Journal of Leukemia
ISSN: 2329-6917

Cui and Lin, J Leuk 2014, 2:3
DOI: 10.4172/2329-6917.1000140

Mini Review Open Access

Circulating miRNAs: Potential Biomarkers for Diagnosis and Prognosis Prediction of Hematological Malignancies

Zhaolei Cui and Donghong Lin*

Department of Clinical Laboratory, School of Medical Technology and Engineering, Fujian Medical University, China

Abstract

MicroRNAs (miRNAs) are small non-coding, single-stranded, endogenous RNAs of 19-25nt in length. They are readily detected in body fluids including serum, plasma, urine, saliva, even circulating cancer cells. With the salient features as high stability, low cost, repeatability of sampling and minimal invasiveness, circulating miRNAs are ideal for development into diagnostic tests. Emerging evidences indicated that circulating miRNAs exert a role as noninvasive biomarkers for cancer diagnostic and prognostic indexes with prospective. In this mini review, emphasis will be given to the application of plasma or serum miRNAs as biomarkers for hematological malignancies focusing on the usefulness for diagnosis and prognosis.

Keywords: Circulating miRNAs; Biomarkers; Hematological malignancies; Diagnosis; Prognosis

Introduction

Malignant tumors have become the number one killer to human health. For its serological diagnosis, blood-based tumor markers, such as Carcinoembryonic Antigen (CEA), Prostate Specific Antigen (PSA) or Carbohydrate Antigen (CA) have gained a lot of recognition in the diagnosis and prognosis prediction of variety malignant neoplasm. Nevertheless, these protein biomarkers suffer from low sensitivity and specificity, especially with respect to their applications in screening for early phase carcinomas or incapability in distinguishing aggressive tumors from the indolent ones. Thus, discovering and developing new tumor biomarkers is a matter of great urgency in clinic.

MicroRNAs (miRNAs) are a class of short, non-coding, single stranded RNAs naturally occurring 19-25 nucleotide and are cleaved from 70-100 nucleotide hairpin precursors by a complex protein system that involves the ribonucleases (RNases) III Drosha and Dicer, Pol-II-dependent transcription and members of the argonaute family [1,2]. This kind of nucleotides have proven to be essential and indispensable in the regulation of gene expression by base pairing with the 3'-untranslated region of a target gene's mRNA, leading to translational inhibition and/or degradation of the target genes. Since their discovery, miRNAs expression profiles in various tumor lesions compared to healthy tissues had been reported to associate with patients' survival and prognosis, which also caused widespread concern of the researchers [3-8].

It has been demonstrated that some miRNAs presented in body fluids such as plasma, serum, urine and saliva in a stable and reproducible fashion, as they are protected from degradation by association with secreted membrane vesicles and/or RNA-binding proteins [9]. Conveniently, such circulating miRNAs released from tumor cells into the body fluids can be measured repeatedly and non-invasively. To date, abnormal serum or plasma concentrations of cell-free miRNAs have been identified in a wide array of cancer types and correlated with patients' survival as well as prognosis [10-15]. In this short review, we have summarized the current reported circulating miRNAs (Table 1) that related to the diagnosis and prognosis in hematological malignancies.

Circulating miRNAs in Hematological Malignancies

A bunch of miRNAs have been demonstrated to be aberrantly expressed in body fluids including serum and plasma. Circulating miRNAs from serum or plasma are in close contact with their cellular counterpart and could easily reflect any abnormality of body blood cells. Therefore, such miRNAs are considered as important indicators to assess the diagnosis and prognosis of patients with hematological malignancies, including Malignant Lymphoma (ML), Acute Myeloid Leukemia (AML), Multiple Myeloma (MM) and Chronic Lymphocytic Leukemia (CLL), etc. At present, only miR-155 is the ultimate common miRNA involved in the above hematological malignancies. As reported, miR-155 plays a crucial role in the pathogenesis of hematological malignancies through regulating cell signal transduction pathways of cell proliferation, differentiation and apoptosis [16].

