MicroRNAs as New Biomarkers for Diagnosis and Prognosis, and as Potential Therapeutic Targets in Acute Myeloid Leukemia

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Abstract: Acute myeloid leukemias (AML) are clonal disorders of hematopoietic progenitor cells which are characterized by relevant heterogeneity in terms of phenotypic, genotypic, and clinical features. Among the genetic aberrations that control disease development there are microRNAs (miRNAs). miRNAs are small non-coding RNAs that regulate, at post-transcriptional level, translation and stability of mRNAs. It is now established that deregulated miRNA expression is a prominent feature in AML. Functional studies have shown that miRNAs play an important role in AML pathogenesis and miRNA expression signatures are associated with chemotherapy response and clinical outcome. In this review we summarized miRNA signature in AML with different cytogenetic, molecular and clinical characteristics. Moreover, we reviewed the miRNA regulatory network in AML pathogenesis and we discussed the potential use of cellular and circulating miRNAs as biomarkers for diagnosis and prognosis and as therapeutic targets.

Keywords: microRNAs; acute myeloid leukemia; biomarkers; therapeutic targets

1. Introduction

Acute myeloid leukemia (AML) is an aggressive hematological malignancy characterized by the abnormal proliferation and differentiation of myeloid progenitor cells [1,2]. This neoplasm is the most common acute leukemia in adult patients and can arise “de novo” or as a secondary event [3]. In particular, secondary AML can derive from a previous clonal disorder of hematopoiesis, such as myelodysplastic syndrome (MDS) or chronic myeloproliferative neoplasm (MPN), or following a previous therapy (chemotherapy or radiotherapy, immunosuppressive drugs or environmental leukemogenic agents) [4,5]. These myeloid malignancies are characterized by acquired common recurrent mutations in hematopoietic progenitors. Gene alterations can contribute to hematopoietic transformation conferring a growth advantage or modifying the expression of key transcriptional
targets in myelopoiesis. These mutations occur in genes with known roles in regulating chromatin and/or methylation states in hematopoietic progenitors (e.g., mixed-lineage leukemia (MLL)), or exert a role in altering epigenetic pattern in myeloid malignancies (e.g., TET methylcytosine dioxygenase 2 (TET2), DNA methyltransferase 3A (DNMT3A), sex combs-like 1 (ASXL1), isocitrate dehydrogenase (IDH) 1 and IDH2). They contribute to the pathogenesis, and could represent attractive targets for directed therapy in myeloid malignancies [6].

AML is a highly heterogeneous disease at molecular and clinical levels; well-identified genetic and cytogenetic aberrations hold a pathogenetic and prognostic relevance in this neoplasm [3]. The new 2016 WHO classification defined six major AML entities incorporating genetic alterations with morphology, immunophenotype, and clinical presentation: (i) AML with recurrent genetic abnormalities; (ii) AML with myelodysplasia-related changes; (iii) therapy-related AML; (iv) AML not otherwise specified; (v) myeloid sarcoma; (vi) myeloid proliferation related to Down syndrome [7]. On the basis of cytogenetic and molecular profile, AML patients can be divided into favorable, intermediate, and adverse prognostic risk groups [3]. AML treatment is currently based on high-intensity induction chemotherapy in eligible patients to achieve complete remission (CR), followed by consolidation regimen, including conventional chemotherapy, as well as hematopoietic cell transplantation [1]. However, patients achieving CR can relapse due to the persistence of minimal residual disease (MRD) [1,8].

It is important to underline, beyond, that AML is perpetuated and maintained by a small population of leukemia initiating cells or leukemia stem cells (LSCs) [9,10]. These cells exhibit similar characteristics of hematopoietic stem cells (HSCs), including the ability to generate identical daughter cells as well as differentiated cells. On the contrary, LSCs have different properties than the AML bulk population [11,12]. These features make LSCs difficult to eliminate with standard chemotherapy, and therefore, result in a source of malignancy resistance and relapse.

MicroRNAs (miRNAs) are evolutionary conserved short non-coding single-stranded RNAs (19–22 nucleotides) [13,14] that negatively regulate mRNA stability [14–16]. They play an essential role in many biological functions, such as cell growth, proliferation, differentiation, and apoptosis [13,17]. Moreover, miRNAs can act as oncogenes or tumor suppressors, contributing to malignant transformation in solid and hematological tumors, including AML [16,18,19]. In addition, miRNAs regulate different mRNA targets, and their modulation can represent a potential therapeutic target in leukemic progenitors, as well as in LSCs. In this context, the identification of miRNA expression patterns in HSCs, LSCs, and leukemic progenitors is required.

miRNA expression is frequently deregulated in AML by different mechanisms, like: (i) copy number alterations; (ii) epigenetic changes; (iii) miRNA location in proximity of oncogenic genomic region due to chromosomal translocation or overexpression of protein-coding gene; (iv) aberrant targeting of miRNA promoter regions by altered transcription factors or oncoproteins; and finally (v) deregulated miRNA processing [14].

During the last 15 years, microarray was a widely used platform to investigate miRNA expression in AML. In particular, many studies identified the expression signatures associated with different AML subtypes, especially with specific molecular and cytogenetic alterations [20]. Recently, the emerging RNA-Sequencing technologies were used to evaluate miRNA abundance and to discover new miRNAs in AML [21].

In this review, we summarized miRNAs differentially expressed in AML subtypes, LSCs, and HSCs, their role in AML pathogenesis, their potential use as disease biomarkers for diagnosis/prognosis and as therapeutic targets.

2. Distinctive Pattern of miRNAs in AML

Molecular and cytogenetic features are currently defined as entities of clinical significance, and are included in diagnostic criteria of AML, according to 2016 WHO classification [7].
Numerous studies demonstrated the existence of distinct miRNA profiles in different AML subtypes, indicating that miRNA signature contributed to AML heterogeneity, and suggesting its potential inclusion in clinical setting [22–43]. In Table 1 were reported all major studies comparing miRNA profile between AML blasts and normal cells, and among AML with recurrent genetic abnormalities [22–43]. Most of the reported studies exhibited high concordance in AML miRNA profile. For example, in patients with NPM1 mutation, different authors found the upregulation of miR-10a, miR-10b, and miR-196b [26,37,38], and the downregulation of miR-192 [36,38]. A common signature was also reported in patients with (8;21) showing the upregulation of miR-126 [22,23] and miR-146a [24,25], while overexpression of miR-155 was strongly associated with FLT3-internal tandem duplication (ITD) alteration [26,34,36,39].

