Circulating microRNAs as minimally invasive biomarkers for cancer theragnosis and prognosis

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INTRODUCTION
In terms of suffering and death, cancer is tragic yet partly preventable. The developments of valid biomarkers to prevent, detect, and treat this devastating disease can save millions of lives. However, the establishment of clinically validated biomarkers for cancer remains an insurmountable task despite the advances in molecular biology. An ideal tumor marker should be measured easily, reliably, and cost-effectively using a minimally invasive assay with high analytical sensitivity and specificity. Results of the last few years have ascertained the quantification of microRNA (miRNA) as a promising approach for the detection and prognostication of cancer. Indeed, an increasing number of studies have shown that circulating cancer-associated miRNAs are readily measured in plasma or serum and they can robustly discriminate cancer patients from healthy controls, as well as distinguishing between good-prognosis and poor-prognosis patients. Furthermore, recent findings also suggest the potential of circulating miRNAs in the screening, monitoring, and treatment of cancer. This article summarizes the most significant and latest discoveries of original researches on circulating miRNAs involvement in cancer, focusing on the potential of circulating miRNAs as minimally invasive biomarkers for cancer theragnosis and prognosis.

Keywords: blood-based biomarker, cancer, circulating microRNA, minimally invasive biomarker, molecular tumor marker, oncomir, prognosis, theragnosis

ROLE OF CIRCULATING miRNAs IN THE MOLECULAR PATHOGENESIS AND PROGRESSION OF CANCER
Previous study has suggested that profiling of circulating miRNAs may help identify promising biomarkers of various pathologic conditions (Ji et al., 2009). In the study of chronic lymphocytic leukemia (CLL), low expression of miR-29b, miR-29c, miR-181 family, and miR-223 were found to be strongly associated with disease progression in CLL cases harboring 17p deletion, whereas high expression of miR-181a in those harboring trisomy 12 suggested more aggressive disease. These biomarkers may be clinically useful to assess the tumor behavior in CLL (Visone et al., 2009). A pilot study also evaluated the circulating miRNAs associated with tumor progression in breast cancer patients. It provided evidence that the relative concentration of miR-155 in serum significantly discriminated primary breast cancer patients from healthy women. Within the primary breast cancer cohort, patients at advanced tumor stages had significantly higher miR-34a than patients at early tumor stages. In the metastatic patients, miR-10b, miR-34a, and miR-155 correlated with the presence of overt metastases (Roth et al., 2010).

DIAGNOSTIC AND PROGNOSTIC VALUE OF CIRCULATING miRNAs FOR CANCER
The releases of miRNAs from malignant cells in body fluids are candidate diagnostics for a variety of cancers. A recent study reported that the release of miRNAs from breast cancer cells into blood, milk, and ductal fluids was selective and that the selection of released miRNAs might correlate with malignancy. In particular, the bulk of miR-451 and miR-1246 produced by malignant mammary epithelial cells was released into the blood, but the majority of these miRNAs produced by non-malignant mammary epithelial cells was...
### Table 1 | A summary of the reported circulating microRNAs.

