Expression of miRNAs Associated with the AML1-ETO, CBFB-MYH1, PML-RARA and AF9-MLL Oncoproteins in Acute Myeloid Leukemia

Keywords: Acute myeloid leukemia; miRNAs; AML1-ETO; CBFB-MYH1; PML-RARA; MLLT3-MLL

Abstract

MicroRNAs (miRNAs) are small noncoding RNAs of 18-25 nucleotides in length that regulate gene expression post-transcriptionally. Moreover, recently miRNA have been implicated in both physiological responses, as well as having critical roles in acute myeloid leukemia. Interestingly, the miRNA expression profile in acute leukemia can discriminate between acute myeloid leukemia with common translocations and imply that the deregulation of specific miRNAs may play a role in the development of leukemia with these associated genetic rearrangements, also the extraordinary stability of miRNAs, makes it suitable to serve as diagnostic and prognostic biomarkers of acute myeloid leukemia. We will review the roles for miRNA here with emphasis on their function in human leukemia and the mechanisms of the AML1-ETO, CBFB-MYH1, PML-RARA and MLLT3-MLL oncoproteins on miRNAs expression in acute myeloid leukemia.

Introduction

Acute myeloid leukemia (AML) is a heterogeneous group of genetically diverse hematopoietic malignancies characterized by the accumulation of primitive myeloid cells arrested at early stages of differentiation and it also is the most common acute leukemia affecting adults, and its incidence increases with age [1-3]. AML has been observed with an incidence of 3.7 per 100,000 persons and an age-dependent mortality of 2.7 to nearly 18 per 100,000 persons [2].

Over the last 30 years, several specific chromosome aberrations have been described in AML [4]. Four major rearrangements in AML are the t(8;21), inv(16), t(15;17), and MLL/11q23 translocations, which account for 30% of all AML cases [5], and have been incorporated in the World Health Organization (WHO) classification as the criteria for sub classification of AML [6]. The t(8;21), t(15;17), and inv(16) have been established as molecular indicators for favorable clinical outcome, whereas MLL-rearrangement is classified as a disease of intermediate or poor prognosis [1,7].

MicroRNAs (miRNAs) are small non-protein-coding RNAs that regulate gene expression at the posttranscriptional level and influence many aspects cellular such as proliferation, metabolism, and apoptosis, etc., they are central in contributing what type of cell a developing cell ultimately becomes [8]. It has been observed that the miRNAs are differentially expressed in hematopoietic tissues and to have an important role both in lineage differentiation and in human hematological malignancies [9-11].

miRNA expression profiling studies have revealed marked differences in miRNA expression between cytogenetic subtypes of AML, including t(8;21), inv(16), and t(15;17), as well as those with less favourable-risk subtypes such as t(11q23)/MLL (mixed lineage leukemia) [12-16], so it has been suggested that the miRNAs are an important tool in molecular classification of the leukemia. In this review, we will summarize the association of the miRNAs expression with AML1-ETO, CBFB-MYH1, PML-RARA and MLLT3-MLL oncoproteins and discussed the mechanism of transcriptional activation and/or repression on miRNAs expression by these oncoproteins, with a specific focus on acute myeloblastic leukemia.

miRNAs Expression and Oncoproteins in AML

AML1-ETO: t(8;21)(q22;q22)

The acute myeloid leukemia (AML)-1 gene (also known as RUNX1) was identified as a target of chromosomal translocation in t(8;21), which is associated with ~15% of AML [17]. This translocation involves the AML1 gene on chromosome 21 and the ETO (MTG8) gene on chromosome 8, and generates an AML1-ETO fusion protein [18]. AML1 is able to form a hetero dimer with CBFB (PEBP2β) and regulate the transcription of target genes by binding to the DNA sequence [19]. Moreover, it has been shown that AML1-ETO blocks the transactivation of various promoters, suggesting it may function as a negative regulator [20].

The microRNA dysregulation associated with AML1/ETO expressed in t(8;21) have been observed [13,21-23] (Table 1). It was reported that AML1-ETO triggers the heterochromatic silencing
of miR-193a and miR-223 by epigenetic silencing through of the binding at AML1-binding sites and recruiting chromatin-remodeling enzymes [21,23]. miR-193a contribute to t(8;21) leukemogenesis by activating the P3K signal pathway, Li, et al. observed that miR-193a and PTEN inhibition by AML1-ETO is the major pathway through which AML1-ETO mediates cell-cycle int(8;21) AML (Figure 1) [23].

On the other hand, it was reported that miR-223 is a direct transcriptional target of AML1-ETO, by recruiting chromatin remodeling enzymes at an AML1-binding site on the miR-223 gene, so AML1-ETO induces heterochromatic silencing of miR-223, also was observed that de-methylating treatment is able to restore functional endogenous mature miR-223, and induced granulocytic maturation of the cells by the increased expression levels of the myeloid differentiation marker CD11b (Figure 1) [21].

CBFB-MYH11; Inv(16)(p13q22)

The inv(16)(p13q22) rearrangement is present in approximately 10% of cases with de novo acute myeloid leukemia (AML) [24]. This chromosomal rearrangement results in the fusion of CBFB and MYH11 genes (CBFB-MYH11 gene fusion) [25]. Patients with this fusion gene define a specific subgroup with a relatively good prognosis [24], CBF beta normally interacts with RUNX1 to form a transcriptionally active complex and it was observed that CBFB-MYH11 plays an important role in oncogenesis, particularly in the process of cell cycle and proliferation regulation [25].