Table 1. MicroRNA (miRNA) expression in acute myeloid leukemias (AML) with recurrent genetic abnormalities.

| Genetic Abnormalities | Upregulated | Downregulated |
|-----------------------|-------------|---------------|
| 8;21q22;p22.1 RUNX1-RUNX1T1 | miR-126, miR-320, miR-328, miR-449b; [22] | miR-9, miR-10a, miR-125b, miR-13a, miR-133a, miR-142a, miR-143, miR-144, miR-181a, miR-182; [22] |
| inv(16)(p13q22) or t(16;14)(q13q32) CBFB-MYH11 | miR-126/126*, miR-146a, miR-191a, miR-193b; [25] | let-7d, let-7c, let-7f, miR-221, miR-222, miR-223; [27] |
| PML-RARA | miR-100, miR-181a, miR-183b, miR-183c, miR-183d, miR-192, miR-222, miR-366, miR-382, miR-424; [23] | miR-17-5p, miR-20a, miR-20b, miR-20c, miR-20d, miR-20e, miR-210, miR-23a, miR-23b, miR-23c, miR-23d, miR-23e, miR-23f, miR-27a, miR-29c, miR-378, let-7b, miR-379, miR-381, miR-423, miR-441, miR-494, miR-495, miR-496, miR-497; [23] |
| 13;1;pl21.3(p23.3) MLLT3-KMT2A | miR-196b; [32] | miR-28a, miR-29b, miR-29c, [34] |
| t(8;16)p11.21q22.1 or t(16;16)p13.1q22.1, GATA2, MECOM | miR-196b; [33] | miR-495; [35] |
| BCR-ABL1 | miR-326; [34] | - |
| mutated NPM1 | miR-10a, miR-10b, miR-19a, miR-19b; [26] | miR-22, miR-127, miR-128a, miR-128c, miR-130a, miR-135a, miR-192, miR-193b, miR-194, miR-204, miR-299, miR-324, miR-326, miR-373, miR-377*, miR-383, miR-429, miR-496, miR-499; [36] |
| | miR-16-1, miR-16-2, miR-17, miR-18a, miR-18b, miR-18c, miR-20, miR-21, miR-24, miR-25a, miR-29b, miR-29c, miR-90, miR-100, miR-102, miR-106, miR-112, miR-112c, miR-151, miR-159, miR-370, miR-371, miR-372, miR-374, let-7a-1, let-7a-2, let-7b-3, let-7c, let-7d, let-7g, let-7h, let-7i, let-7j; [26] |
| | miR-9, miR-10a, miR-10b, miR-145, miR-15a, miR-153a, miR-153b, miR-155, miR-156, miR-159, miR-160, miR-17-3p, miR-181a, miR-181b, miR-183, miR-183a, miR-183d, miR-183e, miR-183f, miR-184, miR-185, miR-186, miR-187, miR-190, miR-194, miR-200a, miR-200b, miR-23a, miR-23b, miR-23c, miR-23d, miR-23e, miR-23f, miR-27a, miR-27b, miR-27c, miR-27e, miR-27f, miR-377, let-7f, let-7g, let-7i; [26] |
| | miR-7, miR-10a, miR-10b, miR-15a, miR-15b, miR-17, miR-17a, miR-18a, miR-18b, miR-18c, miR-20, miR-21, miR-24, miR-25a, miR-29b, miR-29c, miR-90, miR-100, miR-102, miR-106, miR-112, miR-112c, miR-151, miR-159, miR-370, miR-371, miR-372, miR-374, let-7a-1, let-7a-2, let-7b-3, let-7c, let-7d, let-7g, let-7h, let-7i, let-7j; [26] |
| | miR-9, miR-10a, miR-10b, miR-145, miR-15a, miR-153a, miR-153b, miR-155, miR-156, miR-159, miR-160, miR-17-3p, miR-181a, miR-181b, miR-183, miR-183a, miR-183d, miR-183e, miR-183f, miR-184, miR-185, miR-186, miR-187, miR-190, miR-194, miR-200a, miR-200b, miR-23a, miR-23b, miR-23c, miR-23d, miR-23e, miR-23f, miR-27a, miR-27b, miR-27c, miR-27e, miR-27f, miR-377, let-7f, let-7g, let-7i; [26] |

*: complementary strand to microRNA.
Therefore, some studies showed partial overlap in miRNA profile, and this is probably due to different microarray platforms, sample type, or comparison analysis among AML subtypes.

According to cytogenetic and molecular alterations, European LeukemiaNet divided AML patients into three risk groups: favorable, intermediate, or adverse [44]. Each subtype seems to exhibit a unique miRNA signature that distinguishes it from other AML subtypes. For example, Marcucci G et al. reported the increased expression of all members of miR-181 family in patients with favorable risk (cytogenetically normal AML (CN-AML) with CEBPA mutations) [40] and its decreased expression in a high risk subgroup (CN-AML with FLT3-ITD and/or wild-type NPM1) [45]. Similarly, in other studies, miR-181 was also observed increased in cytogenetically abnormal AML (CA-AML) with favorable cytogenetic abnormalities, such as t(15;17) (favorable risk), and decreased in CA-AML with unfavorable cytogenetic alterations, such as MLL-rearrangements (adverse risk) [23,46]. Garzon et al. compared CN-AML with CA-AML patients, identifying a signature in CN-AML of biallelic mutations of CEBPA with favorable cytogenetics [52].

miR-181 expression was also correlated with bone marrow (BM) morphology. Chen et al. demonstrated that mature miR-181 expression was detectable in BM undifferentiated progenitor cells [48]. Moreover, its expression was strongly correlated with the AML morphological subtype, resulting in elevated levels in samples with M1 or M2 French–American–British (FAB) classification, compared with the samples with M4 or M5 morphology [49]. By contrast, in normal BM, miR-181a has been reported to be preferentially expressed in B cells, T cells, monocytes, and granulocytes, which are more closely allied to M4 and M5 subtypes [50]. Another study, instead, compared M1 with M5 miRNA profile, indicating the higher expression of not only miR-181a and miR-181b, but also miR-181a*, miR-181d, miR130a, miR-135b, miR-146a, miR-146b, and miR-663 in FAB M1. Instead, miR-21, miR-193a, and miR-370 were overexpressed in FAB M5 samples [51]. Recently, de Leeuw et al. identified the highest expression of miR-551b in the most primitive cell populations, the HSC and multipotent progenitors; instead, differentiated progenitors, monocytes and lymphocytes, showed decreased and absent miR-551b expression, respectively. This expression pattern might indicate a miR-551b role in early hematopoiesis and stem cells. Therefore, authors hypothesized that its expression in AML might be indicative of an immature leukemia with stem cell features. In fact, they found a high miR-551b expression in undifferentiated AML (FAB M0); on the contrary, miR-551b was not expressed in patients with favorable cytogenetics [52].