| MicroRNA       | Deregulation in cancer                                                                 | Theragnostic and prognostic value                                                                 | Sensitivity | Specificity | AUC       | P value  | Reference                      |
|----------------|--------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------|-------------|-------------|-----------|----------|--------------------------------|
| let-7a         | Decrease in gastric cancer                                                            | Discriminate gastric cancer from healthy controls                                              | –           | –           | –         | 0.002    | Tsujiura et al. (2010)          |
| let-7f         | Decrease in NSCLC                                                                     | Associated with overall survival in NSCLC                                                         | –           | –           | –         | 0.038    | Silva et al. (2011)             |
| miR-1          | Decrease in NSCLC                                                                     | Associated with overall survival in NSCLC                                                         | –           | –           | –         | <0.001   | Hu et al. (2010)                |
| miR-10b        | Increase in breast cancer                                                             | Associated with metastases in breast cancer                                                      | –           | –           | –         | 0.014    | Roth et al. (2010)              |
| miR-17         | Increase in gastric cancer                                                             | Discriminate gastric cancer from healthy controls                                              | 52%         | 93%         | 0.743     | 0.0001   | Zhou et al. (2010)              |
| miR-17 + 106a  | Increase in gastric cancer                                                             | Discriminate gastric cancer from healthy controls                                              | 63%         | 80%         | 0.741     | 0.0002   | Zhou et al. (2010)              |
| miR-17-3p      | Increase in CRC                                                                       | Discriminate CRC from healthy controls                                                         | 64%         | 70%         | 0.717     | <0.0001 | Ng et al. (2010)                |
| miR-17-5p      | Increase in gastric cancer                                                             | Discriminate gastric cancer from healthy controls                                              | –           | –           | –         | 0.05     | Tsujiura et al. (2010)          |
| miR-20b        | Decrease in NSCLC                                                                     | Associated with advanced stages and lymph node metastases in NSCLC                              | –           | –           | –         | <0.01    | Silva et al. (2011)             |
| miR-21         | Increase in CLL harboring 17p deletion                                                 | Associated with overall survival in CLL                                                          | –           | –           | –         | 0.033    | Rossi et al. (2010)             |
| miR-21 + 126 + 210 + 486-5p | Increase in gastric cancer                                                                 | Discriminate gastric cancer from healthy controls                                              | –           | –           | –         | 0.006    | Tsujiura et al. (2010)          |
| miR-21 + 155 + 196a + 210 | Increase in pancreatic adenocarcinoma                                                | Discriminate pancreatic adenocarcinoma from healthy controls                                   | 64%         | 89%         | 0.820     | <0.05    | Wang et al. (2009)              |
| miR-29a        | Increase in CRC                                                                       | Discriminate CRC from healthy controls                                                         | 69%         | 89%         | 0.844     | <0.0001 | Huang et al. (2010)             |
| miR-29a + 92a  | Increase in CRC                                                                       | Discriminate CRC from healthy controls                                                         | 83%         | 85%         | 0.883     | <0.0001 | Huang et al. (2010)             |
| miR-29b        | Decrease in CLL harboring 17p deletion                                                 | Associated with progression in CLL                                                              | –           | –           | –         | <0.01    | Visone et al. (2009)            |
| miR-29c        | Decrease in CLL harboring 17p deletion                                                 | Associated with progression in CLL                                                              | –           | –           | –         | 0.03     | Visone et al. (2009)            |
| miR-30a        | Increase in NSCLC                                                                     | Associated with overall survival in NSCLC                                                         | –           | –           | –         | <0.001   | Hu et al. (2010)                |
| miR-30a-3p     | Decrease in NSCLC                                                                     | Associated with short disease-free survival in NSCLC                                             | –           | –           | –         | 0.009    | Silva et al. (2011)             |
| miR-34a        | Increase in breast cancer                                                              | Discriminate advanced stages from early stages in breast cancer                                 | –           | –           | –         | 0.01     | Roth et al. (2010)              |
| miR-92         | Increase in CRC                                                                       | Discriminate CRC from gastric cancer, IBD, and healthy controls                                 | 89%         | 70%         | 0.885     | <0.0001 | Ng et al. (2009)                |
| miR-92a        | Increase in CRC                                                                       | Discriminate CRC from healthy controls                                                         | 84%         | 71%         | 0.838     | <0.0001 | Huang et al. (2010)             |
| miRNA | Change | Tissue | Discrimination | Sensitivity | Specificity | $p$-value | Reference |
|-------|--------|--------|----------------|-------------|-------------|-----------|-----------|
| miR-106a | Increase in gastric cancer | | Discriminate gastric cancer from healthy controls | 48% | 90% | 0.008 | Tsujiura et al. (2010) |
| miR-106a/let-7a | Increase/decrease in gastric cancer | | Discriminate gastric cancer from healthy controls | 86% | 80% | <0.001 | Tsujiura et al. (2010) |
| miR-106b | Increase in gastric cancer | | Discriminate gastric cancer from healthy controls | – | – | 0.721 | Tsujiura et al. (2010) |
| miR-107 | Increase in CN-AML patients aged ≥60 | Target NFIX in CN-AML | | – | – | | Schwind et al. (2010) |
| miR-144 | Decrease in CN-AML patients aged ≥60 | Associated with adverse prognostic marker FLT3ITD in CN-AML | – | – | <0.05 | Whitman et al. (2010) |
| miR-148a | Increase in CN-AML patients aged ≥60 | Target DNMT3B in CN-AML | | – | – | | Schwind et al. (2010) |
| miR-155 | Increase in CN-AML patients aged ≥60 | Associated with adverse prognostic marker FLT3ITD in CN-AML | – | – | <0.05 | Whitman et al. (2010) |
| | Increase in breast cancer | Discriminate primary breast cancer from healthy controls | – | – | 0.0001 | Roth et al. (2010) |
| | | Associated with metastases in breast cancer | – | – | 0.002 | Roth et al. (2010) |
| miR-181a | Increase in CLL harboring trisomy 12 | Associated with progression in CLL | – | – | <0.05 | Vison et al. (2009) |
| miRs-181a, b, c, d | Decrease in CLL harboring 17p deletion | Associated with progression in CLL | – | – | <0.03 | Vison et al. (2009) |
| miR-181b | Increase in CLL harboring trisomy 12 | miR-181b associated with treatment-free survival in CLL | – | – | 0.006 | Rossi et al. (2010) |
| miR-195 | Increase in breast cancer | Discriminate breast cancer from other cancers and from healthy controls | 88% | 91% | <0.001 | Heneghan et al. (2010a) |
| miR-200a | Increase in pancreatic cancer | Discriminate pancreatic cancer from healthy controls | 84% | 88% | 0.861 | Li et al. (2010) |
| miR-200b | Increase in pancreatic cancer | Discriminate pancreatic cancer from healthy controls | 71% | 97% | 0.850 | Li et al. (2010) |
| miR-208 | Increase in CN-AML patients aged ≥60 | Target ERG in CN-AML | – | – | | Schwind et al. (2010) |
| miR-223 | Decrease in CLL harboring 17p deletion | Associated with progression in CLL | – | – | 0.024 | Vison et al. (2009) |
| miR-302d | Decrease in CN-AML patients aged ≥60 | Associated with early developmental stages and stemness in CN-AML | – | – | <0.05 | Schwind et al. (2010) |

