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# Long non-coding RNAs: emerging functional players in the pathobiology and progression of myeloid leukemia

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Advancements and innovations in transcriptomics and computational biology have revealed long non-coding RNAs (lncRNAs) as some of the major regulators of essential biological processes. Their restricted spatial and temporal expressions as well as ability to interact with nucleic acids (DNA and RNA) and proteins make them key players in chromosome integrity, genomic architecture, and transcriptional and post-transcriptional regulation. Their dysregulation has been associated with numerous diseases and pathological conditions, including cancers. Myeloid leukemia is a malignancy of the hematopoietic system, and its pathobiology has been found to have increasing number of lncRNAs with functional significance. This comprehensive review summarizes a majority of the reported lncRNAs in acute myeloid leukemia (AML) and chronic myeloid leukemia (CML), focusing on the regulatory mechanisms by which they modulate the disease progression and pathogenesis, their potential as diagnostics and prognostic markers, and their feasibility as novel therapeutic targets. We also highlight our recent work on the significance of the lncRNA Hmrhl in CML, which has been found to regulate gene transcription at the chromatin level.

KEYWORDS

**long non-coding RNA, myeloid leukemia, acute myeloid leukemia, chronic myeloid leukemia, prognostic markers, human meiotic recombination hot spot locus**

## 1 Introduction

Advances and applications of high-throughput sequencing technologies along with whole-genome sequencing have increased the focus of the scientific community on the uncharted territory of non-coding RNAs (Frese et al., 2013; Sun and Kraus, 2015). Although the regulatory roles of most small non-coding RNAs are well-characterized, most of the long non-coding RNAs (lncRNAs), which have lengths exceeding 200 nucleotides, remain relatively unexplored. Scientific research efforts from the last decade have confirmed the associations of thousands of lncRNAs with literally every known biological process (Sun and Kraus, 2015; Schmitz et al., 2016). Their functionality is supported by their dynamic expression patterns during development and differentiation as well as their highly specific spatial localization at the tissue/cellular/subcellular levels (Iyer et al., 2015a; Kopp and Mendell, 2018). From the documented functional roles of this enormous repertoire of lncRNAs, it can be concluded that they regulate gene expression and the epigenetic

environment to guide highly precise and complex biological processes; their importance is so far-reaching that it has been considerably underestimated. Regarding the importance of lncRNAs in various biological functions, it is not surprising that they are expressed differentially under various diseases and pathological conditions, such as diabetes, coronary artery disease, neuropsychiatric and neurodegenerative diseases (like schizophrenia and Alzheimer's), and most notably cancers (Wapinski and Chang, 2011; Mitra et al., 2012; Iyer et al., 2015b; Fatima et al., 2015; Lorenzen and Thum, 2016; Schmitz et al., 2016; Lan et al., 2022; Sivagurunathan et al., 2022). The newly released updated Lnc2Cancer3.0 database contains more data on the associations of lncRNAs with cancers (Gao et al., 2021b); there are 9,254 lncRNA–cancer associations, with 2,659 lncRNAs and their associations with 216 human cancer subtypes. In addition to such associations, the Lnc2Cancer3.0 database includes the experimentally supported regulatory mechanisms and biological functions for cancer-related lncRNAs (http://bio-bigdata.hrbmu.edu.cn/lnc2cancer). Although most of these are not fully characterized in terms of their functional relevance and regulatory mechanisms, their potential clinical applications as prognostic markers in the early detection of cancer and as probable drug targets are being increasingly realized (Rittenhouse et al., 2013; Sahu et al., 2015; Bartonicek et al., 2016; Lorenzi et al., 2019).

Myeloid or myelogenous leukemia is a malignancy of the hematopoietic system arising from various acquired and spontaneous genetic mutations that confer the potential of unchecked proliferation without differentiation on the myeloid progenitor cells (Weiskopf et al., 2017). The two subtypes of myeloid leukemia, namely acute and chronic, are characterized by the time period of disease progression. The more fatal acute myeloid leukemia (AML) progresses rapidly, resulting in the accumulation of immature and non-functional blood cells in the bone marrow. Conversely, chronic myeloid leukemia (CML) progresses more slowly and results in the accumulation of relatively mature but still abnormal blood cells (Kelly and Gilliland, 2002). Given the developments in therapeutics, CML patients often have better prognosis than AML patients. Studies have shown that about 90% of individuals with CML survive for 5 years or more after diagnosis, as compared to 30% in the case of AML (Dong Y. et al., 2020; Pulte et al., 2020).

