasma	China	65	NA	P, M	Wang *et al*. 2012[70]
		China	60	60	D	Cai *et al*. 2013[72]
		China	101	91	D	Zhou *et al*. 2015[73]
	Serum	China	55	55 (post-operative)	P, M	Yang *et al*. 2017[74]
miR-21	Plasma	Japan	69	30	D, P	Tsujiura *et al*. 2010[32] Komatsu *et al*. 2013[54]
		China	70	70	D	Li *et al*. 2012[75]
		China	53	20	D	Zheng *et al*.[48]
	Serum	China	174	39	D	Wang *et al*. 2012[76]
		Japan	87	114	D	Shiotani *et al*. 2013[77]
		China	103	NA	M	Song *et al*. 2013[78]
		China	50	50	D	Wu *et al*. 2015[57]
		China	92	89	D	Huang *et al*. 2016[79]
		Poland	20	20	D	Sierzega *et al*. 2017[80]
miR-23b	Plasma	China	138	50	D, P	Zhuang *et al*. 2016[81]
miR-25	Plasma	China	200	200	D	Zhu *et al*. 2014[55]
		China	20	20	D, P	Zhang *et al*. 2014[82]
		China	101	91	D	Zhou *et al*. 2015[73]
		China	65	65	D	Li *et al*. 2017[83]
miR-92a	Plasma	China	200	200	D	Zhu *et al*. 2014[55]
miR-92b	Plasma	China	101	91	D	Zhou *et al*. 2015[73]
miR-93	Plasma	China	65	65	D	Li *et al*. 2017[83]
		China	20	20	D, P	Zhang *et al*. 2014[82]
miR-100	Serum	China	50	47	D	Wang *et al*. 2014[69]
miR-106	Serum	Japan	87	114	D	Shiotani *et al*. 2013[77]
		China	118 (with chemotherapy)	20 (without chemotherapy)	P	Song *et al*. 2017[84]
miR-106a	Plasma	Japan	69	30	D	Tsujiura *et al*. 2010[32]
	All blood	China	90	27	D	Zhou *et al*. 2010[71]
miR-106b	Plasma	Japan	69	30	D	Tsujiura *et al*. 2010[32]
		China	60	60	D	Cai *et al*. 2013[72]
		China	20	20	D, P	Zhang *et al*. 2014[82]
		China	65	65	D	Li *et al*. 2017[83]
miR-107	Serum	Iran	36	36	D	Ayremlou *et al*. 2015[84]
miR-181c	Plasma	China	30	60 (30 gastric ulcer and 30 gastritis)	D	Cui *et al*. 2013[85]
miR-185	Plasma	China	101	91	D	Zhou *et al*. 2015[73]
miR-191	Serum	China	57	58	D	Peng *et al*. 2014[86]
miR-192	Plasma	China	96	36	D	Chen *et al*. 2014[52]
miR-199a-3p	Plasma	China	230	130	D	Li *et al*. 2013[51,87]
miR-200c	All blood	Spain	52	15	D, P	Valladares-Ayerbes *et al*. 2012[49]
	Serum	China	98	100	P	Zhang *et al*. 2015[88]
miR-210	Plasma	China	101	91	D	Zhou *et al*. 2015[73]
miR-221	Plasma	China	60	60	D	Cai *et al*. 2013[72]
miR-222	Plasma	China	114	56	D, P	Fu *et al*. 2014[53]
miR-223	Plasma	China	70	70	D	Li *et al*. 2012[75]
	Serum	China	50	47	D	Wang *et al*. 2014[69]
miR-331	Serum	Poland	20	20	D	Sierzega *et al*. 2017[80]
miR-370	Plasma	Taiwan	40	12	D	Lo *et al*. 2012[89]
miR-378	Serum	China	40	41	D	Liu *et al*. 2012[47]

miR-421	Serum	China	90	90	D	Wu *et al*. 2015[50]
miR-451	Plasma	Japan	56	30	D	Konishi *et al*. 2012[46]
		China	200	200	D	Zhu *et al*. 2014[55]
miR-486-5p	Plasma	Japan	56	30	D	Konishi *et al*. 2012[46]
		China	200	200	D	Zhu *et al*. 2014[55]
miR-664	Serum	China	118 (with chemotherapy)	20 (without chemotherapy)	P, M	Song *et al*. 2017[84]