(Continued)
Table 1 | Continued

| MicroRNA | Theragnostic and prognostic value | AUC | P value | Sensitivity | Specificity | Reference |
|----------|----------------------------------|-----|---------|------------|-------------|-----------|
| miR-451  | Increase in breast cancer        |     | 0.05    | 1          | 1           | Pigati et al. (2010), Decrease in CN-AML patients aged ≥60 |
|          | Associated with malignancy in breast cancer |     | 0.01    | 1          | 1           | Hu et al. (2010) |
| miR-486  | Increase in NSCLC                |     | 0.001   | 1          | 1           | Hu et al. (2010) |
|          | Decrease in NSCLC                |     | 0.01    | 1          | 1           | Pigati et al. (2010) |
| miR-499  | Increase in breast cancer        |     | 0.001   | 1          | 1           | Hu et al. (2010) |
| miR-1246 | Increase in breast cancer        |     | 0.05    | 1          | 1           | Pigati et al. (2010) |

AUC, area under curve; CLL, chronic lymphocytic leukemia; CN-AML, cytogenetically normal acute myeloid leukemia; CRC, colorectal cancer; IBD, inflammatory bowel disease; ITD, internal tandem duplication; NSCLC, non-small cell lung cancer.

An investigation of plasma miRNAs in colorectal cancer (CRC) indicated that miR-29a and miR-92a could significantly discriminate neoplasia from healthy controls, and combined analyses using these two miRNAs revealed higher sensitivity and specificity. These data suggest that plasma miR-29a and miR-92a have strong potential as minimally invasive biomarkers for the detection of CRC (Huang et al., 2010). Another study found that plasma miR-92 also had significant diagnostic value for CRC. This biomarker could significantly differentiate CRC from gastric cancer, inflammatory bowel disease, and normal subjects, suggesting it to be a potential minimally invasive molecular marker for CRC diagnosis (Ng et al., 2009).

In the analysis of serum miRNAs, most pancreatic cancers displayed hypomethylation and over-expression of miR-200a and miR-200b, silencing of S1P1 by promoter methylation, and retention of E-cadherin expression. The elevated serum levels of miR-200a and miR-200b in most patients with pancreatic cancer may have diagnostic utility (Li et al., 2010). On the other hand, profiling of miR-21, miR-155, miR-196a, and miR-210 showed that miRNA profiling in plasma could also differentiate pancreatic adenocarcinoma patients from healthy controls. These results show the feasibility of developing plasma miRNA profiling as a sensitive and specific blood-based biomarker assay for pancreatic cancer that has the potential of translation to the clinic with additional improvements in the future (Wang et al., 2009). Similarly, the concentrations of miR-21, miR-17-5p, miR-106a, and miR-106b were significantly higher in gastric cancer patients than healthy controls, whereas let-7a was lower in gastric cancer patients. The levels of aberrantly expressing miRNAs were also significantly reduced in post-operative samples than pre-operative controls. These findings suggest that detection of circulating miRNAs may provide new complementary tumor markers for gastric cancer (Tsujiiura et al., 2010).

The identification of a patient who is prognostically good or poor is very important for the development of effective treatment approach (Cho, 2011a). Recent findings have revealed a great potential of circulating miRNA signatures as molecular fingerprints to predict survival of cancer patients. Genome-wide serum miRNA-expression analysis found that the levels of four miRNAs (miR-1, miR-30d, miR-486, and miR-499) were significantly associated with the overall survival of non-small cell lung cancer (NSCLC) patients. These four serum miRNA signatures may serve as an independent minimally invasive predictor for the overall survival of NSCLC (Hu et al., 2010). Moreover, the evaluation of plasma miRNAs also detected decreased levels of let-7f, miR-20b, and miR-30e-3p in the vesicles of NSCLC patients than healthy controls. The plasma levels of let-7f and miR-30e-3p were associated with overall survival and short disease-free survival, respectively. These results suggest that plasma vesicle-related miRNAs obtained by minimally invasive methods can serve as circulating tumor biomarkers of discriminating and prognostic values (Silva et al., 2011). On the other hand, quantitative reverse transcription-polymerase chain reaction (qRT-PCR) analysis in CLL patients with chromosome 17p deletion also found that miR-21 expression levels were significantly higher in patients with poor overall survival, whereas lower miR-181b...
expression levels significantly predicted treatment-free survival. A 21FK score (miR-21 qRT-PCR, fluorescence in situ hybridization, Karyotype) was developed to stratify patients according to overall survival and it was found to be a useful tool for distinguishing between good-prognosis and poor-prognosis CLL patients (Rossi et al., 2010).