Diffuse Large B-Cell Lymphoma (DLBCL) is the most commonly-occurring type of Non-Hodgkin's Lymphoma (NHL) and is regarded as a curable disease with a recovery rate of more than 50%. Early investigations had verified that miR-155, miR-21, and miR-210 were higher in the serum of DLBCL patients than in healthy controls [17]. Later, except miR-155, other known tumour-associated miRNAs: miR-15a, miR-16-1, miR-29c and miR-34a [18] in his study, expression of serum miR-15a, miR-16-1, miR-29c, and miR-155 were significantly elevated in DLBCL patients when compared with normal controls, while miR-34a was declined [18]. Since the miR-17-92 polycistronic miRNA cluster exerts a crucial role in both lymphomagenesis and neo-angiogenesis, one study reported the diagnostic as well as the prognostic value of plasma miR-92a which exhibited extremely lower levels in NHL; additionally, miR-92a evinced a strong correlation to relapse rates among patients [19]. Another study by Guo et al. measured plasma miR-221 in natural killer T-Cell (NK/T-cell) lymphoma, with a result that plasma miR-221 was able to distinguish patients from controls, and the research also demonstrated the prognostic value of miR-221 correlated to overall survival [20].

***Corresponding author:** Donghong Lin, Department of Clinical Laboratory, School of Medical Technology and Engineering, Fujian Medical University, 88 Jiaotong Road, Taijiang, Fuzhou, Fujian 350004, P.R. China, Tel: +86059183569212; E-mail: Donghonglin65@163.com

Received June 09, 2014; **Accepted** June 20, 2014; **Published** July 02, 2014

Citation: Cui Z, Lin D (2014) Circulating miRNAs: Potential Biomarkers for Diagnosis and Prognosis Prediction of Hematological Malignancies. J Leuk 2: 140. doi:10.4172/2329-6917.1000140

miRNA	Cancer	miRNA levels	Type of biomarker	References
miR-15a	DLBCL	Increased	Diagnostic	[18]
miR-16-1	DLBCL	Increased	Diagnostic	[18]
miR-21	DLBCL	Increased	Diagnostic	[17]
miR-29c	DLBCL	Increased	Diagnostic	[18]
miR-155	DLBCL	Increased	Diagnostic	[17,18]
miR-210	DLBCL	Increased	Diagnostic	[17]
miR-221	DLBCL	Increased	Diagnostic and prognostic; correlated to OS	[20]
miR-34a	DLBCL	Decreased	Diagnostic and prognostic; correlated to OS	[18]
miR-92a	NHL	Decreased	Diagnostic and predictive; correlated to RFS	[19]
miR-10a-5p	AML	Increased	Diagnostic	[24]
miR-21	AML	Increased	Diagnostic	[22]
miR-93-5p	AML	Increased	Diagnostic	[24]
miR-129-5p	AML	Increased	Diagnostic	[24]
miR-155	AML	Increased	Diagnostic	[22]
miR-155-5p	AML	Increased	Diagnostic	[24]
miR-181b-5p	AML	Increased	Diagnostic and prognostic; correlated to OS	[24]
miR-210	AML	Increased	Diagnostic	[22]
miR-221	AML	Increased	Diagnostic	[22]
miR-320d	AML	Increased	Diagnostic	[24]
miR-523	AML	Increased	Diagnostic	[23]
let-7b	AML	Increased	Diagnostic	[23]
miR-92a	AML	Decreased	Diagnostic; ratio of miR-92a/ miR-638 for diagnosis	[21]
miR-150	AML	Decreased	Diagnostic	[23]
let-7d	AML	Decreased	Diagnostic	[23]
miR-10b	MM	Increased	Diagnostic	[9]
miR-20a	MM	Increased	Diagnostic and prognostic; correlated to shorter RFS	[28]
miR-21	MM	Increased	prognostic	[30]
miR-29a	MM	Increased	Diagnostic	[29]
miR-34a	MM	Increased	Diagnostic	[9]
miR-99b	MM	Increased	Diagnostic	[28]
miR-138	MM	Increased	Diagnostic	[9]
miR-142-5P	MM	Increased	Diagnostic	[29]
miR-148a	MM	Increased	Diagnostic and prognostic; correlated to shorter RFS	[28]
miR-181a	MM	Increased	Diagnostic	[28]
miR-218	MM	Increased	Diagnostic	[9]
miR-221	MM	Increased	Diagnostic	[28]
miR-222	MM	Increased	Diagnostic	[9]
miR-625	MM	Increased	Diagnostic	[28]
miR-660	MM	Increased	Diagnostic	[29]
miR-1243	MM	Increased	Diagnostic	[9]
miR-1274A	MM	Increased	Diagnostic	[9]
miR-1308	MM	Increased	Diagnostic; distinguish MGUS from MM	[26]
miR-103	MM	Decreased	Diagnostic	[9]
miR-130a	MM	Decreased	Diagnostic	[9]
MiR-151-5P	MM	Decreased	Diagnostic	[9]
miR-191	MM	Decreased	Diagnostic	[9]
miR-720	MM	Decreased	Diagnostic	[26]
miR-744	MM	Decreased	Diagnostic and prognostic; correlated to OS	[9]
miR-1246	MM	Decreased	Diagnostic; distinguish MGUS from MM	[26]
let-7d	MM	Decreased	Diagnostic	[9]
let-7e	MM	Decreased	Diagnostic and prognostic; correlated to OS	[9]
miR-1308	MGUS	Increased	Diagnostic; distinguish MGUS from MM	[26]
miR-720	MGUS	Decreased	Diagnostic	[26]
miR-1246	MGUS	Decreased	Diagnostic; distinguish MGUS from MM	[26]
miR-155	CLL	Increased	prognostic	[31]
miR-155	MBL	Increased	prognostic	[31]