D: diagnostic value; P: prognostic value; M: monitoring value

array-based approach on pre- and postoperative samples[46]. The area under the curve (AUC) values for these markers were high, at 0.96 and 0.92, respectively for the diagnosis of gastric cancer[46]. Additionally, genome-wide miRNA expression profiles followed by RT-qPCR assays revealed that circulating miR-378 had an AUC of 0.861 with 87.5% sensitivity and 70.73% specificity[47]. As shown in Table 1, many circulating miRNAs have been previously identified (by our group and others) as promising blood biomarker candidates for the detection of gastric cancer: miR-16, miR-17-5p, miR-18a, miR-19b, miR-20a, miR-21, miR-23b, miR-25, miR-92a, miR-92b, miR-93, miR-100, miR-106, miR-106a, miR-106b, miR-107, miR181c, miR-185, miR-191, miR-192, miR-199a-3p, miR-200c, miR-210, miR-221, miR-222, miR-223, miR-331, miR-370, miR-378, miR-421, miR-451, miR-486-5p, and miR-664, all of which are up-regulated in plasma/serum. These are promising diagnostic biomarkers[32,40,46-55,57,58,69-89].

LOW LEVEL OF CIRCULATING MICRORNAS IN PLASMA/SERUM IN GASTRIC CANCER

Kosaka *et al.*[29,59,60] recently suggested that healthy cells secrete some tumor-suppressor miRNAs as a way of slowing aberrant cell growth. We have previously found that blood-borne tumor-suppressor miRNAs, such as let-7a[32] and miR-375[35,45] were significantly downregulated in comparison to those of normal volunteers. Circulating miRNAs are released from both normal and cancer tissues, and the majority of these tumor-suppressor miRNAs are thought to arise from normal tissues. We therefore hypothesize that the progression of cancer causes healthy cells to become depleted of some tumor-suppressor miRNAs. That hypothesis is supported by our previously data that shows that a decrease in the plasma level of the tumor-suppressor miR-375 in esophageal cancer patients[34] and this[61] is correlated with reduced survival. We have also proposed that tumor progression and the resultant poor prognostic outcomes are correlated with the downregulation of tumor-suppressor miRNAs in the bloodstream[34,35]. As shown in Table 2, various circulating tumor-suppressor miRNAs have previously been identified as promising blood biomarker candidates for the detection and diagnosis of gastric cancer. These include miR-15a, miR-17, miR-26a, miR-31, miR-92a, miR-93, miR-106b, miR-122, miR-181b, miR-195-5p, miR-203, miR-204, miR-206, miR-218, miR-375, miR-503, miR-940, and let-7a, which are downregulated in plasma/serum with a great degree of diagnostic ability[32,52,56,62,75,79,84,90-100].

CIRCULATING MICRORNAS RELATED TO MALIGNANT POTENTIAL, TUMOR RECURRENCE, AND PROGNOSIS BIOMARKERS IN PLASMA/SERUM IN GASTRIC CANCER

Wang *et al.*[70] have reported that high levels of plasma miR-17-5p and miR-20a were significantly correlated with poor overall survival in gastric cancer patients. Valladares-Ayerbes *et al.*[49] have also reported that higher expression levels of miR-200c in blood are associated with poor overall survival. We demonstrated that the postoperative cause-specific survival was significantly poorer in gastric cancer patients with high plasma miR-21 levels than in those with low levels[54]. Moreover, the incidence of vascular invasion was also slightly higher in gastric cancer patients with high miR-21 levels, and multivariate analysis revealed that the presence of high miR-21 plasma levels was an independent prognostic factor[54]. Therefore, various up-regulated circulating miRNAs have previously been identified as blood-based prognostic biomarkers for gastric cancer: miR-17-5p, miR-20a, miR-21, miR-23b, miR-25, miR-93, miR-106, miR-106b, miR-200c, miR-222, and miR-664 [Table 1][49,53,54,70,74,81,82,84,88].