The implications of lncRNAs in myeloid leukemia have only been highlighted in recent years but are increasing steadily. Herein, we review the current status of lncRNAs in myeloid leukemia and attempt to understand/link their dysregulation, functional, and mechanistic aspects with the pathobiology of this disease along with emphasis on their putative therapeutic potential. We also highlight our recent work on the role of the human meiotic recombination hot spot locus (Hmrhl) lncRNA in the pathobiology of CML in K562 as the cellular model (Choudhury et al., 2021).

# 2 Brief overview of lncRNAs

## 2.1 Biogenesis and characteristics of lncRNAs

The lncRNAs owe their name to their lack of an open reading frame and an arbitrary length classification of more than 200 nucleotides that allows them to be called "long" (Mattick et al., 2023). The best method of classifying this vast cluster of heterogenous lncRNAs is still under debate; however, the prevalent trend for categorizing seems to be dependent on their genomic context with respect to a well-established protein-coding gene (PcG) (Figure 1). They can be *intergenic*, acting as standalone units between two coding regions without any overlaps, or they can be *intragenic*, overlapping with PcG annotations. Intragenic lncRNAs can be further classified into *sense* and *antisense* based on the overlap of their coding or non-coding sequences with the parent gene; they may also be *bidirectional* if the transcription of the lncRNA is initiated in close proximity (<1 kb) and opposite orientation to a PcG. The lncRNAs are considered *intronic* when derived entirely from an intronic region of a PcG (Kung et al., 2013; Jarroux et al., 2017) (Figure 1).

Although the expressions of lncRNAs are reported in most taxa, from unicellular eukaryotic organisms to primates, they are not conserved well across different or related species (Ulitsky, 2016; Niederer et al., 2017). Even within a species, their expressions are highly specific to the tissue or developmental stages. Their specificity extends to the subcellular level and is restricted to the nucleus, cytoplasm, or both or in other cellular organelles (like the mitochondria, endoplasmic reticulum, nucleoli, and paraspeckles) (Mas-Ponte et al., 2017; Darbellay and Necsulea, 2020; Bridges et al., 2021). The stabilities of the lncRNAs, like their expressions, are also found to be associated with their physiological roles, with regulatory being more stable than housekeeping RNAs, spliced being more stable than unspliced single-exonic RNAs, and cytoplasmic being more stable than nuclear RNAs (Clark et al., 2012; Ayupe and Reis, 2017).

## 2.2 Action mechanisms employed by lncRNAs

Numerous studies have shown that lncRNAs add yet another layer to the regulatory circuitry controlling gene transcription. Highly specific spatial and temporal expressions of lncRNAs have been directly linked to their regulatory functions in a context-dependent manner (Sun and Kraus, 2015; Kopp and Mendell, 2018). Similar to their expressions, lncRNAs have widely diverse mechanisms of action that usually affect regulation of the PcGs (Yao et al., 2019; Zhao et al., 2020). These properties allow the lncRNAs to act as key players in gene regulation during physiological and developmental processes, including dosage compensation, genomic imprinting, epigenetic regulation, pluripotency, post-transcriptional regulation of mRNAs, and stability/translation modulation of mRNAs (Penny et al., 1996; Sleutels et al., 2002; Ilik et al., 2013; Mercer and Mattick, 2013; Yoon et al., 2013; Yang et al., 2014; Rosa and Ballarino, 2016; Akhade et al., 2017; Yao et al., 2019; Statello et al., 2021).