Yang et al. demonstrated that miR-122 was downregulated in AML with respect to normal controls, and its decreased expression was more frequently observed in FAB M7 with respect to M1–M6 subtypes, and in unfavorable cytogenetic abnormalities, acting as tumor suppressor [53].

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**Table 1. Cont.**

| Genetic Abnormalities | miRNAs | Upregulated | Downregulated |
|-----------------------|--------|-------------|---------------|
| bi-allelic mutations of CEBPA | miR-128, miR-181a, miR-181a*, miR-181b, miR-181c, miR-181d, miR-219-1-3p, miR-219-2, miR-335, miR-335-3p, miR-335-5p, miR-340 | [40] | [40] |
| mutated RUNX1 | miR-21, miR-220, miR-585 | [42] | [42] |
| FLT3-ITD | miR-10a, miR-10b, miR-155, miR-155* | [26] | [26] |
| | miR-181a, miR-181a*, miR-181b, miR-181b* | [34] | [34] |
| | miR-181c, miR-181c* | [40] | [40] |
| | miR-181d, miR-194, miR-34a, miR-488, miR-488-3p, miR-488-5p | [43] | [43] |
| | miR-219-1-3p, miR-299, miR-30c, miR-340, miR-340-3p, miR-340-5p, miR-340-5p* | [39] | [39] |
| | miR-199a, miR-199b, miR-200a, miR-200b, miR-200c, miR-200c* | [42] | [42] |

*: complementary strand to microRNA.
In a recent paper, we evaluated miR-128a expression in AML patients stratified for morphologic features, observing high expression levels of this miRNA in AML with maturation and in acute promyelocytic leukemia cases compared to healthy subject CD34+ [31].

In any case, the majority of reported studies, based on the FAB classification system, needs to be revised according to the 2016 WHO classification [7].

Thus, the all cited literature data highlighted that the aberrant expression of miRNAs contributes to AML heterogeneity.

3. miRNAs Involved in AML Pathogenesis

MicroRNAs alterations are recognized, through various mechanisms, to be involved in AML pathogenesis [54]. In particular, literature data indicate that miRNAs can induce leukemogenesis, altering numerous biological processes, including self-renewal, survival, proliferation, differentiation, and epigenetic regulation. Their involvement in leukemic development and progression is due to their collaboration with deregulated protein (oncogene or tumor suppressor), either by direct control of protein translation, or by working jointly with them to promote malignancy [14,54].

To summarized these concepts, we have illustrated in Table 2 the most important miRNAs found to play a role in AML, specifying for each miRNA the altered expression (up or downregulation), the mechanisms of dysregulation, their targets, and their functional effects in AML pathogenesis [23,28,31–33,41,55–105]. However, literature data revealed that miRNA dysregulation in AML can have different effects on the basis of their expression levels. miR-155, for example, is upregulated respect to healthy subjects having an oncogenic function in AML FLT3-ITD subgroup [91,95]; by contrast, in different AML subsets, it was demonstrated to have a tumor suppressor function [106,107].

Table 2. miRNAs involved in AML pathogenesis.

| miRNA | Altered Expression | Mechanism of Dysregulation | Targets | Functional Effect of Mirna Altered Expression | Refs |
|-------|--------------------|---------------------------|---------|---------------------------------------------|------|
| miR-9 | Up: in MLL-AML | Promoter targeted by MLL-fusion proteins | RHOH, BYRF | Increased proliferation, survival and leukemogenesis in mice | [55] |
|       | Down: in (8;21) AML | | HMGAl2, LIN28B | Increased proliferation and decreased monocytic differentiation | [64] |
|       | Down: in EVI1-induced AML | EVI1 hypermethylates promoter | FOSO1, FOSO5 | Increased proliferation and decreased monocytic differentiation | [7] |
| miR-17-52 cluster | Up: in LSCs in MLL-AML | Activated by MYC | P21 | Increased proliferation, survival, differentiation, self-renewal, colony forming capacity and leukemogenesis in mice | [9] |
|       | | | | Inhibited differentiation and apoptosis, promoted cell proliferation | [9] |
| miR-22 | Up: in MDS/MDS-derived AML | | | | |
|       | | | | | |
| miR-22 | Down: in de novo AML | Downregulated via TET1/GFR1/SP12/SRC3-mediated epigenetic repression and DNA copy-number loss | CRKCI, FLT3, MYC | Increased AML blast cell growth. Decreased differentiation and increased leukemic progression in mice | [61] |
| miR-29b | Down: in various subtypes of AML | Repressed by c-MYC, AKT2, CCND2, TP53, CXCR3, CDK6 | Increased cell growth, leukemic progression in vivo | [63] |
|       | Down: in various subtypes of AML | | | | |
|       | Down: in (8;21) AML | Repressed by c-MYC and TP53 | | Decreased cell growth, decreased apoptosis, leukemic progression in vivo | [55] |
|       | Down: in CEBPA mutated AML | Deregulated via loss of CEBPA, chromosome 7q deletions | SP1, DNMT3A, DNMT3B, SP1 | miR-29b downregulation led global DNA hypermethylation | [75] |
|       | Down: in various subtypes of AML | | | | |
| miR-34a | Down: in CEBPA mutated AML | | E2F3 | Increased proliferation and decreased differentiation | [41] |
|       | Down: in de novo AML | Downregulated via loss of MUC1 | PDL1, PDL1 | Immune dysregulation | [67] |
|       | | | | | |
| miR-99 | Up: in initial diagnosis and relapse | Deregulated via loss of MUC1 | | Inhibited cell apoptosis and increased autophagy | [57] |
|       | Up: in AML-AP9 | Deregulated via loss of CEBPA | | Increased proliferation and decreased differentiation | [57] |
|       | Up: in pediatric-onset AML (M4-ALL) | | | | |

