Review Article

Stem Cell INVESTIGATION

MicroRNAs as biomarkers in leukemia

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Abstract: Current diagnostic and prognostic markers still exhibit biological limitation and seeking novel molecular biomarkers is crucial for early clinical diagnosis and in the development of novel strategies for leukemia therapy. Emerging evidence showed that dysregulated microRNAs (miRNAs) play important roles in cancer including leukemia. In this review, we summarized recent progress on the role of miRNAs in leukemia, mainly focusing on recent findings that suggest the potential of miRNAs as biomarkers for diagnosis and prognosis. Notably, the circulating miRNAs were also discussed for the fact that they can be detected in body fluids, and thus represent a novel source of promising biomarkers that may be applied to clinical settings.

Keywords: MicroRNA (miRNAs); biomarker; leukemia

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Introduction

MicroRNAs (miRNAs) are a novel class of endogenous non-coding RNAs ranging from 19 to 25 nucleotides in size, which regulate gene expression primarily at the post-transcriptional level and thus are involved in many cellular processes, such as cell proliferation, differentiation, and apoptosis (1-3). Recent studies have shown that dysregulated expression of specific miRNAs that function as tumor suppressors or oncogenes is associated with the pathogenesis of human cancers and that specific miRNA expression signatures can be used to effectively classify human tumors (4-6). MiRNAs associated with specific cytogenetic changes and clinical outcomes of different subtypes of leukemia have been reported, demonstrating miRNAs have the potential to be used for clinical diagnosis, prognosis and cancer therapy (7-13).

Human leukemia is classified into acute leukemia and chronic leukemia clinically and pathologically, however, evidence suggests that all leukemia derives from a common leukemic stem cell (LSC) (14). Leukemia is characterized by the abnormal proliferation of blood precursor cells of myeloid or lymphoid origin and the number one cancer killer of children less than 14 years of age (15). Recently, biomarkers of different leukemia subtypes based on genetic, phenotypic, or molecular characteristics have been reported. For examples, the expression of CD38 and ZAP-70 can be used as prognostic marker in chronic lymphocytic leukemia (CLL), while the mutational status of NPM1, FLT3, CEBPA, and MLL are associated with the outcome of treatment for patients with cytogenetically normal acute myeloid leukemia (AML) and can be used to identify AML patients who will benefit from allogeneic stem cell transplantation (SCT) (16,17).

More recently, studies found that miRNAs and long non-coding RNAs (lncRNAs) can be used as biomarkers for diagnosis and prognosis in cancer, revealing that they are a novel source of biomarkers that may be applied to clinical setting (18-21). Here we will review the role of miRNAs in leukemia, mainly focusing on recent findings that suggest the potential of miRNAs as biomarkers for diagnosis and prognosis (*Table 1*). Moreover, the circulating miRNAs were

Table 1 MiRNAs as diagnostic and prognostic biomarkers in leukemia

miRNA	Expression	Biomarker	References
miR-128a, miR-128b	Upregulated in ALL *vs.* AML	Diagnostic	(22,23)
let-7b, miR-223	Downregulated in ALL *vs.* AML		
miR-181a	Upregulated in M1/M2 *vs.* M4/M5	Diagnostic	(23,24)
miR-29a, miR-142-3p	Downregulated in AML	Diagnostic	(25)
miR-424	Downregulated in AML with NPM1mutA	Diagnostic	(26)
miR-155	Upregulated in FLT3-ITD mutation positive AML		
miR-181, miR-30d, let-7a, miR-125b	Downregulated in CLL	Diagnostic	(27,28)
miR-326	Downregulated in CML	Diagnostic	(29)
miR-148, miR-424	Upregulated in T-lineage *vs.* B-lineage ALL	Diagnostic	(30)
miR-151	Downregulated in T-lineage *vs.* B-lineage ALL		
miR-191, miR-199a, miR-181a, miR-181b	Upregulated in AML	Prognostic	(10,23,31)
miR-155	Upregulated in FLT3-ITD mutation positive AML	Prognostic	(23)
miR-375, miR-378, miR-212, miR-9	Upregulated in AML	Prognostic	(32-35)
miR-29b	Downregulated in AML	Prognostic	(36)
miR-181b, miR-223	Downregulated in CLL	Prognostic	(37-40)
miR-21	Upregulated in CLL	Prognostic	(40)
miR-196b	Upregulated in MLL-associated AML	Prognostic	(41)
miR-150, miR-146a	Upregulated in CML	Prognostic	(42)
miR-142-3p, miR-199b-5p	Downregulated in CML		
Circulating miR-92a	Downregulated in acute leukemia	Diagnostic	(43,44)
Circulating miR-150, miR-342	Downregulated in AML	Diagnostic	(45)
Circulating miR-181b-5p	Upregulated in AML	Prognostic	(46)
Circulating miR-195, miR-29a, miR-222, miR-20a, miR-155	Upregulated in B-cell CLL	Diagnostic	(47,48)
Circulating miR-155	Upregulated in T-cell leukemia	Prognostic	(49)

MiRNAs, microRNAs; ALL, acute lymphoblastic leukemia; AML, acute myeloid leukemia; ITD, internal tandem duplications; CLL, chronic lymphocytic leukemia; CML, chronic myelogenous leukemia.

also emphasized for the fact that they can be detected in body fluids making them suitable to serve as biomarkers.