Table 1: Circulating miRNAs reprted to be a biomarker for hematological malignancies (involved some pre-cancerous hematological diseases). Abbreviations: DLBCL, diffuse large B cell lymphoma; AML, acute myeloid leukemia; MM, multiple myeloma; MGUS, monoclonal gammopathy of undetermined significance; CLL, chronic lymphocytic leukemia; NHL, non-Hodgkin's lymphoma; MBL, B-cell lymphocytosis; OS, overall survival; RFS, relapse-free survival.

Currently, many research groups have also reported on the close relationships between circulating miRNA and the pathogenesis, diagnosis, even prognosis of AML. As early as 2009, with the aid of TaqMan miRNA microarray technique, the investigators had found miR-92a dramatically decreased in the plasmas of AML patients; although miR-638 was stably presented in human plasmas, the ratio of miR-92a/miR-638 in plasma had strong potential for clinical application in the detection of leukemia [21]. In pediatric AML, researchers finally observed the serum levels of miR-155, miR-21, miR-210 and miR-221 were elevated [22]. Presently, Fayyad-Kazan et al. reported the expression level of let-7d, miR-150, miR-339, and miR-342 in plasma were decreased whilst that of let-7b, and miR-523 were increased in the AML patients; in addition to its diagnostic proficiency, the data indicated that plasma miR-150 and miR-342 are novel important promising biomarkers in the diagnosis of AML as well [23]. More recently, an additional investigation validated six miRNAs as miR-10a-5p, miR-93-5p, miR-129-5p, miR-155-5p, miR-181b-5p and miR-320d, with significantly increased levels detected in AML compared with control serum samples, among which, miR-181b-5p levels in serum were significantly associated with overall survival [24].

Multiple Myeloma (MM) is a plasma cell malignancy accounts for more than 10% of hematological malignancies [25]. As we know, MM evolves from a pre-malignant condition called Monoclonal Gammopathy of Undetermined Significance (MGUS) which progresses to MM at a rate of 1% in average [9,26]. It is noteworthy that breakthroughs are recently announced for the circulating miRNAs used as new prognosticators for MM [27]. In a former study, three serum microRNAs, miR-720, miR-1308 and miR-1246 were found to have potential as diagnostic biomarkers in MM, in which, miR-720 and miR-1246 generally decrease in MGUS and MM patients. Importantly, miR-720 and miR-1308 together provides a powerful diagnostic tool for distinguishing normal healthy controls, as well as patients with unrelated illnesses, from pre-cancerous myeloma and myeloma patients, while miR-1246 and miR-1308 can distinguish MGUS from MM patients [26]. A study from Huang et al. disclosed that more than 135 miRNA molecules were detected in plasma, of which, six miRNA (miR-148a, miR-20a, miR-99b, miR-221, of miR-181a and miR-625) were significantly elevated in MM patients. Notably, high levels of miR-20a and miR-148a were related to shorter relapse-free survival [28]. Kubiczkova and his colleagues lately reported seven upregulated miRNAs (miR-222, miR-218, miR-34a, miR-1274A, miR-138, miR-10b, miR-1243) and seven downregulated (miR-103, miR-191, miR-130a, let-7d, let-7e, miR-744, miR-151-5p) miRNAs in MM patient

serum, with lower levels of miR-744 and let-7e were associated with shorter overall survival and remission of MM patients. Simultaneously, their data revealed five deregulated miRNAs covered miR-744, miR-130a, miR-34a, let-7d and let-7e in MGUS patients [9]. In addition, the increase of serum miR-142-5p, miR-660 and miR-29a in MM patients were also been validated, of which, miR-29a proved its potent role in discriminating MM sera from healthy controls [29]. Since miR-21 was found to be related with malignant characteristic including tumorigenesis, invasion, and apoptosis resistance, another report from Wang et al. also revealed that circulating miR-21 expression level was significantly upregulated in patients with MM and involved in progression of MM [30].

