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Original Article

Regulatory noncoding RNAs: potential biomarkers and therapeutic targets in acute myeloid leukemia

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Abstract: The noncoding RNAs (ncRNA) comprise a substantial segment of the human transcriptome and have emerged as key elements of cellular homeostasis and disease pathogenesis. Dysregulation of these ncRNAs by alterations in the primary RNA motifs and/or aberrant expression levels is relevant in various diseases, especially cancer. The recent research advances indicate that ncRNAs regulate vital oncogenic processes, including hematopoietic cell differentiation, proliferation, apoptosis, migration, and angiogenesis. The ever-expanding role of ncRNAs in cancer progression and metastasis has sparked interest as potential diagnostic and prognostic biomarkers in acute myeloid leukemia. Moreover, advances in antisense oligonucleotide technologies and pharmacologic discoveries of small molecule inhibitors in targeting RNA structures and RNA-protein complexes have opened newer avenues that may help develop the next generation anti-cancer therapeutics. In this review, we have discussed the role of ncRNA in acute myeloid leukemia and their utility as potential biomarkers and therapeutic targets.

Keywords: Noncoding RNA, AML, acute myeloid leukemia, miRNA, lnc-RNA, circRNA, oncomiRs, LNA

Introduction

Acute myeloid leukemia (AML) is a combative clonal malignancy of hematopoietic stem or progenitor cells, characterized by uncontrolled proliferation and accumulation of undifferentiated myeloid cells, which have highly diverse genetic and epigenetic abnormalities [1]. With a 4.3 per 100,000 annual occurrences (age-adjusted cases from 2014 to 2018), in the United States alone, the median age at diagnosis of AML is 68 years, with a 5-year relative survival rate of 29.5% [2]. The growing understanding of genomics has revealed the molecular complexity of abnormal leukemogenesis in AML, which has significantly aided risk stratification and customized therapeutic strategies for these patients [3-6]. Nevertheless, the long-term survival is less than 30% in patients below the age of 60 and worse in older AML patients with co-morbidities [7, 8]. A substantial number of AML patients, even after achieving complete remission (CR) post-induction chemotherapy, ultimately develop disease relapse or become refractory [9, 10].

There are currently no screening programs or reliable and cost-effective universal biomarkers for the early detection of AML that would influence disease outcomes [11]. Furthermore, even though many readily available blood-based biomarkers for prognosis and prediction of treatment outcome have been evaluated at various stages of treatment and disease, they have not yet reached clinical routine [12].

With the advent of high throughput sequencing technology, noncoding RNAs have been classified and proven to be associated with tumor initiation to its development. Ninety-five percent of the human genome contains noncoding DNA, most of which are transcribed into functional noncoding RNAs, including microRNAs, small interfering RNAs and long noncoding RNAs [13, 14]. In the past, many researchers have shown that ncRNAs are dysregulated in various cancer processes, such as metastasis, drug resistance and cancer stem cell (CSC) initiation and their role as potential therapeutic targets [15-17]. Several miRNAs have reached clinical trials [18, 19]. Furthermore, lncRNAs and circRNAs have shown significant clinical relevance in cancers

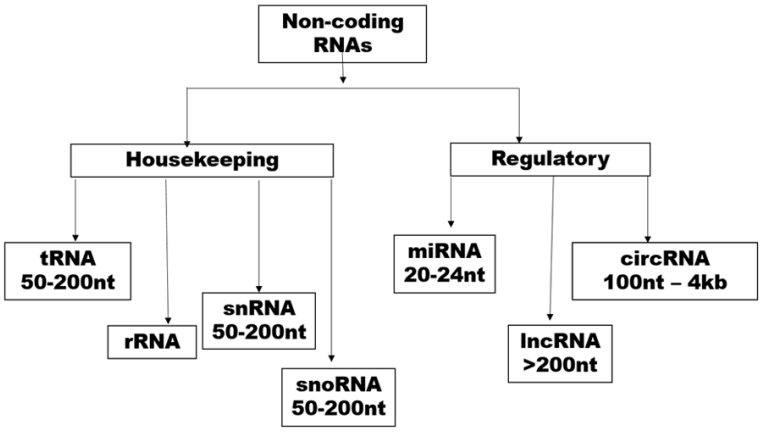

Figure 1. Broad classification of major ncRNAs based on their size and function.