MiRNAs as diagnostic biomarkers

Some studies have revealed that miRNAs may serve as biomarkers in clinical diagnosis. Mi *et al*. demonstrated that miR-128a, miR-128b, let-7b and miR-223 were the most significant and discriminatory between AML and acute lymphoblastic leukemia (ALL) (22). Moreover, large-scale real-time PCR analysis using two of these four miRNAs in the diagnosis of 98 ALL and AML cases could result in an accuracy rate as high as 97-100%, which provides new potential markers for the classification and diagnosis of ALL and AML (22). Zhu *et al*. further confirmed that miR-128, let-7b, miR-223 and miR-181a have a diagnosis value in acute leukemia patients (23). Another study demonstrated that a better diagnostic outcome was achieved by combining miR-29a and miR-142-3p with about 90% sensitivity, 100% specificity, indicating that the expression level of miR-142-3p and miR-29a in peripheral blood mononuclear cells (PBMNC) could be used as novel

diagnostic marker in AML (25). Debernardi *et al.* revealed that miR-181a correlated strongly with the AML morphological subtype (24). It was also found that miR-424 was down-regulated in AML patients with NPM1mutA regardless of FLT3 status, while miR-155 showed up-regulation in patients with FLT3 internal tandem duplications (ITD) with or without NPM1 mutations, suggesting that miR-424 and miR-155 deregulation is involved in the pathogenesis of cytogenetically normal AML with NPM1 and FLT3-ITD mutations, respectively (26). Interestingly, another study reported that the expression signatures of miR-22 and its host gene C17orf91 are associated with specific myeloid leukemia subtypes, implicating their potential application for the classification of leukemia (50).

In CLL, Marton *et al*. identified several miRNAs including miR-181, miR-30d and let-7a that are differentially expressed between CLL lymphocytes and CD19+ control cells (27). Tili *et al*. found that both aggressive and indolent CLL patients show reduced expression of miR-125b and defined a miR-125b-dependent CLL metabolism-related transcript signature, suggesting miR-125b acts as a master regulator and could be an indicator for the adaptation of cell metabolism to a transformed state in CLL (28). In chronic myelogenous leukemia (CML), downregulation of miR-326 may be a possible mechanism for unrestricted activation of Smo signal transducer of the oncogenic Hh pathway and resulted in elevated cell proliferation and decreased rate of apoptosis in CML CD34(+) cells (29). In ALL, miR-148, miR-151 and miR-424 were identified as discriminative of T-lineage versus B-lineage ALL (30).

MiRNAs as prognostic biomarkers

Accumulating evidence has shown that miRNAs can be used as biomarkers to predict the prognosis of patients. In AML, Garzon *et al*. demonstrated that a subset of deregulated miRNAs is associated with outcome and AML patients with high expression of miR-191 and miR-199a had significantly worse overall and event free survival than patients with low expression (10). Another study identified a miRNA signature which was associated with event-free survival in cytogenetically normal AML patients with high-risk molecular features (FLT3-ITD, a wild-type NPM1, or both) and found increased miR-181a and miR-181b were significantly associated with a favorable prognosis (31). Zhu *et al*. also found high expression of miR-181a suggested a better prognosis, while miR-155 can lead to increased myeloid progenitor cells, which may be related to poor prognosis in AML (23). High miR-375 expression was found significantly associated with shorter relapse-free survival (RFS) and overall survival (OS) in pediatric AML patients, demonstrating it may be a novel biomarker to improve the management of pediatric AML patients (32). Overexpression of miR-378 is frequent and may affect treatment outcomes in AML patients, suggesting that miR-378 might have an adverse impact on prognosis in AML (33). Using a large AML patient cohort, miR-212 was found significantly associated with a prolonged OS and RFS, while miR-9 and miR29b indicate poor prognosis in AML (34-36). Using a 45-miRNA profile, Templin *et al*. can predict the class membership of acute leukemia samples with unknown irradiation status, with accuracies of 100%, supporting that the miRNA expression signature can be used as biomarkers of radiation exposure (51).

