Role of microRNAs, circRNAs and long noncoding RNAs in acute myeloid leukemia

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Abstract

Acute myeloid leukemia (AML) is a malignant tumor of the immature myeloid hematopoietic cells in the bone marrow (BM). It is a highly heterogeneous disease, with rising morbidity and mortality in older patients. Although researches over the past decades have improved our understanding of AML, its pathogenesis has not yet been fully elucidated. Long noncoding RNAs (IncRNAs), microRNAs (miRNAs), and circular RNAs (circRNAs) are three noncoding RNA (ncRNA) molecules that regulate DNA transcription and translation. With the development of RNA-Seq technology, more and more ncRNAs that are closely related to AML leukemogenesis have been discovered. Numerous studies have found that these ncRNAs play an important role in leukemia cell proliferation, differentiation, and apoptosis. Some may potentially be used as prognostic biomarkers. In this systematic review, we briefly described the characteristics and molecular functions of three groups of ncRNAs, including IncRNAs, miRNAs, and circRNAs, and discussed their relationships with AML in detail.

Keywords: Acute myeloid leukemia, microRNA, circRNA, Long noncoding RNA

Background

Acute myeloid leukemia (AML) is an aggressive hematological malignancy characterized by abnormal proliferation and differentiation of the immature myeloid cells [1]. Despite a growing list of treatment options, most patients still relapse and die after remission, and the prognosis remains unideal [2]. It is necessary to explore new biomarkers for diagnosis, prognostication, and therapeutic targets of AML so as to develop more effective surveillance and treatment programs.

The discovery of noncoding RNAs (ncRNAs) opens up new prospects for AML diagnosis, prognosis and treatment. ncRNAs are functional small RNA molecules that are not translated into a protein [3]. The DNA molecules that make up the human genome are about 3 billion base pairs, of which about 5–10% are stably transcribed, but protein-coding genes account for less than 2% of the human genome. The remaining 3–8% of the genome are transcribed into non-coding transcripts, i.e., ncRNAs [4–6]. ncRNAs are divided into two categories based on their functions: housekeeping and regulatory, the latter includes miRNAs, circRNAs, and IncRNAs. Regulatory ncRNAs are extensively involved in gene transcription and translation. They are key players in physiological and pathological processes such as cell differentiation, ontogenesis, inflammation, and angiogenesis. There is emerging evidence that miRNAs, circRNAs, and IncRNAs actively participate in the pathogenesis of major hematological malignancies including AML [7]. In this review, we aimed to provide a comprehensive summary of the roles of miRNAs, circRNAs, and IncRNAs in AML, and to illustrate their diagnostic and prognosticating potentials in this disease.

MicroRNA

MicroRNAs (miRNAs) are small RNA molecules of approximately 22 nucleotides that bind to the 3′-untranslated region (3′-UTR) of the target mRNA and negatively regulate the expression of the target gene at the transcriptional level [8]. miRNAs mainly participate in the pathogenesis of AML through the following five mechanisms: copy number alterations, change in the proximity to the oncogenic genomic region due to
chromosomal translocation, epigenetic changes, aberrant targeting of miRNA promoter regions by altered transcription factors or oncoproteins, and finally, dysregulated miRNAs processing [9].

Abnormal miRNA expression and function in acute myeloid leukemia

The molecular and cytogenetic criteria currently defined by 2016 WHO is the most widely used diagnostic tool for AML [10]. Each AML subtype seems to exhibit a unique miRNA signature that distinguishes it from others. For example, Chen et al. reported miR-9, an oncogenic miRNA, was overexpressed in the mixed lineage leukemia (MLL)-rearranged AML patients. Inhibition of miR-9 expression could significantly reduce cell growth/viability and promote apoptosis [11]. Emmrich et al. found miR-9, significantly downregulated in pediatric AML with t(8;21), was characterized by its tumor-suppressive property. Upregulation of miR-9 decreased leukemic growth and induced monocytic differentiation of t(8;21) AML cell lines in vitro and in vivo. Functionally, miR-9 exerted its effects by binding to let-7 to suppress the oncogenic LIN28B/HMGA2 axis [12]. In another study, miR-9-1 was observed to be downregulated in t(8;21) AML. Besides, overexpressed miR-9-1 induced differentiation and inhibited proliferation in t(8;21) AML cell lines [13]. MiR-10a/b was significantly increased in AML patients with t(8;21), t(9;11), NPM1 mutation, and particularly M1, M2, and M3 subtype. Abnormal high expression in those patients led to unlimited proliferation of immature blood progenitors and repressed differentiation and maturation of mature blood cell [14]. Another study showed that miR-10a overexpression was significantly associated with French-American-British (FAB)-M3/t(15;17) subtypes and NPM1 mutation, leading to the lower percentage of bone marrow (BM) blasts, while overexpression of miR-10b was correlated with NPM1 and DNMT3A mutations, resulting in higher percentage of BM blasts [15]. Some studies observed overexpression of the miR-181 in cytogenetic normal AML (CN-AML) patients with CEBPA mutations, FLT3-ITD, and/or wild-type NPM1 and t(15;17) [16–19]. MiR-155 was upregulated in FLT3-ITD-associated AML and targeted the myeloid transcription factor PLI. Knockdown of miR-155 could repress proliferation and induce apoptosis of FLT3-ITD-associated leukemic cells [20].