| miR-155 | Up: in MDS/MDS-derived AML | | | | |
|         | Down: in de novo AML | | | | |
|         | | | | | |
|         | | | | | |
| miR-17 | Up: in MDS/MDS-derived AML | Genomic amplification and upregulation by MLL-fusion proteins | | | |
|         | Down: in de novo AML | | | | |
| miR-22 | Up: in MDS/MDS-derived AML | Increased proliferation, survival, self-renewal and decreased differentiation, miR-22 overexpression led to myeloid malignancy in mice | | | |
| miR-29b | Down: in various subtypes of AML | Repressed by c-MYC, AKT2, CCND2, TP53, CXCR3, CDK6 | Increased cell growth, leukemic progression in vivo | [63] |
| miR-34a | Down: in CEBPA mutated AML | Downregulated via loss of CEBPA, chromosome 7q deletions | SP1, DNMT3A, DNMT3B, SP1 | miR-29b downregulation led global DNA hypermethylation | [75] |
| miR-99 | Up: in initial diagnosis and relapse | Deregulated via loss of MUC1 | | Inhibited cell apoptosis and increased autophagy | [57] |
| miR-155 | Up: in MDS/MDS-derived AML | | | | |
|         | Down: in de novo AML | | | | |
| miR-22 | Up: in MDS/MDS-derived AML | Increased proliferation, survival, self-renewal and decreased differentiation, miR-22 overexpression led to myeloid malignancy in mice | | | |
| miR-29b | Down: in various subtypes of AML | Repressed by c-MYC, AKT2, CCND2, TP53, CXCR3, CDK6 | Increased cell growth, leukemic progression in vivo | [63] |
| miR-34a | Down: in CEBPA mutated AML | Downregulated via loss of CEBPA, chromosome 7q deletions | SP1, DNMT3A, DNMT3B, SP1 | miR-29b downregulation led global DNA hypermethylation | [75] |
| miR-99 | Up: in initial diagnosis and relapse | Deregulated via loss of MUC1 | | Inhibited cell apoptosis and increased autophagy | [57] |
| miR-155 | Up: in MDS/MDS-derived AML | | | | |
|         | Down: in de novo AML | | | | |
| miR-22 | Up: in MDS/MDS-derived AML | Increased proliferation, survival, self-renewal and decreased differentiation, miR-22 overexpression led to myeloid malignancy in mice | | | |
| miR-29b | Down: in various subtypes of AML | Repressed by c-MYC, AKT2, CCND2, TP53, CXCR3, CDK6 | Increased cell growth, leukemic progression in vivo | [63] |
| miR-34a | Down: in CEBPA mutated AML | Downregulated via loss of CEBPA, chromosome 7q deletions | SP1, DNMT3A, DNMT3B, SP1 | miR-29b downregulation led global DNA hypermethylation | [75] |
| miR-99 | Up: in initial diagnosis and relapse | Deregulated via loss of MUC1 | | Inhibited cell apoptosis and increased autophagy | [57] |
Narayan et al. demonstrated in three different murine models of AML (HoxA9/Meis1, MLL-ENL, MLL-AP9) that this is due to different expression levels of miR-155. High doses of this miRNA repressed clonal proliferation, instead, intermediate levels of miR-155 showed an oncogenic function, leading to an increased proliferation and enhancing colony formation [108]. Moreover, this group confirmed...
that the intermediate miR-155 expression level was associated with poor prognosis in pediatric AML patients, suggesting a prevalent oncogenic function in this hematological neoplasm [34,95,108].

miRNAs exert a functional role in leukemogenesis both in vivo and in vitro controlling their mRNA targets. Generally, miRNA–mRNA relationships are related to AML subtypes, and some targets play an important role than others, depending on the AML cytogenetic and molecular signatures [109], as reported in Table 2.

One of the most studied miRNAs in AML, miR-155, for example, negatively regulated the transcription factor PU.1, involved in hematopoietic cell determination [110]. Basova et al. confirmed this data in AML pathogenesis, and reported miR-155 cooperation with Myb. This last acted as an activator of cell proliferation and inhibitor of myeloid maturation, with a hierarchical order of Myb/miR-155/PU.1. Moreover, p53 regulated this axis. Its loss caused the upregulation of the two oncogenes Myb and miR-155, concomitantly with progressive PU.1 downregulation and characterized aggressive AML. The inhibition of the oncogenes Myb and miR-155, or by rescue of PU.1, led to leukemia blast differentiation [111]. miR-155 was able to induce proliferation of myeloid cells, causing a myeloproliferative syndrome after ectopic expression in myeloid progenitors [95]. Ghani et al. suggested that PU.1 activated miR-155 expression inducing quiescent HSC to entry into cell cycle, and thus activated their initial differentiation into a transient myeloid progenitor stage. When PU.1 was removed from its binding site at pre–miR-155, the lack of expression of miR-155 blocked proliferation, thus preventing leukemia, and initiated terminal myeloid maturation. Thus, PU.1 was needed to initiate the expression of this miRNA, but not for its maintenance [112].

miR-17 polycistronic miRNA (miR-17-92 cluster) has been shown to be highly expressed in human MLL-rearranged leukemia [58,59]. Recently, Wong et al. demonstrated that the cyclin-dependent kinase inhibitor p21 was a critical downstream target of this microRNA. Leukemic cells expressing increased levels of miR-17 polycistron displayed a higher frequency of LSCs, a block of differentiation, and increased proliferation associated with reduced expression of p21. Moreover, c-myc was shown to be a critical upstream regulator of miR-17 expression in MLL transformation [58]. Notably, downregulation of the miR-17p-92 cluster can promote myeloid lineage fate in normal cord blood CD34+ HPCs [113].

miR-125b was found upregulated in AML. Chaudhuri et al. demonstrated that miR-125b overexpression led to uncontrolled generation of myeloid progenitors and mature myeloid cells that subsequently caused a highly invasive myeloid leukemia. The authors also showed that Lin28A, an induced pluripotent stem cell gene, was a bona fide primary target of miR-125b in hematopoietic cells. Lin28A downregulation mimicked the preleukemic state induced by miR-125b. [74]. MiR-125b physiologically regulated hematopoiesis [114]. Studies of miRNA expression profiles in multiple hematopoietic subpopulations demonstrated that miR-125b was one of the most expressed miRNAs in HSCs, compared with all other progenitor populations. Moreover, miR-125b was specifically enriched in the long-term HSC population [76]. While its level significantly decreased in committed progenitors, miR-125b was more highly expressed in common lymphoid progenitors than in common myeloid progenitors [115].