due to their relatively complex multiple mechanisms of action and diverse structures [20]. In recent years, liquid biopsies such as circulating tumor cells or circulating ribonucleic acids obtained from blood are emerging. These liquid biopsies may serve as novel and promising-tools for the diagnosis, prognosis prediction, and selection of appropriate treatment options in AML patients [21]. In the current scenario, the utility of cutting-edge technologies such as next-generation deep sequencing has allowed us to characterize ncRNAs in AML. The utility of ncRNAs as potential biomarkers and therapeutic targets is evaluated and is an incessantly evolving area of investigation [22]. The role of ncRNAs in AML pathogenesis, their potential role as biomarkers in diagnosis and prognosis, and the potential for future therapeutics have been discussed here.

Characteristics of noncoding RNAs

The ncRNAs constitute the most significant part of the non-protein coding genome (98%) and play a pivotal role in regulating gene expression via transcription, translation, and RNA splicing. These ncRNAs include micro RNAs (miRNA), small nuclear RNA (snRNA), long noncoding RNA (lncRNA), circular RNAs (circRNA) and PIWI-interacting RNAs (piRNA). Characterization of ncRNAs has become possible with the advent of next-generation sequencing technologies [23]. Based on the size and their functions, ncRNA have been classified into two categories, housekeeping and regulatory ncRNAs. Regulatory ncRNAs can be further classified broadly as miRNAs (20-24 nucleotides), lncRNAs (>200 nucleotides) and circRNAs (**Figure 1**).

Micro RNAs are a highly explored group of ncRNAs containing 20-24 nucleotides that play a pivotal role in post-transcriptional gene regulation. The mature miRNAs are generated from a primary miRNA transcript after undergoing several post-processing steps in the nucleus and cytoplasm. The mature miRNA is bound to the RNA-induced silencing complex (RISC). This complex targets specific mRNAs 3' untranslated region (UTR) based on sequence complementarity, which results in reduced protein formation via various post transcriptional and translational mechanisms [24, 25].

Long noncoding RNAs (lncRNA) forms an emerging class of ncRNAs with multifunctional competence and are longer than 200 nucleotides in length. They are typically transcribed by RNA polymerase II and lack a significant open reading frame [26]. Based on their genomic origin and directionality, they are classified as intergenic lncRNA, intronic, sense and antisense lncRNAs. In cells, different lncRNA molecules may act as signal-regulating elements expressed in a temporal and tissue-tropic manner. These may also act as miRNA sponges that can sequester miRNAs from their target mRNAs. Earlier, lncRNAs were considered unstable due to their low expression, but few were found to be very stable, with half-life of more than 12 hours [27]. According to NONCODEv6.0, over 1,00,000 lncRNAs have been identified and 17948 have been validated in GENCODE consortium (version 37) [28, 29].

CircRNAs are another group of ncRNAs that are covalently closed circular RNAs and highly conserved, stable, and tissue specific [30]. These function as sponges for miRNA and may act as competing endogenous RNAs that negatively influence miRNAs. Due to their natural resistance to exonucleases, circRNA can become highly stable with a half-life of more than 24 hours.

Table 1. Potential miRNAs involved in various cancer-related pathways/target genes in Acute myeloid leukemia

miRNAs	Pathways involved/Target genes
miR-125a	ErbB pathway [78]
miR-125b	Mcl-1 [43, 79]
miR-141	PI3K/Akt/mTOR [80]
miR-181a, b and c	PRKCD, CAMKK1 and CTDSPL [53, 54]
miR-181b	MDR, HMGB1 and Mcl-1 [81, 82]
miR-191-5p, miR-142-3p	PPP2R2A [83]
miR-21, miR-196b	HOX [84]
miR-22-3p, let-7e-5p	PLK1 [85]
miR-29a/b/c	DNMTs [86]
miR-34a	PD-L1 [87]
miR-638	CDK2 [88]

Regulatory role of miRNAs in AML

The miRNAs function through a synchronized regulation of several genes. Recent progress in network biology had shed more light on the systemic level miRNA signalling pathways in AML disease biology [31]. Researchers have identified that deregulation of miR-155 was associated with activation of STAT5 in G-CSF-stimulated hematopoietic stem/progenitor cells isolated (HSCs) from AML patients with over expression of G-CSFRIV. The STAT5 activation correlated with a high miR-155 expression that indirectly regulated CCL2 expression, and CCL2 deficiency was linked to marred secretion of G-CSF [32, 33]. Furthermore, few studies demonstrated the involvement of different miRNAs in regulating various signalling pathways and their target genes in AML (**Table 1**).