MiRNA expression is also associated with morphologic sub-types of AML. MiR-122 expression, as an oncogene, was decreased in BM samples from pediatric patients with FAB subtype M7, and the forced expression of miR-122 in AML cell lines significantly inhibited cell proliferation and reduced the ratio of S-phase cells [21]. Xu et al. recently reported higher expression of miR-196b was observed in pediatric AML with M4/5 subtypes and predicted a poor outcome [22]. Another study compared M1 with M5 samples and noted that expressions of miR-146a/b, miR-181a/b/d, miR-130a, miR-663, and miR-135b were higher in M1, whereas expressions of miR-21, miR-193a, and miR-370 were higher in M5 [23]. Interestingly, in normal BM, miR-181a was enriched in B cells, T cells, monocytes, and granulocytes [24], but its overexpression was less common in monocytic lineage AML subtypes M4 or M5, but more so in M1 or M2 subtypes [25]. The expression levels of miR-195 in both BM and serum were significantly decreased, and pediatric patients with low serum miR-195 level more often had FAB-M7, unfavorable karyotypes, and shorter relapse-free and overall survival (OS) [26].

Changes in miRNA expression levels alter the expressions of downstream genes, promoting AML leukemogenesis [27]. For example, miR-155, acting as an oncogenic miRNA, may participate in the pathogenesis of AML by targeting SHIP1 and downregulating transcription factor PLI expression [28, 29]. This miRNA was regulated by NF-κB, whose activity was partly controlled by the NEDD8-dependent ubiquitin ligases [30, 31]. Schneider et al. reported that miR-155 expression was positively correlated with Meis1 expression level in MLL-rearranged AML and first indicated that the transforming efficacy of MLL-fusions remained unaltered in the absence of miR-155, while knocking out miR-155 did not affect in vitro leukemia formation or progression [32]. Other studies demonstrated that miR-9/9* was aberrantly expressed in myeloid progenitors of most AML cases to inhibit neutrophil differentiation by regulating EGN post-transcriptional level. Moreover, miR-9 could promote proliferation of leukemia cells in adult CD34+ AML with normal karyotype by suppressing Hes1 expression and knockdown of miR-9 could reduce circulating leukemic cell counts in peripheral blood (PB) and BM, attenuate splenomegaly and prolong survival in a xenotransplant mouse model [33, 34]. Li et al. showed that miR-193a expression was downregulated in AML1/ETO-positive leukemia cells because AML1/ETO triggered the heterochromatic silencing of miR-193a by binding at AML1-binding sites and recruiting chromatin-remodeling enzymes. Then the epigenetic silencing of tumor suppressor gene miR-193a led to leukemogenesis in AML with t(8;21) by activating the PTEN/PI3K signal pathway [35]. The latest study found that Erbin was the target of miR-183-5p that negatively regulated the Erbin expression, resulting in enhanced cell proliferation of AML cells via activation of RAS/RAF/MEK/ERK and PI3K/AKT/FoxO3a pathways [36]. MiR-125b, as an oncogenic miRNA, frequently overexpressed in human AML, could promote MLL-AF9-driven murine AML by
TET2-VEGFA pathway. Zhang et al. reported that miR-203 downregulation frequently occurred in CD34+ AML cells in relation to CD34+ cells isolated from patients. Additionally, re-expression of miR-203 inhibited cell proliferation, self-renewal, and sphere formation in LSCs by targeting survivin and Bmi-1 [37].

**MicroRNAs are associated with chemoresistance of AML**

Chemosensitivity is commonly seen in refractory and recurrent AML. Studies have shown that microRNAs are involved in AML chemotherapy resistance in many ways, such as apoptosis, cell cycle and ATP-binding cassette (ABC) transporter-mediated multidrug resistance.

Li et al. reported that miR-181a expression level was lower in the K562/A02 cells than in the K562 cells and could reduce doxorubicin resistance of K562/A02 cells by directly targeting the 3′-UTR of BCL-2 and MCL-1 mRNAs [38]. Similarly, miR-181a was underexpressed in the HL-60/Ara-C cell line compared with HL-60 cell line, while upregulated miR-181a in HL-60/Ara-C cells sensitized the cells to Ara-C treatment and promoted apoptosis by releasing cytochrome C and activating caspase-9/caspase-3 pathway. Functionally, BCL-2 was confirmed as a direct miR-181a target [39]. MiR-182-5p expression levels were higher in blood samples of AML patients than the normal samples. Cellular function indicated miR-182-5p inhibition in AML cells could decrease cell proliferation, promote AML cell apoptosis, and reverse cisplatin (DPD) resistance via targeting BCL2L12 and BCL2 expression [40].

Clinical chemotherapy drugs mainly interfere with cell cycle by inhibiting cellular DNA and RNA synthesis. FoxM1, an established oncogenic factor promoting cell cycle progression, plays a role in this process. MiR-370 expression was decreased in both leukemia cell lines (K562 and HL-60) and primary leukemic cells from patients BM with de novo AML. Ectopic expression of miR-370 in HL60 and K562 cells arrested cell growth and led to senescence, while knockout of miR-370 expression promoted the proliferation of those leukemic cells. Mechanistically, miR-370 played a tumor suppressive role by targeting FoxM1. Moreover, when AML cells were treated with 5-aza-2′-deoxycytidine (a DNA methylation inhibitor), upregulation of miR-370 expression was observed, suggesting epigenetic silencing of miR-370 in leukemic cells [41]. Cyclin D1 is a target protein of PTEN signaling pathway. PTEN mainly negatively regulates PI3K/AKT pathway through lipid phosphatase activity, then degrades Cyclin D1, leading to cell cycle organization in G1 phase. MiR-21 may desensitize leukemia cells to chemotherapy by interfering PTEN expression. Bai et al. reported high miR-21 expression in daunorubicin (DNR) resistant cell line K562/DNR. K562/DNR cell line stable transfected with miR-21 inhibitor was induced drug resistance, while inhibition of miR-21 enhanced cell sensitivity to cytotoxicity. Drug resistance mechanism of miR-21 was associated with regulating PTEN protein expression [42].