It has been found that during the course of CLL, miR-181b decreased in samples of patients with a progressive but not in samples of patients with a stable disease over time, and miR-181b can be as an independent biomarker for the progression of this disease from indolent to aggressive (37,38). Multivariate analysis revealed that the absence of miR-223 was the only independent factor capable of predicting shorter PFS and is a useful biomarker for patients with CLL (39). Another study reported that miR-21 expression levels were significantly higher in CLL patients with poor prognosis and predicted OS, and miR-181b expression levels significantly predicted treatment-free survival, indicating they are prognostic factors (40).

Interestingly, studies showed that a 14-miRNA signature was epigenetically regulated in ALL patients and the methylation status of these miRNAs is a good predictor of ALL outcome after SCT, suggesting that the epigenetic biomarkers have prognostic significance and could improve the stratification of patients into risk groups (52). However, miR-196b resulted in more aggressive leukemic phenotypes and caused much faster leukemogenesis in secondary transplantation than MLL fusion alone in MLL-rearranged leukemia (41). Flamant *et al*. found increased expression of miR-150 and miR-146a, and reduced expression of miR-142-3p and miR-199b-5p after two weeks of imatinib therapy for CML, suggesting that these miRNAs may serve as a novel clinically useful biomarker in CML (42). Analysis of miR-16 expression level in 72 patients with T-lymphoblastic lymphoma/leukemia showed miR-16 is associated with clinical outcome and may be considered as a potential prognostic marker for T-lymphoblastic

lymphoma/leukemia (53).

Circulating miRNAs as diagnostic and prognostic biomarkers

Recent studies have suggested improvements in detecting malignancies using specific extracellular miRNAs in body fluids and circulating miRNAs might be a new class of effective biomarkers (54).

It has been revealed that miR-92a is dramatically decreased in the plasma of acute leukemia patients and the ratio of miR-92a/miR-638 in plasma is very useful for distinguishing leukemia patients from healthy subjects, thus the ratio of miR-92a/miR-638 has strong potential for clinical application as a novel biomarker for detection of leukemia (43). Another study compared miR-92a expression in plasma with its expression in acute leukemia cells and found that the cell to plasma ratio of miR-92a expression was significantly higher in both AML and ALL cells compared with PBMNC from healthy volunteers, implying the ratio of miR-92a expression is a novel blood based leukemia biomarker (44). By analyzing the profile of circulating miRNAs in the plasma of AML patients compared with healthy individuals, it was found that the combination of plasma miR-150 and miR-342 is a novel candidate diagnostic biomarker of AML and potential predictor of relapse (45). Zhi *et al*. revealed the remarkable ability of a 6-miRNA profile to differentiate between AML and normal controls. Especially, miR-181b-5p level in serum is significantly associated with OS, demonstrating miR-181b-5p may serve as a predictor for OS in AML patients (46).

A recent study reported that circulating miR-195, miR-29a and miR-222 levels are the best classifiers to separate B-cell CLL patients from healthy controls. When combining the levels of several miRNAs, including miR-29a, miR-483–5p, miR-195, miR-185, miR-135a* and miR-15a, it provides good separation between ZAP-70+ and ZAP-70– samples and miR-29a is the single best predictor for ZAP-70 expression status. Notably, the level of circulating miR-20a was determined to correlate reliably with diagnosis-to-treatment time (47). To examine the prognostic role of miR-155, Ferrajoli *et al*. measured its expression level in plasma samples of 228 newly diagnosed B-cell CLL patients and found plasma level of miR-155 can be used as biomarker to identify patients with CLL that may not respond well to therapy (48). In adult T-cell leukemia, the elevation of plasma miR-155 and the reduction in miR-126 correlate with poor prognosis, indicating they are novel biomarkers for the assessment of disease stage (49).

Conclusions and perspectives

Improving early cancer detection and diagnosis are critical to successful cancer treatment. Studies have revealed miRNAs function as important regulators in gene regulatory networks and exert crucial roles in cancer progression. Mounting evidence showed that miRNAs have great potential as biomarkers and targets for novel therapeutic approaches in the future. More importantly, recent studies demonstrated that circulating miRNA profiles in plasma and serum reflect physiological or pathological conditions, exhibiting they might be a new class of effective biomarkers. So far, unique miRNA patterns and molecular mechanisms of some miRNAs in different cancers and diseases have been fully studied. It should be noted that some miRNAs have similar expression levels and functions in different cancers or cancer subtypes. It is necessary to further validate the reproducibility and reliability of miRNAs as biomarkers for diagnosis and prognosis in a large scale of clinical samples, making it possible to widely use these miRNAs as biomarkers to detect multiple cancers. It remains a significant challenge to translate the basic research to the clinical setting, however, the important roles of miRNAs in cancer have shed light on their potential applications and will ultimately provide novel strategies for cancer diagnosis and therapy.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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