Role of miRNAs associated with AML stem cells

Recent studies have shown that a few miRNAs were involved in progenitor lineage adherence [34] and regulation of HSCs in normal haematopoiesis by harmonizing the suppression of multiple targets [35-37]. Researchers have reported the role of miR-29a, miR-125a/b and miR-126, in regulating HSC self-renewal [38, 39]. Recently, higher expression levels of exosomal miR-7977 in LSCs than normal $CD34^+$ cells were shown to promote AML. It is probably crucial to disrupting normal hematopoiesis by suppressing poly(rC)-binding protein. It also induced aberrant hematopoietic growth factors in mesenchymal stem cells, ensuing in a hostile microenvironment for the normal stem cells [40]. In a study, researchers demonstrated that miR-34c-5p was significantly down-regulated in AML that correlated with poor prognosis and inadequate response to AML treatment. On the contrary, increased expression of miR-34c-5p induced LSCs senescence *ex vivo,* prevented leukemia development and promoted the eradication of LSCs in immune-deficient mice. This study showed a promising novel treatment strategy for AML patients by targeting LSCs to reinitiate senescence through over expression of miR-34c-5p; and may also be useful in the treatment of other cancers [41]. In other reports, overexpression of miR-29a in normal hematopoietic cells was associated with development of a myeloproliferative disorder that progressed into AML [42], and overexpression of miR-125b led to leukemia [43]. Another study reported that targeting miR-126 in leukemic cells could reduce cell growth by inducing apoptosis [44]. This accumulating evidence shows that these miRNAs could be targeted for the treatment of AML.

The prognostic and functional role of miRNAs in AML

Since miRNAs affect various leukemic processes including proliferation, survival to epigenetic regulation and drug resistance, these function as oncomiRs in many cytogenetically normal AML (CN-AML) and abnormal AML subtypes (**Table 2**). These oncomiRs are involved in leukemia development and progression in collaboration with known oncogenes or tumor suppressors, by targeting their expression level or by participating in an orchestrated fashion with these proteins to enhance malignancy [45-47]. Alteration of miR-125, miR-29, miR-155 and miR-146 have been associated with prognosis and pathogenesis in AML [48]. The miR-29a/b/c have been demonstrated to be oncogenes and tumor suppressors in hematopoietic malignancies [49]. We have summarised the findings of key dysregulated miRNAs consistently shown to play a role in AML disease pathogenesis (**Table 2**). Moreover, we addressed some of the more novel aspects of miRNA biology in AML below for improved strategic therapy design in the future.

Table 2. Deregulated miRNA in acute myeloid leukemia and their role in oncogenesis (data taken from miRCancer database) [89]

miRNA (dysregulation)	Function/clinical relevance and targets
hsa-let-7a (up)	● Regulates expression of CASP3 in APL, which decreases cell proliferation. ● Dysregulation of let-7a in CN-AML: associated with NPM1 and FLT3 mutation and clinical characteristics.
hsa-mir-1 (up)	● Deregulation of miR-1, miR486 in CN-AML: associated with NPM1 and FLT3 mutation and clinical characteristics.
hsa-mir-101-3p (up)	● Related with miRNA profiling of exosomes from Marrow-Derived Mesenchymal Stromal Cells in patients with AML.
hsa-mir-10a/b (up)	● miRNA-10a/bare associated with regulation of myeloid differentiation in AML. ● has-miR-10b regulates the proliferation and apoptosis of pediatric AML via targeting of HOXD10.
hsa-mir-125a/b (up)	● miR-125b promotes MLL-AF9-driven murine AML involving a VEGFA-mediated non-cell-intrinsic mechanism. ● miR-125b helps in proliferation of human AML cells by targeting Bak1.
hsa-mir-155 (up)	● miRNA-155 serve as potential biomarker in haematological malignancies in serum-derived extracellular vesicles. ● Associated with drug targeting of miR-155 via the NEDD8-activating enzyme inhibitor Pevonedistat in FLT3-ITD AML.
hsa-mir-19a/b (up)	● Up regulation in bone marrow predicts poor prognosis and disease recurrence in de novo AML.
hsa-let-7c (down)	● Promotes granulocytic differentiation in AML.
hsa-mir-122 (down)	● Decreased expression is associated with a poor prognosis in childhood AML, shows therapeutic potential.
hsa-mir-125a-3p/b (down)	● Inhibits TIM-3 Expression in AML cell line. ● High expression inhibits AML cells invasion, proliferation and promotes cells apoptosis by targeting NF-kB pathway.
hsa-mir-199a-1/2/b (down)	● Inhibits proliferation and promotes apoptosis in children with AML by targeting caspase-3. ● A novel tumor suppressor miRNA in AML with prognostic implications.
hsa-mir-29a/b/c (down)	● Regulates the expression of the nuclear oncogene Ski. ● The dual epigenetic role of PRMT5 in AML: gene activation and repression via histone arginine methylation. ● Down-regulation of miR-29c is a prognostic biomarker in AML and can reduce the sensitivity of leukemic cells to decitabine.
hsa-mir-92a (down)	● Inhibits proliferation and induces apoptosis by regulating Methylenetetrahydrofolate dehydrogenase 2 (MTHFD2) expression in AML. ● Circulating miR-92a, miR-143 and miR-342 in Plasma are Novel Potential Biomarkers for AML.

