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The role of microRNAs in acute myeloid leukemia

R Katherine Hyde and P Paul Liu*

Address: Genetics and Molecular Biology Branch, NHGRI/NIH, 49 Convent Drive, Bethesda, MD 20892, USA

* Corresponding author: P Paul Liu (pliu@mail.nih.gov)

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Abstract

MicroRNAs (miRs) are short (18-22 nucleotides) non-coding RNAs that are important in regulating gene expression. MiR expression is deregulated in many types of cancers, including leukemias. In acute myeloid leukemia (AML), the expression of specific miRs has been linked with both prognostically and cytogenetically defined subgroups. Recent studies have shown that deregulation of miR expression is not simply a consequence of AML but a potential contributer to leukemogenesis. This commentary will focus on select findings that describe the different mechanistic roles for miRs in the development of leukemia.

Introduction and context

Acute myeloid leukemia (AML) is a heterogeneous disease that is often classified by the presence of specific, recurrent chromosomal alterations that generate unique oncogenic fusion genes. These alterations are associated with the expansion of cells that have arrested at different stages of differentiation, and have distinct prognoses and gene expression profiles (reviewed in [1,2]). Recently, it has been shown that different subtypes of AML are also associated with distinct microRNA (miR) profiles.

MiRs are small non-coding RNAs that are thought to regulate gene expression by base pairing with the 3′ untranslated region of a target gene mRNA, leading to degradation and/or translational repression. Each individual miR is thought to have multiple target genes and it has been proposed that miRs may represent a mechanism for cells to quickly change the expression of a large number of genes, as required during processes such as differentiation. Consistent with this hypothesis, it has been shown that the profile of expressed miRs changes significantly during hematopoietic differentiation (reviewed in [3,4]).

Different subtypes of AML have also been associated with different miR expression profiles. Multiple studies have shown that unsupervised clustering using miR expression strongly correlates with known morphological and cytogenic subgroups [5-8]. In addition, it has been shown that distinct miR expression signatures correlate with AML survival rates [12]. There are extensive reviews concerning miR expression and AML subgroups and prognoses, (see e.g., [13,14]).

The relationship between the expression of a specific miR (or group of miRs) and AML subtype has important implications for prognosis and treatment of AML [11,12]. However, as it is known that miR expression changes with normal hematopoietic differentiation [3,4], it is possible that the differential expression of many miRs in AML could be due to the stage at which differentiation arrest of the leukemic blasts occured and may not have a causal role in the leukemic process. However, some recent studies have described a mechanistic role for individual miRs in the development of AML and will be the focus of this review.

Major recent advances

One of the first studies to show a role for a specific miR in AML was Li *et al.* [8]. They found that increased expression of miR-126/126* was not only associated with the AML subgroups carrying the related chromosomal alterations t(8:21) and inv(16), it also inhibited apoptosis and increased AML cell viability. They also

showed that this effect was likely mediated through decreased expression of the miR-126/126* target, which encodes the tumor suppressor PLK2 (Polo-like kinase 2). Interestingly, Li *et al*. [8] showed that the increased expression of miR-126/126* was likely mediated by promoter hypomethylation.

Recent evidence suggests that repression of miR-29b may also play a causative role in the AML subgroups defined by t(8:21) and inv(16). Decreased expression of miR-29b was shown to indirectly cause increased expression of the tyrosine kinase KIT [15] and contribute to leukemogenesis. This finding is of particular interest in regard to t(8:21) and inv(16) AMLs because gain-of-function mutations in KIT are known to be associated with decreased survival in patients in this AML cytogenetic subgroup [16].

Causative roles for miRs have also been described in AMLs with fusion genes involving the mixed-lineage leukemia (*MLL*) gene. Popovic *et al*. [17] showed that the *MLL-AF9* fusion gene caused overexpression of miR-196b and that expression of this miR was required for *MLL-AF9*-induced immortilization.

A similar role for the miR-17-92 cluster in leukemias expressing *MLL* fusion genes has also been identified. Like miR-196b, individual miRs in the miR17-92 cluster were shown to be overexpressed in leukemias with *MLL* rearrangements, which increased proliferation and decreased apoptosis [18,19]. Interestingly, Mi *et al*. [18] showed that *MLL* fusion proteins were capable of binding the promoter region of the miR17-92 cluster and activating the expression of the individual miRs. This indicates that these miRs not only play a functional role in *MLL*-rearranged AML, but are also direct targets of the fusion genes.

A potential role for miR-125b-2, located on chromosome 21, has recently been connected to trisomy 21/Down syndrome-related acute megakaryoblastic leukemia (DS-AMKL) [20]. Overexpression of miR-125b-2 was shown to increase proliferation and self-renewal, and these effects were accentuated in the presence of the *GATA1* mutation that results in the expression of GATA1s (the short isoform), which is present in nearly all cases of DS-AMKL [21,22]. In addition, Klusmann *et al*. [20] identified two potential downstream targets of miR-125b-2, *DICER1* and *ST18*, both of which are genes previously shown to be downregulated in cancer.

Future directions

The examples discussed in this review indicate that deregulated expression of miRs can be an important step in leukemogenesis and that the expression of miRs can be affected by a number of different mechanisms. Continued investigation into the role of miRs and their target genes promises to yield new insights into the mechanisms of leukemogenesis. Most importantly, miRs may represent an important target for the development of new therapeutics for the treatment of AML. As an individual miR is likely to affect the expression of several different genes, therapies directed at miRs could potentially target multiple leukemogenic processes.

Abbreviations

AML, acute myeloid leukemia; DS-AMKL, Down syndrome-related acute megakaryoblastic leukemia; miR, microRNA; MLL, mixed-lineage leukemia.

Competing interests

The authors declare that they have no competing interests.

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