There has been very little research of circulating miRNAs in Chronic Lymphocytic Leukemia (CLL) and B-cell lymphocytosis. Currently, only miR-155 was identified in circulating microvesicles from individuals with MBL and CLL. The prognostic role of plasma miR-155 in CLL was reflected that patients who failed to achieve a complete response exhibited higher miR-155 expression levels when compared with those who experienced complete respons, and it can be regarded as biomarkers for the risk of progression in MBL as well [31].

Conclusions and Perspective

For the diagnosis of hematological malignancies, obtaining a marker from the bone marrow is an invasive procedure for patients, so it is imperative that a minimally invasive, repeatable test that can be discovered and constructed. There is now a greater possibility of employing serum or plasma miRNAs as applicable biomarkers for cancer diagnosis and prognosis. So, circulating miRNAs reveal a tremendous prospect to be developed as useful cancer biomarkers, which heralding a new era in the diagnosis and treatment for tumor in future. Nevertheless, some of the miRNAs such as miR-155, seems to be prevalent and is associated with different hematological malignancies. Other miRNAs as miR-21 and miR-221 also cover a broad spectrum of hematological neoplasms, hinting a lacking of specificity in clinic diagnosis. Hence, the use of circulating miRNAs as diagnostic biomarkers is a double edged sword which still warrants further investigations.