Table represents selected deregulated miRNAs involved in disease progression with a known clinical impact and have in vivo/in vitro evidences.

MicroRNAs as diagnostic and prognostic tool in AML

The panoptic studies have demonstrated that miRNAs can be utilized as diagnostic markers in AML [50]. Up-regulation of let-7a-2-3p and down-regulation of miR-188-5a in cytogenetically normal AML patients have been associated with longer overall survival (OS) and event free survival (EFS) [51]. High miR-181 expression in AML acts by downregulation of toll-like receptor and interleukin 1β and HOXA7, HOXA9, HOXA11, and PBX3 [52-54]. miR-181b was down-regulated in relapsed and refractory AML patients contributing to drug resistance. Overexpression of miR-181b could enhance drug sensitivity and apoptosis in AML at least partially through direct suppression of its target genes, HMGB1 and Mcl-1. **Table 3** shows miRNAs associated with prognosis in AML. Here we

Table 3. miRNAs associated with poor or favourable prognosis in Acute myeloid leukemia [31, 56]

Poor prognosis	Favourable prognosis
let-7a-3, miR-9-5p, miR-26a, miR-29b/c, miR-34a, miR-124, miR-124-1, miR-126, **miR-146a***, miR-155, **miR335***, **miR-210***, miR-155-5p, miR-181b, miR-1885p, miR-191	let-7a-2-3p, **miR-10a***, miR-20a, miR-25, miR29a/b, **miR-34a***, miR-96, miR-135a, miR-142, **miR-150***, **miR-203***, **miR-212***, miR-409-3p, miR-204

*miR-IDs in bold were found associated with poor or favourable prognosis most frequently.

have highlighted the efforts being made towards moving miRNA research as disease biomarkers as well as advances in miRNA-targeting therapeutic strategies in AML.

Role of deregulated miRNAs in drug resistance in AML

The older AML patients treated with single drug decitabine (DNA hypomethylating agent) have shown treatment response with higher expression of miR-29b. Indeed, miR-29b expression levels serve as a predictive factor for stratifying older AML patients to decitabine treatment [55, 56]. The ability of miR-29b to target DNA methyltransferases might explain the phenomenon of decitabine response associated with miR-29b. In a study cohort, higher expression of miR-29c was associated with poor survival in AML patients compared to healthy patients [57]. Authors have also reported that patients with reduced miR-29c expression could achieve complete remission after treatment with high dose chemotherapy (daunorubicin + cytarabine) or low dose cytarabine or azacytidine. In contrast, higher miR-29c expression was associated with an increased tendency to relapse after patients achieved complete remission [57].

A large number of studies on miRNA expression and therapeutic resistance to intensive AML treatment have been reported, allowing miRNAs to be classified into two categories (**Table 4**). Increased expression of Category-I miRNAs is associated with chemotherapy sensitivity on the other hand decreased expression mediates chemotherapy resistance. Alternately, Category-II miRNAs increased expression indicates therapeutic resistance, whereas reduced expression indicates therapeutic sensitivity, as summarized in **Table 4**.