**POTENTIAL OF CIRCULATING miRNAs IN SCREENING, MONITORING, AND TREATMENT OF CANCER**

Cancer is often diagnosed at a late stage with concomitant poor prognosis. Developing minimally invasive biomarkers that can diagnose cancer, particularly at an early stage, may improve its outcome. Evaluated by qRT-PCR, a panel of four plasma miRNAs (miR-21, miR-126, miR-210, and miR-486-5p) yielded 86% sensitivity and 97% specificity in distinguishing NSCLC patients from the healthy controls. Furthermore, the panel of miRNAs produced 73% sensitivity and 97% specificity in identifying stage I NSCLC patients. These results confirm that altered expressions of the miRNAs in plasma may provide potential blood-based biomarkers for NSCLC at an early stage (Shen et al., 2011).

To determine whether circulating miRNAs were tumor specific, a panel of oncomirs in the whole blood of pre-operative cancer patients (melanoma, breast, colon, prostate, and renal cancers) were assessed. Elevated circulating miR-195 was found to be breast cancer specific and it could significantly differentiate breast cancer from other cancers and from healthy controls (Heneghan et al., 2010a). Furthermore, the circulating levels of miR-195 and let-7a decreased in breast cancer patients post-operatively to levels comparable with healthy controls (Heneghan et al., 2010b). These findings suggest that circulating miRNAs have potential use as breast cancer biomarkers for early stage disease and they may also prove to be useful in clinical management during the peri-operative period. In fact, the detection of occult cancer cells in peripheral blood has recently received a great deal of attention regarding the prediction of post-operative cancer recurrence and for novel strategies of adjuvant therapy. In the peripheral blood samples from post-operative gastric cancer patients, the levels of miR-17 and miR-106a were significantly higher than those in healthy controls. These results indicate that the detection of miRNAs in peripheral blood may also be a tool for monitoring circulating tumor cells in patients with gastric cancer (Zhou et al., 2010).

In primary cytogenetically normal acute myeloid leukemia (CN-AML) patients aged 60–69 years, FLT3-internal tandem duplication (ITD) was found to be significantly associated with overall survival and shorter disease-free survival. It was revealed that FLT3-ITD-associated miRNA-expression signatures included over-expressed miR-155, as well as under-expressed miR-144 and miR-451. These miRNA-expression signatures may provide biologic insights for novel therapeutic approaches in older CN-AML patients with molecular high risk (Whitman et al., 2010). Conversely, low BAALC and ERG expression levels were identified to be associated with better outcome in older CN-AML patients aged ≥60 years. HOX genes and HOX-gene-embedded miRNAs were up-regulated in low BAALC expressers, whereas low ERG expressers presented with up-regulation of miR-148a which targeted DNMT3B. These miRNA-expression signatures may aid in identifying new targets and novel therapeutic strategies for older patients with low BAALC and ERG expressions (Schwind et al., 2010).

**CONCLUSION**

MicroRNA is a cutting-edge topic in the scientific and medical fields, the identification of oncomirs as blood-based biomarkers proceeds at a fast pace (Cho, 2011b). Numerous promising developments have been elucidated using omics technologies in cancer research (Cho, 2010d). The applications of microarray, microfluidics, nanofluidics, next generation sequencing, qRT-PCR, and bioinformatics have enabled the discoveries of a number of circulating miRNAs as potential biomarkers for cancer theragnosis and prognosis. These blood-based biomarkers have a revolutionary impact on cancer research over recent years. A number of circulating miRNAs have been found to be promising molecular tumor markers for early detection or survival prediction, some were even revealed to be involved in cancer progression or metastasis. The prospect for circulating miRNAs as minimally invasive biomarkers for cancer is excellent, although there are some challenges that the researchers have to conquer before these small non-coding RNAs can be fully understood and utilized (Cho, 2011c). With the accessibility of large sample sets, the range of technologies available, and the increasing evidences that there is a signature of changes derived by cancer in blood which may contribute to theragnosis and prognosis, all suggest that circulating miRNAs, perhaps accompanying other markers, will become widely used minimally invasive biomarkers for cancer in the future.

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