It was found that miR-126/miR-126* is up regulation in CBFB-MYH11-positive AML [13]. Also was reported that the enforced expression of miR-126 and its star strand in AML cell lines inhibited the apoptotic potential and facilitated cell survival [13,26,27]. In addition to the elevated expression of miR-126/126* in CBF AMLs was associated with promoter demethylation, but not with amplification or mutation of the genomic locus (Figure 2) [13,26]. Therefore, miR-126/126* is considered as oncogene to be involved in leukemogenesis of inv(16)/CBFB-MYH11-positive AML (Figure 2).

PML-RARA; t(15;17)(q22;q12)

The fusion transcript of PML-RARA is detectable in approximately 10% of AML patients [28], and becomes a major player disturbing proper promyelocytic differentiation [29]. This chromosomal rearrangement results in the fusion of PML gene on chromosome 15q21, and RARA gene on chromosome 17q21, and to the formation of the resultant chimeric oncoprotein PML-RARA [30]. PML-RARA heterodimers act of a negative manner on RARA, and have higher affinity to CoR and HDAC than RARA-RXR, resulting in enhanced hyper-methylation of the DNA [31]. Thus, PML-RARA appears linked to transcriptional perturbation of miRNA genes and several miRNAs, which are down regulated in PML-RARA-positive AML (Table 1) [32,33].

It was reported that the miR-210, miR-23a/24-2, miR-342 and let-7c are directly repressed by the PML-RARA oncoprotein in acute promyelocytic leukemia(APL) cells [32,33] by epigenetic silencing through of the binding at RARA-binding sites and recruiting chromatin-remodeling enzymes, and this correlated with the recruitment of the co repressors around the retinoid acid response elements (RARE) of miR-342 and promoters together with a sharp decrease in lysine 9 trimethyl-histone H3 (H3K9me3) at the RARE site proximal to the transcription start site (Figure 3) [33]. Therefore, miR-210, miR-23a/24-2, miR-342 and let-7c family might have an important role in AML pathogenesis.

The expression of miR-107 is a target the transcription factor NFI-A [34], which participates with C/EBPs in the suppression in the human granulopoietic lineage differentiation, and in the contribution of miR-223 to the NFI-A transcriptional regulation [35]. miR-342 is associated in the stimulate of granulocytic differentiation [36]. Interestingly, the target of miR-342 is MEIS1, MEIS2 is a member of the TALE family of homeodomain genes, which they are closely related with the normal hematopoiesis [37]. The importance of MEIS1 in human leukemogenesis was underscored by the finding that it was frequently up-regulated in AML and ALL samples [38,39]. Besides, it is known that let-7 family members are involved in differentiation and development, as well as in anti proliferative functions, by targeting the RAS oncogene and the non-histone DNA binding protein HMGA2 [40,41].

AF9-MLL; t(9;11)(p22q23)

The t(9;11) that results in fusion of the MLL gene at 11q23 and the AF9 gene at 9p22. At the molecular level, t(9;11)(p22q23) have different fusion types resulting from various breakpoints within the MLL and AF9 break point cluster regions. All fusion types cause expression of an aberrant chimeric mRNA consisting of a 5’-MLL portion and a 3’-AF9 portion [42-44]. Patients with MLL-rearranged AML are often associated with poor prognosis, and effective targeted therapies are not available [45,46]. Dysregulation of miRNAs has been frequently observed in AML, including those carrying MLL-rearrangements (Table 1) [13,47,48].

The microRNA miR-150, a critical regulator of hematopoiesis, it was observed a downregulation of miR-150 in 5MLL-AF9-leukemia,
besides that miR-150 down-regulates Myb expression in large part by directly targeting its 3' -UTR [48]. Bcl-2, an anti-apoptotic protein known to be regulated by c-Myb, which it has been, reported upregulated in MLL-AF9 leukemia [49]. The MLL-AF9 oncogene blocks apoptosis by inhibition of miR-150 and regulate the Myb and Bcl2 expression in AML (Figure 4). Therefore, the miR-150-dependent derepression of Myb, is an important contributor to the transformation process induced in MLL-AF9AML.

miR-424 and miR-503 are miRNAs that are repressed by the MLL-AF9 leukemogenic fusion (Table 1) [47]. Both of these microRNAs directly target cell-cycle (and cell-cycle regulators. Likewise, it was observed that miR-424 and miR-503 down regulate the anti-differentiative miR-9 by targeting a site in its primary transcript (Figure 4), miR-9 was found up regulated in MLL-AF9-positive cells [47]. This data suggest the combined effects of multiple microRNAs and MLL-AF9 oncogene in acute myeloid leukemia.

Conclusions

In summary, we have highlighted a broad network of miRNA expression in human acute myeloid leukemia. Some have oncogenic activity while others a have tumor suppressive role. miRNAs may be used as new molecular targets for the development of novel therapeutic strategies. Moreover, we could use the miRNAs expression profiling to inform the clinic on diagnosis and prognosis of the AML, or maybe allow for more targeted chemotherapy treatment.

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Citation: Organista-Nava J, Gómez-Gómez Y, Illades-Aguiar B, Leyva-Vázquez MA. Expression of miRNAs Associated with the AML1-ETO, CBFB-MYH11, PML-RARA and AF9-MLL Oncoproteins in Acute Myeloid Leukemia. J Hum Anat Physiol 2015;1(1): 5.

ISSN: 2575-7563

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Acknowledgements: J.O.N and Y.G.G. were recipients of fellowships from the Programa de Apoyo a los Estudios de Posgrado, Universidad Nacional Autónoma de México (PAEP-UNAM).