Long noncoding RNAs in AML

LncRNAs are emerging as an appealing biological marker for diagnostic and prognostic purposes because of their tissue and disease-specific nature [58]. LncRNAs can be used as an indicator or predictor of disease stage by their differential expression levels compared to normal tissue [59]. Although many lncRNA expression-related studies have been performed, systematic study of lncRNA expression in acute myeloid leukaemia has not yet been conducted. Researchers used RNA sequencing and quantification of lncRNA expression in 274 intensively treated AML patients in a Swedish cohort to demonstrate whether lncRNA-based molecular subtypes exist and are prognostic. Their study classified lncRNAs into four subtypes and validated their findings in an independent patient cohort (TCGA-AML) [60]. It was demonstrated that lncRNA expression profiling could provide valuable information for better risk stratification of AML patients. Researchers have conducted a similar study and discovered that upregulated lncRNA in AML was linked to a lower level of DNA methylation. It was also demonstrated that LOC285758 promotes AML cell proliferation by raising histone deacetylase-2 expression and higher expression of LOC285758 in patients associated with a worse prognosis [61]. Various studies reported aberrant expression of lncRNAs in AML as summarized in **Table 5**.

LncRNA in chemotherapeutic resistance of AML

Despite the availability of therapeutics for haematological malignancies, drug resistance appears to be a roadblock to successful treatment. Researchers in human cancers have demonstrated the mechanisms underlying lncRNA-mediated drug resistance. Furthermore, lncRNAs regulate the expression of genes involved in various processes, including drug metabolism in cells, cell repair, cell death, cell transformation, and stemness, all of which may contribute to drug resistance, either directly or indirectly in human diseases, including hematological malignancies. Treatment with anticancer drugs causes changes in gene expression, not

Table 4. Micro RNAs linked to therapeutic response in acute myeloid leukemia (AML) [37]

Groups	Clinical data	Experimental data
High expression associated with sensitivity (Category-I)	miR-181a [52, 53, 90] let-7f [90] miR-10 [91] miR-135a [84] miR-9-3p [92] miR-96 [93] miR-409 [84]	miR-181a [94] miR-128 [95] miR-331 [96] let-7f [90] let-7a [97]
High expression associated with resistance (Category-II)	miR-125b [98] miR-126 [44, 99] miR-210 [100] miR-196b [84] miR-199a [101] miR-191 [101] miR-644 [84]	miR-125b [102] miR-126 [99] miR-20a [103] miR-32 [104]

just in coding genes but also in noncoding genes such as lncRNAs. LncRNA-driven mechanisms of resistance to a variety of anticancer drugs have been extensively studied. Different types of drugs cause different drug resistance mechanism, which may have multiple contributing factors [62]. Some of the findings have been tabulated for lncRNAs and their potential role in drug resistance in AML (**Table 6**).

CircRNAs and their role in AML

CircRNAs are another group of covalently closed circular RNAs that are highly conserved, stable, and tissue-specific [30]. In recent years circRNA have received significant attention in the classification, diagnosis and treatment of hematological malignancies, including AML. They function as sponges for miRNA. Certain circRNAs can interfere with miRNAs by acting as competing endogenous RNAs. Due to their natural resistance to exonucleases, circRNAs become highly stable with a half-life of more than 24 to 48 hours. The specificity of circRNA to developmental stages and tissues makes its research area of paramount importance [63-65]. Here, we have discussed the fundamental roles of circRNAs and highlighted the gene alteration in the molecular pathogenesis of AML (**Table 7**).

CircRNA associated with drug resistance in AML

The relapse in AML patients has been a major challenge because of chemoresistance. Multiple genes and noncoding RNAs together contribute to chemoresistance in AML. In recent years, a plethora of research demonstrated the key role of circRNAs in mediating drug resistance, making circRNAs an important therapeutic target in AML therapy. The studies on the deregulated circRNA have suggested that the overexpression of circPVT1 develops the resistance to vincristine in AML [66]. Similar microarray expression study of doxorubicin resistant THP1 cell determined altered expression of 49 circRNAs and over expression of circPAN3 involved in drug resistance in recurrent and refractory AML [67]. A cell line based study had shown the association of circPAN3 in mediating drug resistance in AML via regulating autophagy [68]. The circPAN3 is predicted to have interaction with miRNAs, miR-153-5p, and miR-183-5p. Moreover, miR-153-5p and miR-183-5p have shown to interact with X-associated inhibitor ofapoptosis protein (XIAP), which has been evidenced as a drug resistance in AML [69-71].