Table 2. Low level of circulating microRNAs in plasma/serum in gastric cancer

miR	Sample	Ethnicity	Gastric cancer patietns	Control	Value	Ref.
miR-15a	Serum	China	118 (with chemotherapy)	20 (without chemotherapy)	P	Song *et al*. 2017[90]
miR-17	Serum	China	40	36	D	Zeng *et al*. 2014[91]
miR-26a	Plasma	China	285	285	D	Qiu *et al*. 2016[92]
miR-31	Serum	China	92	89	D	Huang *et al*. 2016[79]
miR-92a	Serum	China	92	89	D	Huang *et al*. 2016[79]
miR-93	Serum	China	118 (with chemotherapy)	20 (without chemotherapy)	P	Song *et al*. 2017[84]
miR-106b	Serum	China	40	36	D	Zeng *et al*. 2014[91]
miR-122	Plasma	China	96	36	D	Chen *et al*. 2014[52]
miR-181b	Serum	China	92	89	D	Huang *et al*. 2016[79]
miR-195-5p	Serum	China	62	36	D, P	Shen *et al*. 2016[93]
	Plasma	Turkey	20	190	D	Gorur *et al*. 2013[94]
miR-203	Serum	China	92	89	D	Huang *et al*. 2016[79]
		Japan	130	22	P, M	Imaoka *et al*. 2016[62]
miR-204	Serum	China	115	40	P, M	Chen *et al*. 2016[95]
miR-206	Serum	China	150	150	D	Hou *et al*. 2016[96]
miR-218	Plasma	China	70	70	D	Li *et al*. 2012[75]
	Serum	China	68	56	P	Xin *et al*. 2014[97]
miR-375	Serum	China	NA	NA	D	Zhang *et al*. 2012[98]
miR-503	Serum	China	68	32	D, P	Wu *et al*. 2016[99]
miR-940	Plasma	China	110	30	D	Liu *et al*. 2016[56]
let-7a	Plasma	Japan	69	30	D	Tsujiura *et al*. 2010[32]
	Serum	China	80	NA	D	Wang *et al*. 2013[100]

D: diagnostic value; P: prognostic value; M: monitoring value

Regarding tumor-suppressor miRNAs, Imaoka *et al.*[62] reported that serum expression of miR-203 was significantly lower in stage IV than in stages I-III of gastric cancer patients. Serum miR-203 expression was significantly lower in gastric cancer patients with worse malignant potential, as indicated by higher T stage, vessel invasion, and nodal, peritoneal, and distant metastases. Low expression of serum miR-203 was correlated with poor disease-free survival and overall survival. This low expression was an independent predictive marker for metastases, including nodal, peritoneal, and distant metastases, and a poor prognosis in gastric cancer patients[62]. Therefore, various downregulated circulating miRNAs have been identified as blood-based prognostic biomarkers for gastric cancer: miR-15a, miR-93, miR-195-5p, miR-203, miR-204, miR-218 and miR-503 [Table 2][62,84,90,93,95,97,99].