It is known that leukemic cells release extracellular vesicles (EVs) that modify target cells in BM microenvironments by transferring their metabolic, protein, and genetic content, such as mRNA, DNA, and miRNA [116,117]. EV miRNAs act to create a favorable BM microenvironment that sustains and support leukemia [117–119]. In this context, Hornick et al. showed a direct effect of AML exosome (Exo) miRNAs compromising hematopoiesis of healthy hematopoietic stem and progenitor cells (HSPCs) [120]. This study suggested that leukemia-derived Exo were sufficient to induce systemic impairment of hematopoiesis, demonstrating that miR-150 and miR-155 and their regulatory network were sufficient to suppress HSPC clonogenicity. [120]. Similarly, Razmkhah et al. demonstrated that AML BM microvesicles (MVs) induced colony formation and increased expression of two leukemic oncomiRs, miR-21 and miR-29a, in healthy HSPCs [121]. In addition, Horiguchi et al. revealed that miR-7977 in EVs from AML/myelodysplastic syndrome induced a reduction of hematopoietic-supportive capacity of normal BM mesenchymal stem cells [122].
4. Differential Expression of MiRNAs in HSCs and LSCs

It is well established that miRNAs play a role in the regulation of normal hematopoiesis and in HSC maintenance. Similarly, miRNAs regulated the behavior of LSCs, their self-renewal and development [11,54]. In fact, LSCs showed a differential expression of miRNAs with respect to HSC. Therefore, modulation of miRNA aberrantly expressed in LSC and, consequently, the regulation of their targets could determine the elimination of resistant LSCs, by inducing apoptosis or by sensitizing them to chemotherapy [123].

Although many studies reported miRNA profiles of primary AML cell bulk, as described above, little is known about miRNA expression in LSCs.

Recently, de Leeuw et al. compared LSCs (CD34+ CD38−) versus HSCs, and LSCs versus leukemic progenitors (CD34+ CD38+), all from the same AML BM, identifying multiple differentially expressed miRNAs. In particular, they found miR-551b, miR-10a, miR-151-5p, miR-29b, and miR-125b were higher expressed in HSCs than in LSCs, while miR-181b, miR-221, miR-21, and miR-22 were expressed at lower levels in HSCs than in LSCs [82]. Information about their role in leukemia pathogenesis are reported in Table 2.

It was also reported miR-126 increases in LSCs and HSC compared to leukemic progenitors, suggesting miR-126 as a stem cell-associated miRNA [82]. It was found to restrain cell cycle progression, prevent differentiation, and increase self-renewal of LSCs, in vivo, by regulating the phosphatidylinositol-3-kinases/Protein Kinase B/mechanistic target of rapamycin (PI3K/AKT/MTOR) signaling pathway that drives LSC self-renewal and chemotherapy resistance. Interestingly, it also exerted an opposite functional effect in LSCs with respect to HSC; in fact, reduced miR-126 levels induced HSC expansion in vivo, while impaired LSC maintenance [81]. Finally, miR-126 inhibition caused apoptosis and decreased clonogenic capacity of LSCs [79,82].

Other altered miRNAs in LSCs were involved in development of leukemia. Wong et al. showed that miR-17 polycistron maintained LSC potential in a mouse model of MLL-AML by modulating the expression of the cyclin-dependent kinase inhibitor p21 [58]. Moreover, in MLL-AML, the inhibition of miR-196 and miR-21 reduced LSCs in vivo [124].

Han et al. reported that miR-29a was highly expressed in HSC and primary human LSC, but downregulated in more committed progenitors; this work suggested miR-29a role in the regulation of early hematopoiesis and in the initiation of AML by converting myeloid progenitors into self-renewing LSC [125].

Comparing LSCs versus leukemic progenitors, it was found miR-1274a, miR-886, and miR-1305 were more lowly expressed in LSCs with respect to leukemic progenitors, while miR-126-5p, miR-126-3p, miR-22, miR-335, and mir-150 were more highly expressed in LSCs than in leukemic progenitors [82].

Interestingly, MVs released by LSC were able to promote proliferation and migration, and to inhibit apoptosis of AML cells. Restoration of miR-34a in LSC not only inhibited LSC proliferation, but also generated MVs containing a high level of miR-34a, which could revert the effects of LSC-MVs on AML cells [126].

Collectively, the reported studies suggested that miRNA targeting in LSC could be a potential strategy to eradicate leukemic cells. Further studies are necessary to define this aspect.

5. miRNAs as Biomarkers in AML

miRNAs have several properties of good biomarkers, such as their presence in various biological fluids (e.g., serum, plasma, urine, saliva, etc.), sequence conservation between human and animal models, and available sensitive measurement methodologies [127].

Moreover, they show high stability and survive in unfavorable conditions, such as extreme variations in pH, boiling, multiple freeze–thaw cycles, and extended storage [128].

The majority of miRNAs are intracellularly localized; however, they are also cell-free: (i) protected into apoptotic bodies and EVs; (ii) associated with proteins of the Argonaute (AGO) family; (iii) joined with high-density lipoprotein [128]. These miRNAs are generally defined as circulating miRNAs.
Emerging evidence shows that circulating miRNAs have been gaining importance for their ability to provide early, sensitive, and non-invasive biomarkers in solid and hematologic cancers [129–131]. In particular, different studies have identified as candidates specific circulating miRNAs as new biomarkers in AML disease [132,133].

As mentioned above, miRNA expression profile is aberrant in AML and, besides being associated with genetic alterations, hold a diagnostic and prognostic relevance. The evaluation of a single or panel of miRNAs with potential diagnostic/prognostic impact could implement data from cytogenetic, gene mutations, and gene expression profiles.

In Table 3 it’s reported cellular and circulating miRNAs with diagnostic power, selected from the most significant diagnostic studies based on receiver operator characteristic (ROC) curve analysis [134–140].

