Meta Gene 16 (2018) 182–188

Contents lists available at ScienceDirect

Meta Gene

journal homepage: www.elsevier.com/locate/mgene

Differential expression profiles of miRNAs and correlation with clinical outcomes in acute myeloid leukemia

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ARTICLE INFO

Keywords:
microRNA expression
acute myeloid leukemia
clinical outcomes
cancers

ABSTRACT

Background: MicroRNAs (miRNAs) are known for their pivotal roles in the regulation of gene expression through degradation or translational repression of their target messenger RNAs (mRNAs). Mounting evidence implicates miRNAs as the main actor in leukemia pathogenesis, thus miRNAs emerged as attractive targets for therapeutics.
Aim: Based on the available data from previous studies, this review focuses on the expressions and effects of particular miRNAs on the clinical outcomes in acute myeloid leukemia (AML) patients and strategies adopted for the treatment of AML using miRNA-based technology.
Conclusions: Deregulated expressions of miRNAs pose significant impact on the clinical outcomes in AML patients. MicroRNA therapeutics indeed has a tremendous potential in the treatment of AML.

1. Introduction

Hematopoiesis, or generation of blood cells particularly in the bone marrow is a well-organized process governed by multifaceted regulatory mechanisms involving both intrinsic and extrinsic factors that control the self-renewal and differentiation of hematopoietic stem cells (HSCs) (Fiedler and Brunner, 2012; Hong et al., 2015). Currently, accumulating experimental evidences have demonstrated that microRNAs, short noncoding RNA molecules of approximately 22 nucleotides in length are also involved in fine-tuning lineage specific differentiation (lymphoid and myeloid lineages) and self-renewal activities of HSCs (reviewed in (Garzon and Croce, 2008; Hong et al., 2015). According to Seita and Weissman (2010), self-renewal in this context refers to the ability of HSCs to generate their identical daughter cells without differentiation. Experimental evidence for specific miRNAs such as miR-181, miR-223 and miR-142 that involved in hematopoietic lineage differentiation was first reported by Chen et al. (2004) *via* cloning approximately 100 miRNAs from mouse bone marrow. In this study, miR-181 was found to be highly expressed in the thymus, while miR-223 on the other hand was found exclusively in the bone marrow. Moreover, up-regulation of miR-142 was also reported in all tested hematopoietic tissues (Chen et al., 2004). Subsequent studies reported that specific miRNAs are differentially expressed in every phase of hematopoiesis. For example, previous *in vitro* and *in vivo* study by Lu et al. (2008) reported that miR-150 drives megakaryocyte-erythrocyte progenitors (MEP) differentiation towards megakaryocytes at the expense of erythroid cells. Besides, this miRNA was also responsible in the control of B and T cell differentiation within the lymphoid lineage (Xiao et al., 2007; Zhou et al., 2007). Furthermore, erythropoiesis was positively regulated by miRNAs such as miR-451, miR-16 and miR-144, and negatively regulated by miR-150, miR-155, miR-221 and miR-222 (Bruchova et al., 2007; Dore et al., 2008).

In addition to their pivotal roles in regulating normal hematopoietic function, ample evidence also shows the effect of deregulated miRNAs in hematopoiesis, which, caused aberrant self-renewal of HSCs or oncogenic transformation into leukemic cells (Hong et al., 2015). Possible explanation for this miRNA-mediated oncogenic transformation of normal into cancerous cells may be due to their location at the fragile sites and genomic regions associated with cancer (Calin et al., 2004). Four human leukemia subtypes, chronic lymphocytic leukemia (CLL), chronic myeloid leukemia (CML), acute lymphoblastic leukemia (ALL), and acute myeloid leukemia (AML) are classified based on the type of blood cells being affected (myeloid or lymphoid) and cell differentiation stage (acute or chronic) (Dell'Aversana and Altucci, 2012). Cancer-specific miRNAs associated with each of leukemia subtypes were extensively reported in the previous studies (for reviews see (Barbarotto and Calin, 2008). As for AML, differentially expressed miRNAs may serve as useful biomarkers in predicting the clinical outcomes in AML patients (Marcucci et al., 2011; Babashah et al., 2012; Diaz-Beya et al., 2014; Yeh et al., 2016). This review summarizes on the clinical