Chemotherapy drug resistance is also associated with efflux of hydrophobic drugs out of cells. ABC transporter and P-glycoprotein (P-gp), encoded by the MDRI gene, play pivotal roles in this process [43, 44]. MiR-381 and miR-495 were strongly underexpressed in K562/ADM cells. Restoring expression of miR-381 or miR-495 reduced expression of the MDRI gene and its protein product P-gp, and increased drug uptake via targeting the 3′-UTR of the MDRI gene [45]. In the drug-resistant cell line HL-60/VCR, miR-138 was significantly downregulated. Enhanced miR-138 expression significantly downregulated P-gp expression level and MRP1 transcription to promote doxorubicin-induced apoptosis and reversed HL-60/VCR resistance to P-gp dependent and P-gp independent drug delivery [46]. Besides, Feng et al. found that the expression of miR-331-5p and miR-27a was negatively correlated with MDR1 expression, and the upregulation of miR-331-5p and miR-27a decreased MDR1 expression and increased the sensitivity of K562-resistant cell line to doxorubicin [47].

**MicroRNAs and DNA methylation**

Aberrant DNA methylation is an important epigenetic modification in the pathogenesis of AML. DNA methyltransferases are mainly divided into two types: DNMT1 and DNMT3. The former maintains methylation, and the latter performs de novo methylation [48]. Garzon et al. demonstrated that miR-29b directly targeted DNMT3A and DNMT3B and indirectly targeted DNMT1, leading to DNA hypomethylation and tumor suppressor gene reactivation [49]. The indirect inhibition of DNMT1 was mediated by a zinc finger-like structural transcription factor SPI, which bound directly to the DNMT1 promoter region to start transcription [50]. MiR-29b downregulates SPI expression, thereby disrupting SPI-dependent DNMT1 transcription [11]. Another example of DNMTs inhibition was hypomethylating tumor suppressor P15INSK4b which could reduce susceptibility to myeloid leukemia in mouse model [51]. Phase 2 data of decitabine in elderly AML patients confirmed that miR-29b upregulation in BM cells could reduce the expression of DNMTs, enhance the effect of DNA hypomethylating agents, and therefore improve the remission rate [52].

MiR-29b could, however, be downregulated by SPI, as well as KIT. KIT overexpression has been observed in various tumors, including AML, and it promotes malignant cell proliferation [53]. Liu et al. identified that aberrant activation of KIT resulted in decreased MYC-dependent miR-29b expression and increased SPI
expression, the latter then interacted with the NF-κB/HDAC complex to further inhibit miR-29b expression and transactivate KIT [54].

Contrary to miR-29b, which suppressed leukemogenesis, miR-221 was able to contribute to the aggressive nature of AML via the NCL/miR-221/NF-κB/DNMT1 network. A group in China designed a nanoparticle that delivered anti-miR-221 antisense RNA in to leukemia cells. The nanoparticle could directly reactivate tumor suppressor gene p27kip1 by annihilating miR-221 and upregulate other tumor suppressor gene expressions by downregulating DNMT1. In mouse model, the nanoparticle showed promising therapeutic outcome [55].

Gene targets of miRNA may overcome the suppression or even downregulate the respective miRNA by DNA hypermethylation. For example, miR-375 could suppress HOXB3 expression and cause AML cell proliferation arrest and colony reduction. In return, HOXB3 enhanced DNMT3B’s binding to the promoter of miR-375, leading to DNA hypermethylation and lower expression of miR-375 [56].

**The role of exosomal microRNAs in acute myeloid leukemia**

Exosomes are cell-derived, biologically active membrane-bound vesicles. The role of exosomes in hematopoiesis is receiving increasing attention. In 2015, Hornick et al. identified a set of miRNAs enriched in AML exosomes from the NOD/SCID/IL-2γnull (NSG) mice serum, such as let-7a, miR-99b, miR-146a, miR-150, miR-155, miR-191, and miR-1246. These serum exosomal miRNAs could potentially be used for early detection of AML [57]. Barrera-Ramirez et al. later sequenced miRNAs from exosomes isolated from AML patients’ marrow samples and from healthy controls. Of the five candidate miRNAs identified by differential packaging in exosomes, miR-26a-5p and miR-101-3p were significantly increased in AML, while miR-23b-5p, miR-339-3p, and miR-425-5p were significantly decreased, but the role and target genes of these exosomal miRNAs were still unknown [58]. Some of them might be AML tumor suppressors. Another study found that exosomes isolated from cultured AML cells or AML mice plasma were enriched with miR-150 and miR-155. Hematopoietic stem/progenitor cells (HSPCs) co-cultured with either of the two exosomes experienced impaired clonogenicity through the miR-150- or miR-155-mediated suppression of c-Myc, a transcription factor involved in HSPC differentiation and proliferation [59]. Moreover, Huan et al. found that the Molm-14 exosome was also enriched in miR-150. This exosome was responsible for decreasing migration of AML cell lines and reducing the surface expression of CXCR4 [60].

Some exosomal miRNAs may promote AML leukemogenesis. In a recent study, miR-7977 was found to have higher levels in AML exosomes than those from normal CD34+ cells. It might be a critical player in disrupting normal hematopoiesis via suppression of poly(rC)-binding protein. It also induced aberrant production of hematopoietic growth factors in mesenchymal stem cells, resulting in a hostile microenvironment for the normal stem cells [61].

Leukemia stem cells (LSCs) are believed to be the primary source of exosomes. Shedding harmful miRNAs via exosomes might be a mechanism of LSCs’ self-protection. Peng et al. discovered that miR-34c-5p was significantly downregulated in AML (excluding APL) stem cells compared to normal HSPCs. Increased expression of miR-34c-5p could induce LSC senescence ex vivo via both p53-dependent and independent CKD/Cyclin pathways. LSC could generate miR-34c-5p deficiency by actively packing and transporting miR-34c-5p out of the cells in exosomes. In return, miR-34c-5p could suppress exosome-mediated transfer via a positive feedback loop through RAB27B, a molecule that promotes exosome shedding. By targeting RAB27B, miR-34c-5p could enrich its intracellular level and induce LSC senescence [62].