Table 3. miRNAs as diagnostic biomarkers in AML.

| miRNA          | Expression | Specimen   | Refs  |
|----------------|------------|------------|-------|
| miR-29a, miR-142-3p | under-expression | PBMCs      | [134] |
| circulating miR-10a-5p | over-expression | serum      | [135] |
| circulating miR-10a-5p, miR-93-5p, miR-129-5p, miR-155-5p, miR-181b-5p, miR-320d | over-expression | serum      | [136] |
| circulating miR-92a, miR-143, miR-342 | under-expression | plasma     | [137] |
| circulating miR-150, miR-342 | under-expression | plasma     | [138] |
| circulating miR-155 | over-expression | serum EVs  | [139] |
| circulating miR-370 | under-expression | serum      | [140] |

Abbreviations: PBMCs, peripheral blood mononuclear cells; EVs, extracellular vesicles.

In our recent work, we demonstrated that EV miR-155 was highly expressed in AML with respect to healthy subjects; notably, ROC curve analysis revealed that this miRNA could be a potential new biomarker in AML [139].

We also summarized, in Table 4, miRNAs involved in AML prognosis, reporting their expression level, origin, and their impact in predicting relapse or progression, as well as their relationship with overall survival (OS) and relapse free survival (RFS) [29,33,34,45,46,70,135,136,140–162].

Table 4. miRNAs as prognostic biomarkers in AML.

| miRNA          | Expression   | Prognostic Impact                                | Specimen       | Refs  |
|----------------|--------------|--------------------------------------------------|----------------|-------|
| miR-9          | overexpression | unfavorable OS and RFS                          | BMMCs          | [141] |
| miR-24         | overexpression | shorter OS                                       | BMMCs/PBMCs    | [142] |
| miR-26a, miR-29b, miR-146a | overexpression | shorter OS                                       | BMMCs          | [143] |
| miR-29a        | underexpression | shorter OS and RFS                              | BMMCs          | [144] |
| miR-29b        | underexpression | poorer OS                                       | BMMCs/PBMCs    | [145] |
| miR-96         | underexpression | lower OS and RFS                                | BMMCs/PBMCs    | [146] |
| miR-99a        | overexpression | worse OS and EFS                                | BMMCs          | [70]  |
| miR-124-1      | underexpression | longer OS RFS                                   | BMMCs          | [147] |
| miR-135a, miR-409-3p | underexpression | higher cumulative incidence of relapse          | BMMCs/PBMCs    | [148] |
| miR-181a, miR-181b | overexpression | decreased risk of an event (i.e., lack of complete remission, relapse, or death) | BMMCs          | [45]  |
| miR-181a       | overexpression | favorable prognosis                              | BMMCs          | [149] |
| miR-181a, miR-181b, miR-181d | overexpression | longer OS                                       | not specified  | [46]  |
| miR-181a       | overexpression | higher CR rate, longer OS                       | BMMCs          | [150] |
| miR-181b       | overexpression | lower CR rates, shorter RFS and OS              | BMMCs          | [151] |
| miR-181b       | overexpression | better prognosis and lower probability of relapse | BMMCs          | [152] |
| miR-188-5p     | underexpression | longer OS and EFS                               | not specified  | [153] |
Table 4. Cont.

| miRNA(s) | Expression | Outcome | Cell Type | Reference |
|----------|------------|---------|-----------|-----------|
| miR-191, miR-199a | overexpression | worse prognosis (worse overall and event free survival) | BMMCs | [34] |
| miR-199b, miR-644 | overexpression | shorter OS | leukemic blasts | [33] |
| miR-212 | overexpression | better OS, higher CR rate, better EFS and RFS | BMMCs/PBMCs | [29] |
| miR-328 | underexpression | poor OS and shorter RFS | plasma | [154] |
| miR-331 | overexpression | worse response to therapy and shorter OS | BMMCs | [155] |
| miR-375 | overexpression | shorter RFS and OS | BMMCs | [156] |
| miR-378 | overexpression | shorter RFS | BMMCs | [157] |
| miR-3151 | overexpression | shorter DFS and OS | PBMCs | [158] |
| let-7a-3 | overexpression | shorter OS and RFS | BMMCs | [159] |
| let-7a-2-3p | overexpression | longer OS and EFS | not specified | [153] |
| circulating miR-10a-5p | overexpression | shorter OS | serum | [135] |
| circulating miR-181b-5p | over-expression | worse OS | serum | [136] |
| circulating miR-183 | overexpression | shorter OS and RFS | serum | [160] |
| circulating miR-210 | overexpression | shorter OS and RFS | serum | [161] |
| circulating miR-335 | overexpression | shorter OS and RFS | serum | [162] |
| circulating miR-370 | underexpression | shorter RFS and OS | serum | [140] |

Abbreviations: BMMCs, bone marrow mononuclear cells; PBMCs, peripheral blood mononuclear cells; OS, overall survival; RFS: relapse free survival; EFS: event free survival; DFS, disease free survival; CR: complete remission.

Of note, discovery of new sensitive and specific biomarkers may be clinically useful in MRD monitoring. Notably, circulating miRNAs could be exerting an important relevance in this context, and their quantification could be more accurate over conventional biomarkers. In this setting, Hornick et al. investigated Exo miRNAs as minimally invasive biomarkers in AML. They developed a xenograft model for high-risk AML. In mouse serum Exo, they detected a panel of biomarkers, miR-150, miR-155, and miR-1246, that resulted in equal sensitivity for detection of MRD, when compared to conventional immuno-phenotypic cell evaluation [163].

Despite the appealing use of circulating miRNAs as novel biomarkers, optimization and standardization of purification and quantification are needed to translate basic research into clinical practice. Further studies are required to promote the future use of EV analysis in clinical applications. In particular, accurate procedures concerning sample collection, EV isolation and storage, as well as EV-miRNA quantification, are necessary to improve the use of EVs as biomarkers [127,164].

6. miRNAs as Therapeutic Targets

Drug resistance against conventional chemotherapy in AML is one of the major reasons of treatment failure [165]. Current therapies in AML are able to rapidly target dividing blast populations, but have limited capacity to eradicate the functionally distinct LSCs, responsible for disease resistance and relapse [79]. Hence, the identification of new therapeutic strategies in AML is of paramount importance. In this context, miRNA-based therapeutic approaches may provide a novel promising strategy.