References

1. Calin GA, Croce CM (2006) MicroRNA signatures in human cancers. Nat Rev Cancer 6: 857-866.
2. Marcucci G, Mrózek K, Radmacher MD, Bloomfield CD, Croce CM (2009) MicroRNA expression profiling in acute myeloid and chronic lymphocytic leukaemias. Best Pract Res Clin Haematol 22: 239-248.
3. Yong FL, Law CW, Wang CW (2013) Potentiality of a triple microRNA classifier: miR-193a-3p, miR-23a and miR-338-5p for early detection of colorectal cancer. BMC Cancer 13: 280.
4. Li W, Xie L, He X, Li J, Tu K, et al. (2008) Diagnostic and prognostic implications of microRNAs in human hepatocellular carcinoma. Int J Cancer 123: 1616-1622.
5. Li Y, Xu Z, Wang K, Wang N, Zhu M (2013) Network analysis of microRNAs, genes and their regulation in human bladder cancer. Biomed Rep 1: 918-924.
6. Song S, Zhou J, He S, Zhu D, Zhang Z, et al. (2013) Expression levels of microRNA-375 in pancreatic cancer. Biomed Rep 1: 393-398.
7. Lodewijk L, Prins AM, Kist JW, Valk GD, Kranenburg O, et al. (2012) The value of miRNA in diagnosing thyroid cancer: a systematic review. Cancer Biomark 11: 229-238.
8. Gailhouste L, Ochiya T (2013) Cancer-related microRNAs and their role as tumor suppressors and oncogenes in hepatocellular carcinoma. Histol Histopathol 28: 437-451.
9. Kubiczkova L, Kryukov F, Slaby O, Dementyeva E, Jarkovsky J, et al. (2014) Circulating serum microRNAs as novel diagnostic and prognostic biomarkers for multiple myeloma and monoclonal gammopathy of undetermined significance. Haematologica 99: 511-518.
10. Mar-Aguilar F, Mendoza-Ramírez JA, Malagón-Santiago I, Espino-Silva PK, Santuario-Facio SK, et al. (2013) Serum circulating microRNA profiling for identification of potential breast cancer biomarkers. Dis Markers 34: 163-169.
11. Boeri M, Verri C, Conte D, Roz L, Modena P, et al. (2011) MicroRNA signatures in tissues and plasma predict development and prognosis of computed tomography detected lung cancer. Proc Natl Acad Sci U S A 108: 3713-3718.
12. Liu H, Zhu L, Liu B, Yang L, Meng X, et al. (2012) Genome-wide microRNA profiles identify miR-378 as a serum biomarker for early detection of gastric cancer. Cancer Lett 316: 196-203.
13. Nguyen HC, Xie W, Yang M, Hsieh CL, Drouin S, et al. (2013) Expression differences of circulating microRNAs in metastatic castration resistant prostate cancer and low-risk, localized prostate cancer. Prostate 73: 346-354.
14. Zhao A, Li G, Péoc'h M, Genin C, Gigante M (2013) Serum miR-210 as a novel biomarker for molecular diagnosis of clear cell renal cell carcinoma. Exp Mol Pathol 94: 115-120.
15. Allegra A, Alonci A, Campo S, Penna G, Petrungaro A, et al. (2012) Circulating microRNAs: new biomarkers in diagnosis, prognosis and treatment of cancer Int J Oncol41: 1897-1912.
16. Seddiki N, Brezar V, Ruffin N, Lévy Y, Swaminathan S (2014) Role of miR-155 in the regulation of lymphocyte immune function and disease. Immunology 142: 32-38.
17. Lawrie CH, Gal S, Dunlop HM, Pushkaran B, Liggins AP, et al. (2008) Detection of elevated levels of tumour-associated microRNAs in serum of patients with diffuse large B-cell lymphoma. Br J Haematol 141: 672-675.
18. Fang C, Zhu DX, Dong HJ, Zhou ZJ, Wang YH, et al. (2012) Serum microRNAs are promising novel biomarkers for diffuse large B cell lymphoma. Ann Hematol 91: 553-559.
19. Ohyashiki K, Umezu T, Yoshizawa S, Ito Y, Ohyashiki M, et al. (2011) Clinical impact of down-regulated plasma miR-92a levels in non-Hodgkin's lymphoma. PLoS One 6: e16408.
20. Guo HQ, Huang GL, Guo CC, Pu XX, Lin TY (2010) Diagnostic and prognostic value of circulating miR-221 for extranodal natural killer/T-cell lymphoma. Dis Markers 29: 251-258.
21. Tanaka M, Oikawa K, Takanashi M, Kudo M, Ohyashiki J, et al. (2009) Down-regulation of miR-92 in human plasma is a novel marker for acute leukemia patients. PLoS One 4: e5532.
22. Xie H, Chu Z, Wang H (2012) Serum microRNA expression profile as a biomarker in diagnosis and prognosis of acute myeloid leukemia. J Clin Pediatr 30:421-424.
23. Fayyad-Kazan H, Bitar N, Najar M, Lewalle P, Fayyad-Kazan M, et al. (2013) Circulating miR-150 and miR-342 in plasma are novel potential biomarkers for acute myeloid leukemia. J Transl Med 11: 31.
24. Zhi F, Cao X, Xie X, Wang B, Dong W, et al. (2013) Identification of circulating microRNAs as potential biomarkers for detecting acute myeloid leukemia. PLoS One 8: e56718.
25. Kyle RA, Rajkumar SV (2008) Multiple myeloma. Blood 111: 2962-2972.
26. Jones CI, Zabolotskaya MV, King AJ, Stewart HJ, Horne GA, et al. (2012) Identification of circulating microRNAs as diagnostic biomarkers for use in multiple myeloma. Br J Cancer 107: 1987-1996.
27. Rocci A, Hofmeister CC, Geyer S, Stiff A, Gambella M, et al. (2014) Circulating miRNA markers show promise as new prognosticators for multiple myeloma. Leukemia.
28. Huang JJ, Yu J, Li JY, Liu YT, Zhong RQ (2012) Circulating microRNA expression is associated with genetic subtype and survival of multiple myeloma. Med Oncol 29: 2402-2408.
29. Sevcikova S, Kubiczkova L, Sedlarikova L, Slaby O, Hajek R (2013) Serum miR-29a as a marker of multiple myeloma. Leuk Lymphoma 54: 189-191.
30. Wang X, Li C, Ju S, Wang Y, Wang H, et al. (2011) Myeloma cell adhesion to bone marrow stromal cells confers drug resistance by microRNA-21 up-regulation. Leuk Lymphoma 52: 1991-1998.
31. Ferrajoli A, Shanafelt TD, Ivan C, Shimizu M, Rabe KG, et al. (2013) Prognostic value of miR-155 in individuals with monoclonal B-cell lymphocytosis and patients with B chronic lymphocytic leukemia. Blood 122: 1891-1899.