**MicroRNAs as biomarkers for prognosis in acute myeloid leukemia**

miRNAs have many properties of good AML prognostic biomarkers, such as wide presence in various tissues, highly conserved sequences, and easy and sensitive detection, as well as stability under extreme conditions [63, 64]. Mounting studies have shown that miRNAs can be used to predict outcome in CN-AML. Zhang et al. reported miR-216b overexpression as an independently poor prognostic factor for CN-AML and may provide a valuable biomarker associated with disease recurrence in AML [65]. In 224 patients with CN-AML, high miR-362-5p expression was associated with older age and shorter OS compared with low expressers [66]. Diaz-Beya et al. reported that high miR-3151 expression was commonly found in AML patients and obtained shorter disease-free, OS, lower CR rate and higher cumulative incidence of relapse compared with low expressers [67]. The underexpression of miR-328 in AML patients had poor clinical outcome and may provide a diagnostic and prognostic biomarker [68]. MiR-34a expression was negatively correlated with aggressive clinical variable. Patients with low miR-34a expression showed shorter overall and recurrence-free survival [69]. Xu et al. reported miR-135a as an independent prognostic factor for outcome in AML and a tumor suppressor in AML by inversely regulating HOXA10 expression [70]. Moreover, patients with high expression levels of
miR-146a and miR-3667 tended to have more favorable prognoses than their low expression counterparts [71], while underexpression of miR-122, miR-192, miR-193b-3p, miR-204, and miR-217, as well as miR-340 had been well studied to be unfavorable prognostic predictors of AML [72–77].

Some polymorphic miRNAs only had prognostic impact in certain subtypes. MiR-204 has two sites of variations: one is the upstream flanking region (rs718447 A > G), and the other is the gene itself (rs112062096 A > G). Butrym et al. demonstrated that miR-204 rs718447 GG homozygosity was a risk factor and associated with short survival [78].

Some miRNAs biomarkers might be helpful in selecting patients for allogenic hematopoietic stem cell transplant (allo-HSCT). High miR-425 level was associated with significantly longer OS and event-free survival (EFS) in non-transplant patients, but this association was not observed in post allo-HSCT patients. Instead, patients with downregulated miR-425 did better if they had allo-HSCT, suggesting that low miR-425 level might be an indication for transplant [79]. Overexpression of miR-99a predicted adverse prognosis in AML patients irrespective of transplant status, necessitating the investigation of novel alternative treatment in miR-99a overexpressors [80]. Moreover, high expression of miR-98 correlated with good clinical outcome in AML patients treated with chemotherapy alone [81].

miRNAs have potential prognostic value complementing information gained from gene mutations. MiR-181 family, which has been associated with CEBPA mutations and FLT3-ITD and/or NPM1 wild-type in CN-AML, did demonstrate prognostic value [17]. Marucci et al. reported favorable clinical outcomes in CN-AML patients with miR-181 overexpression and CEBPA mutations or miR-181 overexpression with FLT3-ITD [82]. In BM mononuclear cells of 113 de novo AML patients, miR-19b overexpression had more frequently occurred and high miR-19b expression had a higher frequency of mutations of U2AF1 and IDH1/2 genes and associated with poor prognosis and disease recurrence in AML [83]. AML patients with low miR-186 expression were frequently observed, and harbored lower complete remission rate and shorter OS, while miR-186high patients had a significantly higher frequency of CEBPA mutation [84]. These findings suggested that measuring miRNA may have potential advantages for predicting prognosis of AML compared to assessed gene mutations such as DMNT3A, FLT3-ITD, NPM1, and CEBPA. In published studies, univariate and multivariate analysis showed that miR-98, miR-99a, miR-340, miR-216b, and miR-34c had independent stronger prognostic impact on EFS and OS (P < 0.05) than gene mutations in FLT3-ITD, NPM1, DMNT3A, RUNX1, CEBPA, and TP53 [80, 81, 85, 86].

To summarize, miRNA researches in AML have yielded important results. The major miRNAs and their roles in AML were listed in Table 1.

Circular RNAs
Circular RNAs (circRNAs) are ubiquitous, stable, and conserved non-coding RNAs. They are closed circular RNA molecules and lack the 3′- and 5′-ends, different from the linear RNAs [141]. This structure was first described in viroids but later was also found in eukaryotic cells [142]. There are four types of circRNAs, namely exonic circRNAs (ecircRNAs), circRNAs from introns, exon-intron circRNAs (ElicRNAs), and intergenic circRNAs [143].

Aberrant circRNA expression levels in acute myeloid leukemia
With the help of sequencing technology, more than 10,000 circRNAs in human have been identified [144, 145]. Aiming to pinpoint circRNAs that correlated with AML, Li et al. [146] used circRNAs microarray and characterized the expression profile of circRNAs in CN-AML, in which 147 circRNAs were upregulated and 317 circRNAs were downregulated compared with healthy control. An interesting phenomenon was that while hsa_circ_0004277 was one of the most significantly downregulated circRNAs in AML, its expression level was restored in patients who achieved complete remission, and the level post-remission was the same as healthy control, but it significantly dropped if the patient became relapse-refractory. Their findings suggested that hsa_circ_0004277 could be a potential diagnostic biomarker in detecting early relapse. Another circRNA, circPVT1, was overexpressed in AML harboring oncogene MYC amplification [147], and this association could hint that circPVT1 might impact the survival of AML patients.