The principal approach to target miRNAs was the manipulation of their expression, by the replacing of cancer suppressive miRNAs or by the inhibition of overexpressed oncogenic ones [166]. The replacement therapy employs miRNA mimics (double stranded oligonucleotides) delivered by viral [167] or synthetic vectors, such as lipid-based nanocarriers, amphiphilic star copolymer, inorganic nanoparticles polymeric and dendrimer-based vectors [166,168,169]. These vectors are essential to avoid degradation and to increase cellular uptake of synthetic miRNAs [169].

A consistent number of reports have shown encouraging results of miRNA-based therapeutic approaches, in both in vitro and in vivo studies. For example, miR-29b, an AML tumor suppressor [64], was overexpressed in AML blasts, by nanoparticle-based delivery system, decreasing leukemic cell growth and improving the survival of AML-xenograft mouse model [169]. These data were confirmed in another in vivo study in which miR-29 family member restoration caused a dramatic reduction of
AML engraftment in mouse BM, associated with relieved splenomegaly, decreased neoplastic infiltration, decreased cell proliferation, and increased apoptotic activities in spleens [63]. Xu et al., instead, demonstrated that the overexpression of miR-150 in vitro inhibited proliferation and clonogenic growth, and attenuated tumorigenic activity of LSCs, downregulating the expression of cancer stem cell factors like Nanog, Notch2, and CTNNB1. Moreover, an in vivo study confirmed that miR-150 overexpression progressively abrogated tumor growth [89]. The inhibition of leukemia progression was also demonstrated by forced expression of miR-22 and miR-193a. In particular, Jiang et al. demonstrated that the overexpression of miR-22, by nanoparticles, significantly suppressed leukemic cell viability and growth in vitro, and repressed leukemia development and maintenance in vivo [61]. Instead, Li et al. showed that miR-193a restoration by synthetic miRNA contributed to the blockage of malignant-cell proliferation in t(8;21) AML xenograft model [99]. Moreover, Yang et al. described miR-122 as tumor suppressor miRNA in childhood AML, and showed that a miR-122 mimic efficiently inhibited cell proliferation and cell cycle of HL-60 AML cell line [53]. Another potential candidate for miRNA therapy in AML is miR-34. Wang et al. showed that overexpression of this miRNA in AML cell lines reduced both mRNA and cell surface protein expression of PD-L1, an inhibitory immune checkpoint molecule, suggesting the potential role of miR-34a mimic also in AML immunotherapy [68].

The second miRNA-based therapeutic approach is the silencing of aberrantly expressed miRNAs using anti-miRNA oligonucleotides (AMOs), miRNA sponges, or miRNA masking [170]. These synthetic oligonucleotides have sequences complementary to endogenous mature miRNA, and competitively prevent the interaction between miRNAs and their targets [166]. MiR-126, for example, high expressed in CN-AML, was silenced in in vivo models, causing a reduction of LSCs and showing no toxic effect on normal hematopoietic functions. In this study, Dorrance et al. identified a potential novel therapeutic approach to treat AML patients and prevent relapse [79]. Literature data also indicated that miR-181 inhibition could provide a new strategy for AML therapy [171], increasing the differentiation of myeloid progenitors, reducing the engraftment and the infiltration of leukemic HSPCs into BM and spleen, and ameliorating symptoms of leukemia in AML CD34+ HSPC xenograft mice [171]. Another miRNA involved in leukemogenesis seemed to be miR-9; Tian et al. demonstrated that its knockdown in vivo suppressed malignant cell proliferation, decreased leukemic cell counts both in blood and BM, and reduced splenomegaly [172]. Velu et al., instead, studied the combination of miR-21 and miR-196b silencing in murine models of MLL-AF9 leukemia [124]. They demonstrated that co-treatment with both antagonirs improved the outcome of MLL-AF9 leukemia, and did not show toxicity in vivo. In this study, they tested both antagonir with or without a cholesterol modification, demonstrating highest efficacy of anti-miRNAs with lipoprotein particles (the commercial ones) in vivo [124].

Emerging evidence revealed that modification of miRNA expression levels can increase the sensitivity to chemotherapy or other drugs. In this context, Chen et al. demonstrated that overexpression of let-7a, in xenograft mouse of primary human AML cells, increased the cytarabine (Ara-C) efficacy respect to single chemotherapeutic treatment and extended survival of mice [173]. Also, the overexpression of miR-150 in vitro reduced cell viability of two AML cell lines treated with Ara-C [89]. Moreover, Lu et al. reported that, also, forced miR-181b expression rendered leukemic cells more sensitive to doxorubicin and Ara-C in vitro [174]. Gao et al., instead, demonstrated a synergistic apoptotic effect of 5-azacytidine and miR-193a mimic combination in AML cell line, Kasumi-1, suggesting miR-193a restoration as a potential adjuvant therapy in c-KIT-positive AML [100]. In a recent study, it was also demonstrated that the upregulation of miR-217, a tumor suppressor in AML, induced in vitro chemosensitivity to doxorubicin [165]. Additionally, it was reported that ectopic expression of miR-133, a tumor suppressor for EVI1-overexpressing AML cells, increased drug sensitivity specifically in this subset of AML [175].

Instead, Lechman et al. suggested miR-126 inhibition as a strategy to overcome LSC chemoresistance, and to increase the sensitivity of anti-proliferative drugs [81]. Furthermore, targeting of miR-21 and miR-196b increased the effect of induction chemotherapy in xenograft model of MLL leukemia [124].
Another interesting concept concerns the effects of existing drugs on miRNA expression. For example, lenalidomide, a drug approved for the treatment of multiple myeloma and MDS, induced endogenous expression of miR-181 with significant tumor growth inhibition in AML xenograft mouse models [176]. Additionally, Khalife et al. reported that MLN4924 drug (Pevonedistat), decreasing NF-κB activation, downregulated oncogenic miR-155 levels in FLT3-ITD+ AML cell lines and reduced leukemic phenotypes, in both in vitro and in vivo models [177].

The identification of miRNA target genes can help to understand the multiple mechanisms involved in AML [165], and can represent another important tool to provide targeted AML treatment strategies [166]. For example, miRNA activity can be regulated by blocking its access to the target mRNA. A recent study showed that the activity of two oncomiRs, miR-9 and miR-17, could be antagonized by the induction of two RNA binding proteins, RBM38 and DND1, whose function is to protect mRNAs from miRNA-mediated cleavage [178].