Preclinical validation of miRNA therapeutics

The development of a bioinformatics program for identifying miRNA-binding sites in target genes and their corresponding implicated biological pathways, along with an expanding platform of *in vitro* and *in vivo* preclinical research models has helped expedite the translation of miRNAs into clinical medicine. The recent increase in the characterization of miRNAs and their mRNA targets relevant to AML disease progression opens the door for therapeutic manipulation of miRNAs in AML. Mimicking tumor suppressor via synthetic miRNAs or direct-

Table 5. Aberrant expression of lncRNAs in AML

Gene Name (Up/down-regulated)	Mechanism	Clinical response and parameters
HOTAIR (upregulated)	Works as a sponge for miR193a regulates the c-kit expression and LSC self-renewal mechanism	Poor DFS and OS, Higher BM blast count and lower platelets and hemoglobin counts [105-107]
H19 (upregulated)	Associated with ID2 expression	Reduced CR rate, shorter OS, Highest in M2 AML and also correlated with older age and sex [108]
MALAT (upregulated)	It affects apoptosis, proliferation by upregulating miR-96	Generally upregulated in M5 subtype, correlated with shorter OS [109, 110]
NEAT1 (downregulated)	Known to impair myeloid cell differentiation, regulates miR-23a-3p	Represses the expression of miR-23a-3p, and therefore promoted SMC1A [111]
HOXA-AS2 (upregulated)	Could negatively regulate the expression of miR-520c-3p	Plays a role in the resistance of AML cells to adriamycin [112, 113]
CRNDE (upregulated)	Promotes cell proliferation and inhibits apoptosis	Higher expression in M4 and M5, correlated with overall survival time in cell line study [114]
PANDAR (upregulated)	Interacts with NF-YA and inhibits pro-apoptotic gene expression	Reduced CR rate, poor survival and correlated with older age [115]
RUNXOR (upregulated)	Interacts with H3K27 methylase EZH2 and RUNX1 promotes AML cell growth by sequestering miR-155	Expression Raised in t (8;21) AML [116]
UCA1 (upregulated)	Acts as a sponge for miR-193a activates PI3K/AKT and JAK/STAT signalling pathways	Higher expression in patients having CEBPA mutations; Raised in ADR-resistant pediatric AML cases [117]
IRAIN (downregulated)	Possibly, it Interacts with the IGF1R promoter	shorter RFS, OS; refractory response to chemotherapy [118]
CCDC26 (upregulated)	Regulates AML cell proliferation via c-Kit expression	Correlated with older age, reduced CR rate and shorter OS [119]
TUG1 (upregulated)	reduces miR-34a expression and contributes to ADR resistance	Poor-risk stratification, and worse event-free survival and OS [120]
MEG3 (downregulated)	Inhibits tumorigenesis via P53 dependent and independent manner	Aberrant methylation leads to shorter OS [121]

Table 6. LncRNAs and their potential role in drug resistance in AML

lncRNA	Functional role in drug resistance	Clinical outcome/References
MEG3	positively regulating ALG9 through sponging miR-155	Contributes drug resistance in AML [122]
UCA1	Inhibits glycolysis via miRNA-125a/hexokinase2 pathway	Knockdown of UCA1 suppresses chemoresistance in pediatric AML [123]
SNHG5	Regulates SOX4 expression through competitive binding to miR-489-3p	knockdown of SNHG5 could down-regulated SOX4 levels in vivo in AML patients and cell lines [124]
HOTAIR	Modulates c-KIT expression through sponging miR-193a	Higher HOTAIR predicted worse clinical outcome compared with those with lower HOTAIR in AML [106]

Table 7. Role of circRNAs in AML and their clinical impact

CircRNA	Mechanism	Clinical Impact
Circ-Vimentin (VIM)	Up regulated in AML patients. Involved in regulation of lymphocyte adhesion and migration	Associated with poor clinical outcome. It could be a diagnostic biomarker and treatment target [125]
circ-PVT1	Highly expressed in AML bone marrow cells. Work as a sponge for let-7 and miR-125	It could be a potential therapeutic target [126]
hsa-circ_0004277	Low expression in the AML	Associated with AML progression [127]
hsa_circ_0075001	Negatively correlated with the TLR signalling pathway	Biomarker for Classification and risk stratification [128]
circ-PAN3	Sponge for miR-153 and miR-183	Associated with recurrence and drug resistance [68]

Table 8. Preclinical miRNA based therapeutics in AML [25]