In vitro and in vivo experiments have confirmed that the fusion circRNAs are derived from a fusion gene produced by chromosomal translocation. The study by Guarnerio et al. discovered PML/RARA-derivative f-circPR, and MLL/AF9-derivative f-circM9, and both promoted malignant transformation, chemoresistance, and leukemia cell survival [148]. AML1 transcription factor complex is the most common target for leukemia-associated chromosomal translocations. HIPK2 is part of the AML1 complex and activates AML1-mediated transcription. Li et al. screened mutations of the HIPK2 gene in 50 cases of AML and found two missense mutations (R868W and N958I) of HIPK2 that are localized to nuclear regions with conical or ring shapes [149]. Hirsch et al. detected circular RNAs of NPM1. They found that the circular NPM1 transcript, i.e., has_circ_0075001, had lower expression in healthy volunteers.
## Table 1 miRNAs in acute myeloid leukemia

| miRNAs | Genetic abnormalities | Altered expression | Targets | Function | Reference |
|--------|-----------------------|--------------------|---------|----------|-----------|
| miR-9  | t(8;21)(q22;q22.1) RUNX1-RUNX1T1; mutated NPM1; biallelic mutations of CEBPA | ↑ in MLL-rearranged AML | RHOH, RYBP | miR-9 was upregulated by MLL-AF9 and increased MLL-AF9-mediated cell transformation in murine hematopoietic progenitor cells in vitro and in vivo. Mice transplanted with BM progenitors that overexpressed both MLL-AF9 and miR-9 (MLL-AF9+ miR-9) had higher frequency of c-Kit+ blast cells in the BM, spleen, and peripheral blood than MLL-AF9 mice. Moreover, MLL-AF9+ miR-9 leukemic cells had a higher frequency of immature blasts | [11] |
|        | ↓ in t(8;21) AML | HMG2A2, LIN28B | Increase proliferation and decrease monocytic differentiation | [12] |
|        | ↓ in RUNX1-RUNX1T1(+)AML | RUNX1, RUNX1T1, RUNX1- RUNX1T1 | RUNX1-RUNX1T1 triggered the heterochromatin silencing of miR-9-1, resulting in hypermethylation of the miR-9-1 promoter in t(8; 21) AML. Silencing of miR-9-1 promoted expression of target genes (RUNX1, RUNX1T1, and RUNX1- RUNX1T1), which inhibited differentiation and promoted the proliferation of t(8; 21) AML cell lines | [13] |
| miR-21 | Mutated NPM1; mutated RUNX1 | ↑ in K562/DNR | PTEN | Decreased cell sensitivity to daunorubicin | [42] |
|        | ↓ in various subtypes of AML | AKT2, CCND2 | Increase cell growth, leukemic progression in vivo | [91] |
|        | ↓ in various subtypes of AML | MCL-1, CDXC6, CDK6 | Increase cell growth, decrease apoptosis, leukemic progression in vivo | [92] |
| miR-22 | PML-RARA; mutated NPM1 | ↑ in K562 cells | DNMT1A, DNMT3B | Increase DNA methylation and hypermethylation | [49] |
|        | ↓ in NK cells | SP1 | Uregulate KIT contributing to malignant proliferation | [54] |
| miR-34a | Biallelic mutations of CEBPA | ↓ in CEBPA mutated AML | E2F3 | Increase proliferation and decrease differentiation | [95] |
| miRNAs       | Genetic abnormalities                                                                 | Altered expression | Targets                      | Function                                                                                       | Reference |
|--------------|----------------------------------------------------------------------------------------|--------------------|------------------------------|------------------------------------------------------------------------------------------------|-----------|
| miR-34b      | Mutated RUNX1; inv(16)(p13.1q22) or t(16;16) (p13.1;q22)                               | ↓ in initial diagnosis and relapse | PDL1, HMG1                  | Immune dysregulation, inhibit cell apoptosis and increased autophagy                          | [96]      |
| miR-34c-5p   |                                                                                       | ↓ in CEBPA mutated AML cell lines | CREB                        | Survival signaling pathways                                                                 | [97]      |
| miR-99a      | Mutated RUNX1; inv(16)(p13.1q22) or t(16;16) (p13.1;q22)                               | ↑ in initial diagnosis and relapse | RAB27B                      | High miR-99a expression could predict worse outcome in AML patients undergoing allo-HCST     | [80]      |
| miR-103      |                                                                                       | ↑ in t(8;21)(q22;q22.1) RUNX1-RUNX1T1; PML-RARA; mutated NPM1 | SMARCA5, H52ST3, HOXA1      | Regulate self-renewal, inhibiting differentiation and cell cycle entry                       | [99]      |
| miR-125b     |                                                                                       | ↑ in t(8;21)(q22;q22.1) RUNX1-RUNX1T1; PML-RARA; mutated NPM1 | COP1                        | Increase drug resistance of KS62 cells to ADR                                               | [100]     |
| miR-126      |                                                                                       | ↑ in t(8;21) and inv(16) AML    | PLK2                        | Inhibit cell apoptosis and increase cell viability                                           | [101]     |
| miR-135a     |                                                                                       | ↑ in AML cell lines            | NF-κB                       | Inhibits human AML cells invasion, proliferation and promotes AML apoptosis                  | [102]     |
| miR-139-5p   |                                                                                       | ↑ in AML                       | JUN, 2018 #227              | Antiapoptotic                                                                                  | [103]     |
| miR-143      |                                                                                       | ↑ in AML cell lines            | TRAF7                       | Suppresses apoptosis by downregulating TRAF7, which blocks the c-FLIP pathway                 | [104]     |
| miR-144-3p   |                                                                                       | ↑ in AML                       | HOXA10                      | Overexpression of miR-135a inhibits the proliferation and cell cycle and promotes cellular apoptosis | [70]      |
| miR-146a     |                                                                                       | ↑ in AML                       | EIF4G2                      | Repressing the translation initiation, specifically inducing the translation of cell cycle inhibitor p27 Kip1 | [114]     |
| miR-143      |                                                                                       | ↑ in AML cell lines            | ERK5                        | Increase granulocyte surface marker Ly6G and a more mature morphology toward granulocytes induces apoptosis | [115]     |
| miR-144-3p   |                                                                                       | ↑ in AML cell lines            | NRP2                        | Antiapoptotic                                                                                  | [116]     |
| miR-146a     |                                                                                       | ↑ in del(5q) MDS               | TIRAP                       | Inappropriate activation of innate immune signaling in HSPCs and megakaryocytic abnormalities | [117]     |