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https://doi.org/10.1016/j.mgene.2018.03.001
Received 14 September 2017; Received in revised form 21 February 2018; Accepted 2 March 2018
Available online 03 March 2018

evidences from the existing literatures that linked the expression of miRNAs with the clinical outcome in AML patients. On that basis, we focused on the expression patterns of specific miRNAs with prognostic values as reported by a number of research groups. In addition to that, several therapeutic strategies in the manipulation of miRNA activity for the treatment of AML are also discussed.

2. MicroRNA expression and clinical implications in AML patients

Current studies have demonstrated that differential miRNA expression profiles have significant impact on the clinical outcome of AML patients, and that cytogenetic risk factors and molecular markers are important factors for AML prognosis (Marcucci et al., 2011; Diaz-Beya et al., 2014). This section covers current research findings on the expression profiles and clinical implications of miRNAs in AML patients. The results of the included studies are summarized in Table 1. A collective of studies have suggested that dysregulation of miRNAs in AML are associated with poor prognosis. Qian and colleagues identified the expression pattern of miR-378 and its clinical significance in 84 AML patients. They found that increased miR-378 expression in 26 of 84 (31%) of AML patients was associated with lower hemoglobin level and shorter relapse-free survival (RFS), indicative of its adverse prognostic effect in AML. Furthermore, up-regulation of miR-378 expression was also correlated with FAB-M2 subtype and t (8;21) compared to others (Qian et al., 2013). There have been conflicting reports on the role of miR-378 on cancers, since it may elicit its oncogenic and tumor suppressive effects depending on the tissue types (Qian et al., 2013). In colorectal cancer, miR-378 act as tumor suppressor gene and reduced expression of miR-378 was associated with poor overall survival (Li et al., 2014; Zhang et al., 2014). Conversely, miR-378 was reported to enhance cell survival, decrease apoptosis as observed from reduced caspase-3 activity and promotes tumor growth and angiogenesis by targeting the Suppressor of Fused (SuFu) and Tumor Suppressor Candidate 2 (TUSC2, or known as Fus-1) expression (Lee et al., 2007). In addition, miR-378 also was shown to promote cell migration and invasion in cancer (Chen et al., 2012), thereby suggesting the role of miR-378 as oncogenic microRNA. In view of these results, further studies are warranted to confirm the prognostic significance of miR-378 in AML.

In another study, Xu and colleagues studied the diagnostic and prognostic relevance of miR-155 in 83 *de novo* pediatric AML. Their report showed an undisputed correlation between miR-155 expression with the white blood cell (WBC) count, serum lactate dehydrogenase (LDH) and C-reaction protein (CRP) values in peripheral blood as well as miR-25/miR-196b expression levels and increased miR-155 expression was associated with *C-KIT* mutation besides affecting patients overall survival (OS) (Xu et al., 2015). It has been reported in the previous study that both initial LDH and CRP values were indicative of cancer severity (Abaza et al., 2010), and that WBC count was identified as one of the risk factors in pediatric AML (Meshinchi and Arceci, 2007). Taking into accounts of the results from these studies, it can be concluded that miR-155 expression profile serve as an indicator for predicting patients prognosis in childhood AML (Xu et al., 2015). Contrary report from Garzon et al. (2008b) showed that miR-155 expression was associated with WBC, peripheral and bone marrow blast percentage, and high miR-155 expressers in patients harbouring *FLT3-ITD* mutation was associated with unfavourable outcome (Garzon et al., 2008b; Yohe, 2015).