Therapy	Delivery method	Targets	In vivo (Interpretations)
miR-22 mimic	G7 poly (amidoamine) dendrimer nanoparticles	CRTC1, FLT3, MYCBP	Improved survival in xenotransplanted mouse models [73]
miR-29b mimic	Transferrin-conjugated anionic lipid-based nanoparticle	DNMT3A/B, DNMT1, CDK6, FLT3, KIT	Improved Survival and splenomegaly in NSG mice xenografted with MV4-11 cells [129]
miR-126 antagomiR	Transferrin or CD45.2-conjugated lipid-based nanoparticle	MMP7, CHD7, JAG1	Improved overall Survival in NSG mice engrafted with human AML primary blasts and MLL FLT3-ITD mouse model [74]
miR-21/miR-196b antagomiRs	Naked antagomiR delivered via implanted osmotic pumps	N/A	Improved survival in combination with induction chemotherapy in MLL-AF9 xenotransplantation model [130]
miR-181a mimic	Transferrin-conjugated anionic lipid-based nanoparticle	KRAS, NRAS, MAPK1	Improved Survival and splenomegaly in NSG mice xenografted with MV4-11 cells [131]

Table 9. miRNA Therapeutic molecules in the clinical trials for the treatment of various diseases

Therapeutic molecules	Treatment of Disease	Target miRNA	Clinical trial stage
Miravirsen (SPC3649)	Hepatitis C virus (HCV) infection	miR-122	Phase II
MRX34	Various types of Cancers	miR-34a	Phase 1
RGLS4326	Polycystic kidney disease (PKD)	miR-17	Phase I
RG-101	Viral effect	miR-122	Phase 1B
Cobomarsen (MRG-106)	Cutaneous T-cell lymphoma (CTCL)	miR-155	Phase-I
MRG-107	Amyotrophic lateral sclerosis (ALS)	miR-155	Entering in Phase-1
Remlarsen (MRG-201)	Different type of fibrosis such as cutaneous fibrosis, idiopathic pulmonary fibrosis etc.	miR-29	Phase-I

ly inhibiting oncomiRs using locked nucleic acid (LNA) oligonucleotide inhibitors could have a promising therapeutic potential. The adequacy of miRNA-based therapeutics in AML was demonstrated by delivering miR-29b employing transferrin-formed lipid nanoparticles *in vitro* and *in vivo* mice models [72]. Delivery of miR-29b prompted diminished leukemic cell development and improved survival in the AML mouse model, attributed to miR-29b downregulating CDK6, FLT3, DNMTs, and KIT. These target genes are involved in various cellular processes in AML. This study demonstrates the ability of miRNA-based treatment to affect multiple pathways simultaneously. The miR-based therapeutic studies have shown exciting results preclinically both *in vitro* and *in vivo* [73-75], as summarized in **Table 8**.

Studies of miRNAs as medical intervention drugs in clinical trials

The FDA recently approved the first small-interfering RNA (siRNA) drug, that holds great promise for therapeutic small RNA (200 nucleotides) drugs. Patisiran, a siRNA drug, is approved to treat a rare polyneuropathy caused by hereditary transthyretin-mediated (hATTR) amyloidosis. It works by binding and degrading the transthyretin messenger RNA transcript [76, 77]. Several miRNA molecules are currently undergoing clinical trials. The first miRNA molecule that entered into the clinical trial is Miravirsen, a modified anti-sense oligonucleotide against miR-122 for the treatment of hepatitis C virus. It is undergoing Phase II clinical trials in several countries, including US, Slovakia, Netherlands and Germany. A few of the miRNA based therapeutics for the treatment of various other diseases other than AML are summarised in **Table 9**.

Conclusion

Recent advances in our understanding of the role of noncoding RNAs and alterations in their expression patterns in hematological malignancies have opened newer avenues. Therein, we may very likely witness the advent of new therapeutic options, diagnostic and prognostic biomarkers based on ncRNAs from the laboratory to the clinic in the near future. The ncRNAs involved in drug resistance, and their role in diagnostics, and risk stratification in AML could lead to personalized therapy by predicting their response to treatment. Moreover, the inclusion of expression profiles of ncRNAs in AML classification could improve patient risk stratification. The promising pre-clinical data on miR-based therapeutic studies both *in vitro* and *in vivo* holds great potential as future therapeutics for AML.

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Disclosure of conflict of interest

None.

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