Knockout in del(5q)MDS/AML
| miRNAs | Genetic abnormalities | Altered expression | Targets | Function | Reference |
|--------|----------------------|--------------------|---------|----------|-----------|
| miR-143-5p | ↓in elderly AML patients | CXCR4, Smad4 | Suppress the migration abilities of leukemia cells and promote cell cycle entry in leukemia cells | [122] |
| miR-149-5p | ↑ | FASLG | Targeting FASLG led to suppression on cell apoptosis | [123] |
| miR-150 | PML-RARA | ↓in various subtypes of AML | NANO-G | Increase proliferation, colony, and sphere formation, increase tumor growth in vivo | [124] |
| miR-150 | ↓ | EIF4B, FOXO4, PRKCA, TET3 | Increase cell growth and inhibits apoptosis in vitro and in vivo | [125] |
| miR-155 | enriched in exosomes isolated from cultured AML cells | c-MYB | Hematopoiesis is suppressed by releasing exosomes that contain miR-150/miR155 targeting c-MYB | [59] |
| miR-181a | ↑ | KRAS, NRAS, and MAPK1 | Targeting the RAS-MAPK-pathway | [126] |
| miR-182-5p | ↑ in AML cell lines and patients blood sample | BCL2, L12 | Promote cell proliferation, and reverse cisplatin (DDP) resistance | [40] |
| miR-192 | ↓ in various subtype of AML | CCNT2 | Increase proliferation and cell cycling, decrease differentiation | [128] |
| miR-193a | ↓ in AML1/ETO-positive leukemia cells | PTEN/P3K signal pathway | AML1/ETO triggers the heterochromatin silencing of microRNA-193a (miR-193a) by binding at AML1-binding sites and recruiting chromatin-remodeling enzymes, which expands the oncogenic activity of AML-ETO, resulting in leukemogenesis | [35] |
| miR-193b | Biallelic mutations of CEBPA; mutated NPM1 | CCND1, KIT, KRAS, or SOS2 | Apoptosis and a G1/S-phase block | [74] |
| miR-196b | t(9;11)(p21.3;q23.3) MLL3-KMT2A; mutated NPM1 |↑ | Increase proliferation and survival, and decrease differentiation and replating potential | [129] |
| | ↑ in MLL-associated AML | HOXA9 | Inhibit differentiation, promote cell proliferation, and induce leukemic progression in mice | [130] |
| | ↑ in MLL-associated AML | Meis1 FAS | | |
| miR-204 | Mutated NPM1 | ↑ in AML cells | BIRC6 | Lead to AML cell apoptosis | [131] |
| | ↑ in NPM1C+ AML | HOXA10 Meis1 | | |
| miR-221 | t(8;21)(q22;q22.1) RUNX1-RUNX1T1; CBFB-MYH1; mutated NPM1 | ↑ in AML | NCL/miR-221/NF-κB/DNMT1 network | Involve in DNA hypomethylation | [55] |
| miR-223 | t(8;21)(q22;q22.1) RUNX1-RUNX1T1; CBFB-MYH1; | ↓ in t(8;21) AML | Myeloid differentiation block | [133] |
than in AML cell lines, and its expression was positively correlated with total NPM1 expression, but not with the status of NPM1 mutation [150]. Nevertheless, none of the current studies have elucidated the role of circRNA in AML pathogenesis.

The AML-related circRNAs and their roles in AML have been summarized in Table 2.

### Long noncoding RNA

Long noncoding RNAs (lncRNAs) are noncoding RNAs that are more than 200 nucleotides in length and lack a meaningful open reading frame [159]. lncRNAs are classified into intergenic lncRNAs, intron lncRNAs, sense lncRNAs, and antisense lncRNAs [160]. In cells, different lncRNAs may act as (1) a signal molecule, expressed at specific time and in specific tissues, regulating the expression of certain genes; (2) a miRNA sponge; (3) a leader molecule, directing RNAs that bind to RNA-binding proteins to reach regulatory sites, and regulating the expression of the relevant gene; and (4) a scaffold molecule, being a central platform for the assembly of other molecules.

### lncRNAs involved in acute myeloid leukemia pathogenesis

lncRNAs play an important role in BM cell differentiation and are subjected to differentiation-inducing therapies. HOTAIRM1 and NEAT1 are two important examples. HOTAIRM1 is a myeloid-specific lncRNA that is transcribed from the locus between the HOXA1 and HOXA2 genes. In the initial studies of lncRNAs in AML, HOTAIRM1 was found to be a regulator of myeloid differentiation and maturation by affecting the expression levels of integrin genes such as ITGA4 (CD49d) and ITGAX (CD11c). Knocking down HOTAIRM1 would prohibit all-trans retinoic acid (ATRA)-induced granulocytic differentiation [161]. The fact that HOTAIRM1 came from the HOXA cluster might imply that it could...
regulate nearby genes in the HOXA cluster, although this warranted further investigation. The other lncRNA, NEAT1, was significantly downregulated by PML-RARα in de novo APL samples compared with those of healthy donors. In NB4 cells, silencing NEAT1 could block ATRA-induced differentiation [162]. The roles of HOTAIRM1 and NEAT1 in normal hematopoiesis and leukemogenesis are awaiting further elucidation.