MVs represent another important tumor suppressive miRNA vehicle. In a recent work, it was hypothesized that miRNA contents of LSC-derived MVs (LMVs) can be reprogrammed, altering the effects of LMVs on cancer cells [126]. In particular, MVs isolated from human AML cell line KG-la, previously transfected with miR-34a mimic, were used to inhibit proliferation and migration of AML cell by the modulation of caspase-3 and Tim-3 levels [126].

Despite the above described miRNA-therapeutic approach advantages, there are still many challenges to be solved before introducing it into the clinic. Furthermore, although the literature suggests limited toxicity of some of these miRNAs in various model systems, clinical trials are necessary to evaluate whether this preclinical promise will be recapitulated in human patients. Likewise, concentration and dose plans need to be evaluated for efficacy and toxicity, and the long-term effects following miRNA therapy must be assessed. Additionally, as the therapeutic potential of different miRNAs has been investigated, the combination of multiple miRNAs could be evaluated as a possible miRNA therapy in AML.

Nevertheless, a major limitation preventing the development of miRNA-based therapies is the difficulty to deliver drugs to BM, and the necessity of using higher doses to elicit a therapeutic effect [14].

7. Long Non-Coding RNAs Can Interfere with miRNA Function in AML

Although a broad range of non-coding RNAs has been discovered, miRNAs and long non-coding RNAs (lncRNAs) are the best studied. LncRNAs are RNAs longer than 200 nucleotides. Based on the genomic locations where lncRNAs are transcribed, they can be classified into sense, overlapping with at least part of another gene in the same strand; antisense, overlapping with at least part of another gene on the opposite strand; intronic, originating from the intron of another gene; intergenic, not overlapping with any gene; and chimeric, resulting from fusion products due to chromosomal rearrangements [179].

LncRNAs could promote the strength of specific enhancer–promoter looping, contributing to gene activation [179].

Their expression is tightly controlled, and exhibits higher cell specificity than proteins, including lineage-determining transcription factors [180]. LncRNAs play an important role in several biological processes, including cell development, differentiation, proliferation, invasion, and migration [181]. LncRNAs regulate gene expression at the epigenetic, transcriptional, and post-transcriptional level [182].

Aberrant expression of miRNAs and lncRNAs has been described in all types of cancers [183,184].

In AML, aberrant expression of lncRNAs contributes to initiation, maintenance, and development of leukemogenesis [179]. They are involved in chromatin remodeling, as well as transcriptional and post-transcriptional regulation, through a variety of chromatin-based mechanisms and via cross-talk with other RNA species. LncRNAs can function as decoys, scaffolds, and enhancer RNAs [185]. Moreover, lncRNAs competed with endogenous miRNAs in AML.
A lncRNA, CCAT1, for example, was found overexpressed in AML; it repressed monocytic differentiation, and promoted AML cell growth by sequestering miR-155 [186]. In accord with Palma’s study [107], Chen’s work showed that miR-155 has a pro-differentiation and anti-proliferation role in FLT3 wild-type AML cells [186], in contrast to its oncogenic function reported in FLT3-ITD mutated AML [91,187]. These data suggested that the gene regulation by miR-155 is complex, as it targets both tumor suppressor genes or oncogenes, and its function in a specific subtype of AML is likely subject to disease context and cell type [107,186].

An oncogenic activity of lncRNA was also shown by HOTAIR that competitively binds miR-193a, an important tumor-suppressor miRNA, thus modulating the expression of c-Kit in AML cells [188]. The lncRNA HOTAIRM1, instead, was associated with myeloid differentiation; it also had pivotal roles in the degradation of oncoprotein PML-RARA, by acting as a microRNA sponge, sequestering miR-20a, miR-106b, and miR-125b, whose targets are autophagy-associated genes [189].

Moreover, Mangiavacchi et al. showed that the host non-coding transcript of miR-223, linc-223, is a functional lncRNA that controls proliferation and differentiation of AML cells by binding miR-125-5p. This lncRNA is an oncogenic miRNA upregulated in primary AML where linc-223 was instead downregulated [190].

In conclusion, lncRNA functions introduce an extra layer of complexity in the miRNA-target network, making it necessary to study the interactions between miRNAs and lncRNAs, both to shed light on AML pathogenesis and on therapy.

8. Conclusions

miRNAs have emerged as a class of gene expression pivotal regulators contributing to AML pathogenesis and as potential biomarkers. Actually, miRNA analysis has not yet been included in AML clinical practice. Specific miRNA expression could help clinicians to classify subtypes, to determine prognosis, and to predict the response of treatment in AML.

Particular attention should be given to circulating miRNA, both free or contained in EVs, which are easy to collect with a non-invasive peripheral blood sample. In addition, while malignant cells are usually reduced after treatment, circulating RNAs can still be detected. Finally, miRNA analysis, through advanced next generation sequencing, will provide more details on miRNAs, and also lncRNAs involved in leukemia onset and progression. This information supports the concept that circulating miRNAs, in addition to current clinical AML parameters, could have significant value as new AML biomarkers for detection of disease progression. They can also serve as indicators of therapeutic response, and in MRD detection in a future clinical practice.

Another approach to improving AML outcomes could be the potential use of miRNAs as therapeutic targets. miRNA modulation could be obtained through new strategies by using miRNA inhibitors or mimics.

Moreover, miRNA therapy in combination with current chemotherapy could potentially eradicate LSCs.

Actually, the main problems in developing miRNA therapy are the identification of the best miRNA candidates and the design of miRNA delivery vehicles that confer higher stability to the therapeutic candidate, avoiding potential toxicities and off target effects [191]. Many complexities and mysteries remain in miRNA biology; miRNA studies will be key to our understanding of how to improve their use in an AML clinical setting.

The role of miRNAs in AML is reported in a schematic diagram in Figure 1.
Figure 1. Schematic diagram of microRNAs role in AML. MicroRNAs are involved in pathogenesis and are considered as biomarkers and therapeutic targets in AML. Red arrows indicate overexpression of oncomiR and downexpression of tumor suppressor miR which cause AML; lightning and two-headed arrow indicate targeting and restore, respectively; green arrows indicate decreased oncomiR or increased tumor suppressor miR levels that block AML; red cross indicates AML block.

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