MiR-155, mapped to 21q21.3, is a hematopoietic tissue specific miRNA that negatively regulate myelopoiesis and erythropoiesis by targeting *CREBBP*, *CXCR4*, *JUN*, *MEIS1*, *PU.1*, *AGTRI*, *AGTRII*, *FOS* and *GATA3* (Georgantas et al., 2007; Dixon-McIver et al., 2008). In AML, down-regulation of SH2 domain-containing inositol 5′-phosphatase (*SHIP1*) by miR-155 leading to the activation of oncogenic AKT signalling pathway (Xue et al., 2014).

Apart from being linked with FAB-M1, M2 and M3 subtypes (Zhang et al., 2009; Zheng et al., 2012), up-regulation of miR-100 in 106 *de novo* pediatric AML was also associated with FAB-M7 subtype, unfavourable cytogenetic abnormalities and reduced relapse-free and overall survival (Bai et al., 2012). *In-vitro* reports from Zheng et al.

Table 1
MicroRNAs expression status and clinical implications in acute myeloid leukemia.

Study	No. of patients/ samples	miRNA	Expression	Results	Prognostic significance
Qian et al. (2013)	84	miR-378	Up-regulated	Low hemoglobin level; reduced RFS; FAB-M2 subtype; t (8;21)	Unfavourable
Xu et al. (2015)	83	miR-155	Up-regulated	WBC count, LDH and CRP values; *C-KIT* mutation; reduced OS and associated with miR-25/miR-196b expression levels	Unfavourable
Garzon et al. (2008b)	60	miR-155	Up-regulated	WBC; peripheral and bone marrow blast percentage	Unfavourable
Bai et al. (2012)	106	miR-100	Up-regulated	FAB-M1, M2, M3 and M7 subtypes; unfavourable cytogenetic abnormalities; reduced RFS and OS	Unfavourable
Zheng et al. (2012)	48 patients; bone marrow samples	miR-100	Up-regulated	*In-vitro*: Increased cell proliferation; induce granulocyte-monocyte differentiation arrest by targeting *RSBP3*	Unfavourable
Li et al. (2013)	102	Let-7a-3	Up-regulated	Reduced RFS and OS	Unfavourable
Wang et al. (2016)	113	miR-215	Down-regulated	High WBCs; FLT3/ITD mutation; reduced OS in non-M3 AML and CN-AML patients	Unfavourable
Diaz-Beya et al. (2014)	238	miR-196b	Up-regulated	Reduced OS; miR-644 identified as independent prognostic factor in favourable molecular subcategory	Unfavourable
		miR-644	Down-regulated		
		miR-135a		High relapse risk; identified as independent prognostic factor in unfavourable molecular subcategory	
		miR-409-3p			
Zhang et al. (2016)	112	miR-186	Down-regulated	Reduced OS and CR rate; affects whole AML and non-M3 AML groups without *CEBPA* mutation	Unfavourable
Yang et al. (2017)	112	miR-34c	Down-regulated	High WBCs; reduced OS in whole cohort AML, non-M3 and CN-AML; identified as independent risk factor in whole cohort AML, non-M3 and CN-AML	Unfavourable
Jinlong et al. (2015)	153	Let-7a-2-3p	Up-regulated	Increased EFS and OS	Favourable
		miR-188-5p	Down-regulated		
Chen et al. (2014)	83	miR-124	Down-regulated	FAB-M3 and t (15;17); a trend for longer RFS and OS	Favourable
Sun et al. (2013)	167[a] 409[b]	miR-212	Up-regulated	Increased OS, EFS and RFS; up-regulation of CCL3, CCL4 and CCL5 genes	Favourable

RFS: relapse-free survival, FAB: French-American-British classification for AML; WBC: white blood cell, OS: overall-survival, EFS: event-free survival.
[a] AML patients that belongs to discovery cohort group.
[b] AML patients that belongs to validation cohort group.