Other lncRNAs participate in regulating AML cell proliferation, cell cycle, and apoptosis. A typical example is lncRNA PVT1 [163]. The coding sequence of PVT1 on the chromosome is adjacent to MYC. Functional acquisition of MYC and PVT1 due to amplification of 8q24.21 is observed in approximately 10% of AML patients [164]. In AML cell lines, overexpression of PVT1 could induce apoptosis and necrosis, probably through downregulating c-MYC expression [165, 166]. UCA1 is another lncRNA that might have the capability to modulate AML cell proliferation; silencing of UCA1 by short hairpin RNA would result in a significantly slower cell proliferation and G1 cell cycle arrest. UCA1 could promote proliferation by inhibiting the expression of the cell cycle regulator p27kip1 [167]. Similarly, CRNDE could coordinate the proliferation and differentiation of AML cells as demonstrated by Wang et al. in their experiment with the U937 cell line [168]. At present, most of the lncRNA studies in AML are ex vivo, and the detailed mechanisms of lncRNA regulating cell proliferation remain to be investigated.

### LncRNA expression in AML with recurrent genetic mutations

Distinct lncRNA expression patterns have been observed in different AML subtypes, reflecting the heterogeneity of this disease. AML is most common in older patients (age ≥ 60) although they often have a worse prognosis [169, 170]. Numerous studies have identified characteristic lncRNA profiles in age ≥ 60 CN-AML patients with recurrent genetic mutations such as FLT3-ITD, NPM1, CEBPA, and RUNX1 mutations. 

#### FLT3-ITD-related lncRNAs

Wilms’ tumor 1 (WT1) expression positively correlates with FLT3-ITD in patients with AML [171]. Benetatos et
expression predicted a poor prognosis [177]. Mutation-associated lncRNA XLOC_109948 whose high employing RNA-sequencing identified another NPM1 and death [176]. Apart from them, a recent study acid-dependent modulator of myeloid cell differentiation ulated in the NPM1 coiled-coil domain containing 26 (CCD26) is also upreg-ulated in CN-AML patients with biallelic CEBPA mutations and could promote cell proliferation [167]. Another study reported that HOXB-AS3 was the most downregulated lncRNA in CEBPA-mutated AML while it was upregulated in NPM1-mutated AML [174].

**NPM1 mutation-related IncRNAs**

Besides the aforementioned HOXB-AS3 [175], the coiled-coil domain containing 26 (CCD26) is also upregulated in the NPM1-mutated AML and is a retinoic acid-dependent modulator of myeloid cell differentiation and death [176]. Apart from them, a recent study employing RNA-sequencing identified another NPM1 mutation-associated IncRNA XLOC_109948 whose high expression predicted a poor prognosis [177].

**RUNX1 mutation-related IncRNAs**

Fernando et al. first characterized CASC15, a conserved IncRNA upregulated in pediatric AML with RUNX1 muta-tion. High expression of CASC15 led to myeloid-predominant BM development, decreased engraftment, and colony formation. Researchers also found that CASC15 positively regulated YY1-mediated SOX4 promoter [178].

**Prognostic value of IncRNAs in acute myeloid leukemia**

IncRNA expression level could predict AML clinical features and outcomes. A published study has confirmed that IncRNAs can assist to predict clinical outcome in older patients with CN-AML. In the basic of 148 CN-older (age > 60 years) AML patients, Garzon et al. evaluated the associations of IncRNA expression with clinical characteristics, gene mutations, and outcome and built a IncRNA score including 48 IncRNAs for independently outcome prognosis [179]. Li et al. reported that SNHG5 overexpression was frequently observed in AML patients with advanced FAB classification and unfavorable cytogenetics. Furthermore, a higher SNHG5 expression level was also associated with shorter OS [180]. Yang et al. have determined the PANDAR expression level and its clinical significance in 119 de novo AML patients. AML patients expressing a higher level of PANDAR were associated with low complete remission rate and adverse prognosis in comparison with those with lower expression of PANDAR [181]. Moreover, high HOTAIR expression was associated with adverse clinical outcomes [182]. Based on 64 de novo non-M3 AML pa-tients, Pashaiefar et al. found that low expression of IRAIN was independently associated with adverse prognosis: higher white blood cell count and blast counts and shorter OS and relapse-free survival. Besides, pa-tients with refractory response to chemotherapies and those with subsequent relapse were more likely to show a lower initial IRAIN expression [183].

TUG1 has been in the spotlight of AML research. Higher TUG1 expression level occurred in AML pa-tients with monosomal karyotype, FLT3-ITD mutation, and poor-risk and correlated with higher white blood cell counts and worse event-free survival and overall sur-vival [184]. Luo et al. investigated the correlation of TUG1 expression with clinicopathological features and its predictive value for treatment response and survival profiles in refractory or relapsed AML patients age ≥ 60 years. They demonstrated that AML patients with higher TUG1 expression had shorter OS, and a lower rate of complete response and overall response than those with lower TUG1 expression [185].

Overall, there are only a few published reports of IncRNAs’ prognostic value in AML; thus, more profound works are required to investigate the association of IncRNAs, clinical characteristics, mutations, and outcome. The researches on AML-related IncRNAs are summarized in Table 3.