DIFFERENT EXPRESSION LEVELS OF SOME CIRCULATING MIRNAS BETWEEN PLASMA AND SERUM IN GASTRIC CANCER

From the viewpoint of liquid biopsy using blood miRNAs, many issues must still be addressed before novel findings can be translated into clinically useful and noninvasive screening strategies for gastric cancer patients. Because plasma includes more abundant proteins, such as coagulation factors, than does serum, miRNA profiles in the plasma of cancer patients differ considerably from those in the serum[63], as has been shown in esophageal cancer[37,64] and pancreatic cancer[63]. In gastric cancer, the expression levels of some circulating miRNAs, such as miR-17, miR-92a, miR-93, and miR-106b, moved in opposite directions in the plasma and serum [Tables 1 and 2]. Although detailed mechanisms remain unknown, the data strongly suggest that these issues should be considered in future clinical applications of cancer treatments.

FUTURE PERSPECTIVES ON CIRCULATING TUMOR-SUPPRESSOR MICRORNAS FOR TREATMENT TARGETS IN GASTRIC CANCER

Multiple researchers have recently examined therapeutic miRNA-based drugs by using synthetic miRNA

mimics[101]. Various efforts have been made to develop miRNA-based therapies in the past several years, and two studies have shown particular promise. The first study focused on the therapeutic silencing of disease-associated miRNAs using miRNA inhibitors. Miravirsen (Santaris Pharma) is one of several promising miRNA inhibitors; it can bind to miR-122 and inhibit its biogenesis. Miravirsen was developed for the treatment of hepatitis C and is currently under evaluation in clinical trials[65-67]. The second study examined therapeutic miRNA-based drugs through the use of synthetic miRNA mimics. Recently, a phase I clinical trial using the miRNA mimic MIRX34 (Mirna Therapeutics, Inc.) was performed[68]. MIRX34 is a synthetic miRNA mimic of the tumor suppressor miR-34 and was administered to patients with primary or metastatic liver cancer. This trial was ended because of serious adverse immune-related effects. The administration of tumor-suppressor miRNA mimics continues to bear undesirable risks and negative, unexpected physiological effects because multiple genes, regulating multiple biological functions, can be impacted by miRNAs. Restoring tumor-suppressor miRNAs, which are abundantly detected in the plasma/serum of healthy individuals but lowered in patients with cancer [Table 2], may minimize the physiological risks of systemic administration. We recently reported that restoring and maintaining the miR-107 plasma level significantly inhibited tumor progression in mice[61]. The systemic delivery of tumor-suppressor miRNAs in gastric cancer patients may thus provide significant advantages because effects can be repeatedly examined repeatedly using blood-based miRNA levels.

CONCLUSION

The development of liquid biopsy-based analyses could improve diagnosis and therapy for patients with gastric cancer. As a liquid biopsy, circulating miRNAs have the potential to diagnose gastric cancer at an early stage, predict prognosis and recurrence, evaluate patient status and therapeutic efficacy, and provide optimal, individualized treatment strategies. It should be noted that the present review is limited by examining a relatively small number of retrospective cohort studies. Additional research with large cohorts or prospective clinical trials with longer follow-up periods are therefore necessary to confirm the usefulness of candidate miRNAs. Translation into clinically useful gastric cancer treatments also requires significant additional work. The physiological effects of tumor-suppressor miRNAs must be examined in greater detail before they can be safely administered systemically, and their tumor-suppressive functions must be validated *in vivo* before clinical use. Delivery systems for miRNAs must be further refined to surmount problems such as cellular uptake and bloodstream stability. Finally, more powerful anticancer tumor-suppressor miRNAs should be found by examining the plasma of patients with different cancers, through methods such as microarray analysis, next-generation sequencing, and digital PCR-based approaches. Currently under evaluation, these strategies will likely provide the future's next innovations.

DECLARATIONS

Authors' contributions

Designed the research and wrote the paper: Komatsu S
Collected the data and performed data analyses: Komatsu S, Kiuchi J, Imamura T
Reviewed the paper: Komatsu S, Ichikawa D, Otsuji E

Availability of data and materials

Not applicable.

Financial support and sponsorship

None.

Conflict of interest

All authors declared that there are no conflicts of interest.

Ethical approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

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