**IncRNAs and circRNAs can interfere with miRNA function in AML**

It has recently been learned that aberrant expression of IncRNAs and circRNAs in AML can change the function of specific miRNAs contributing to initiation, mainten-ance, and development of leukemogenesis. In 2011, Salmena et al. proposed a competing endogenous (ceRNA) hypothesis that IncRNAs competitively binds to endogenous miRNAs in AML. A IncRNA, H19, for example, was found overexpressed in BM samples from patients with AML-M2; it promoted AML cell proliferation by sequestering miR-19a/b [186]. The IncRNA NEAT1 that competitively binds miR-23a-3p, an oncogenic miRNA, thus modulating the expression of SMC1A in AML cells, which affected myeloid leukemia cell proliferation and apoptosis [187]. UCA1 is a func-tional IncRNA that promoted cell proliferation, migra-tion, and invasion of human AML cells via binding miR-126 [188]. In accord with Zhang et al.’s study, its expression was abnormally upregulated following doxorubicin-based chemotherapy and knockdown of UCA1 helped overcome chemoresistance in pediatric AML by suppressing glycolysis via binding miR-125a
FTX is another lncRNA involved in chemoresistance, and it controlled the expression of ALG3 by binding miR-342 [193]. HOXA cluster antisense RNA 2 (HOXA-AS2) was significantly upregulated in BM samples from AML patients after treatment with adriamycin-based chemotherapy and sponged miR-520c-3p to contribute to chemoresistance in AML [195].

An oncogenic activity of lncRNA was also shown by HOTAIR that regulating the expression of c-Kit in AML cells through competitively binding to miR-193a, an important tumor-suppressor miRNA to predict a poor clinical outcome [190]. HOTAIRM1, a lncRNA located in the HOXA genomic region, is related to myeloid differentiation which sequestered miR-20a, miR-106b and
miR-125b, all of which targets autophagy-associated genes, leading to the degradation of oncprotein PML-RARA. Moreover, Chen et al. showed that CCAT1 is an oncogenic lncRNA that upregulated c-Myc via its ceRNA activity on miR-155 to repress monocytic differentiation and promote cell growth [192]. The host non-coding transcript of miR-223 of linc-223, found downregulated in AML, is a functional lncRNA which regulated proliferation and differentiation of AML cells by binding miR-125-5p [203].

In recent years, the research of circRNAs, as one of ncRNAs, is focused on their function as “miRNA sponges” in the complex endogenous RNA networks. A circRNA HIPK2, for example, sponged miR-124-3p to regulate the differentiation of all-trans retinoic acid (ATRA)-induced NB4 cells [155]. Chen et al. [151] reported that circANAPC7 was significantly upregulated in AML and used an Arraystar human circRNAs microarray and bioinformatics analysis to predict when ANAPC7 might bind miR-181 family to participate in AML pathogenesis. An oncogenic activity of circRNA was also shown by DLEU2, which was highly expressed in AML, that inhibited miR-496 expression to promote cell proliferation and inhibit cell apoptosis [157]. A circular RNA 100290, which as an oncogenic circRNA was upregulated in AML, showed that it sponged miR-203 to control AML cell proliferation and apoptosis [152]. Moreover, Shang et al. demonstrated the circRNA PAN3 controlled AML chemoresistance by sequestering miR-153-5p and miR-183-5p, [153]. Moreover, Ping et al. showed that circ_0009910, upregulated in AML BM and predicting adverse outcome of AML patients, sponged miR-20a-5p to promote cell proliferation and inhibit [154].

In combination, lncRNAs and circRNAs introduce a complex layer in the miRNA target network, respectively, while lncRNA HOTAIRM1 and circ_0009910 can bind with the same miRNA, miR-20a, to play a different function in AML. The connections of these three ncRNAs involved in AML is shown in Fig. 1. But how lncRNAs and circRNAs compete with each other to bind with the same miRNAs remains unclear, thus making it necessary to further explore the relationship between lncRNAs and circRNAs in AML, to illustrate AML pathogenesis and therapy.

![Fig. 1 The connections of three ncRNAs involved in AML](image-url)
Conclusion
ncRNAs are widely recognized as critical participators in AML pathogenesis. Indeed, specific ncRNA expression could assist clinicians to classify subtypes, to evaluate prognosis, and to predict the response of drug treatment in AML. In this review, we discussed miRNAs, circRNAs, and IncRNAs, involving in subtypes, molecular function, chemoresistance and prognosis in AML, and the interactions between three major ncRNAs. Currently, the role of miRNAs in AML is most studied, but the mechanisms of miRNAs in AML still remain complex and unclear owing to miRNAs target genes ranging from tens to hundreds and involving different signaling pathways. In recent years, IncRNAs and circRNAs are introduced into miRNA network one after another and can be used as ceRNA of miRNAs and miRNAs sponge to regulate miRNA expression in AML. In our review, we reported that some IncRNAs such as UCA1 and lnc223 could target the same miRNA, miR-125, to control proliferation, apoptosis, and differentiation, and IncRNA HOTAIRM1 participated in autophagy pathway by binding with miR-125. MiR-125 has been reported to promote MLL-AF9-driven murine AML by TET2–VEGFA pathway and target autophagy-associated genes, leading to the degradation of oncoprotein PML-RARA. CircRNA_0009910 could also bind miR-20 via competing with IncRNA HOTAIRM1 to regulate proliferation and apoptosis. However, whether these three IncRNAs directly affect MLL-AF9-driven AML and autophagy, the target genes of miR-20 are not clear. Thus it is important to find the crossover miRNAs of the three ncRNAs to help illustrate the connections among these three ncRNAs. However, currently, there is very little literature on this subject and the connection networks of the three ncRNAs are required for further study. Subsequently, we will also trace relative studies and update the interaction networks of miRNAs, IncRNAs, and circRNAs.

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LF and JLS conceptualized the review. YL wrote the manuscript. YL and LZC prepared the figure and tables. YFP, TTQ, LQ and HYZ revised the review. ZHC, XYK and LF critically reviewed and edited the manuscript. All authors read and approved the final manuscript.

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