A significant number of studies have supported the notion that the functional aspects of lncRNAs are solely dependent on their inherent properties, such as the folding patterns that allow binding and interactions with other nucleic acids and proteins to allow modulation of local (*in-cis*) as well as distal (*in-trans*) gene regulations (Guo et al., 2016; Zampetaki et al., 2018). LncRNAs can also form DNA–RNA duplex/triplex structures that anchor the

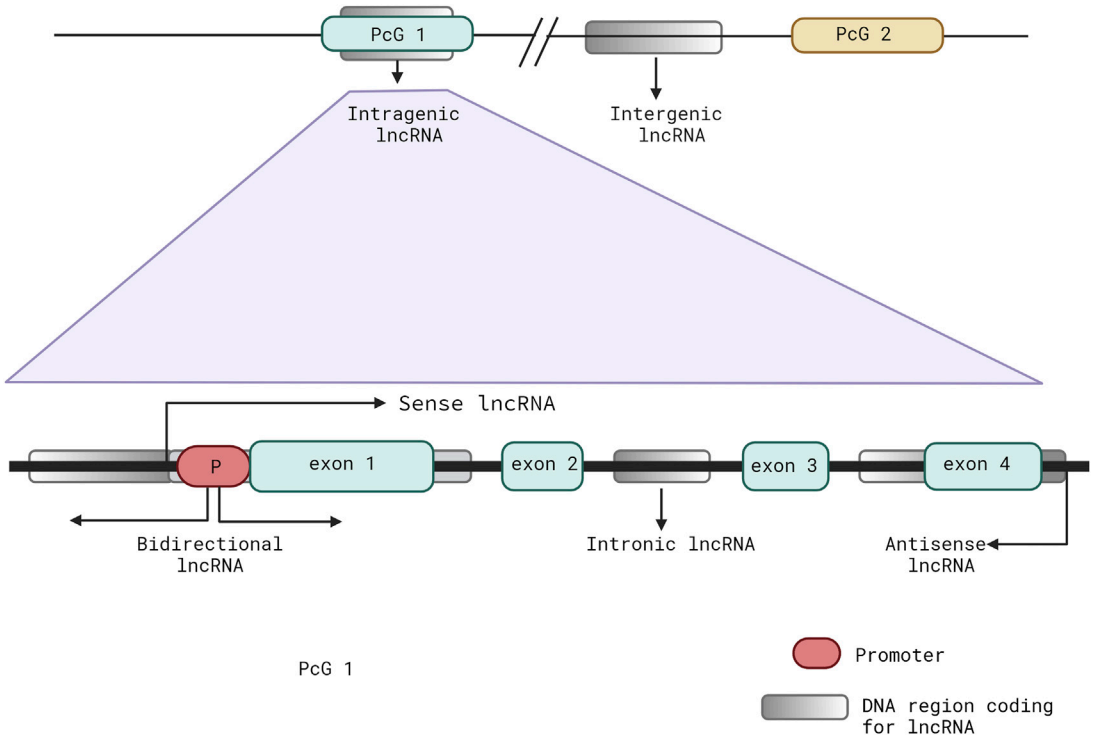


FIGURE 1
Schematic representation showing the common classifications of long non-coding RNAs (lncRNAs) depending on their locations and biogenesis with respect to a well-established protein-coding gene (PcG).

associated effectors to active chromatin sites, such as promoters or enhancers (Schmitz et al., 2010; Mondal et al., 2015; Li et al., 2016). Numerous lncRNAs act as chromatin regulators by interacting with the chromatin-modifying complexes and causing selective activation or repression of genes depending on the chromatin complexes (Kopp and Mendell, 2018; Mishra and Kanduri, 2019; Senmatsu and Hirota, 2020). LncRNAs can bind to chromatin complexes and guide them to their specific target loci; for example, the lncRNA ANRIL binds to the Polycomb group of proteins and recruits them to the target gene loci (Yap et al., 2010; Holdt et al., 2013); furthermore, lncRNAs can act as scaffolds/bridges to bring together complexes for their suppressive or activation functions (Jeon and Lee, 2011) (Figure 2). For example, the lncRNA ANRIL bridges the PRC2 and YY1 proteins that are required in the formation of the silencing complex.

Enhancer-derived lncRNAs (eRNAs) can also promote higher-order chromatin organization, like chromatin looping, to allow interactions between long-distance regulatory elements (like the enhancers and promoters) (Chen H. et al., 2017; Fanucchi and Mhlanga, 2017; Wang Y. et al., 2020). A well-established role of the lncRNAs is in genomic imprinting, a phenomenon in which one of the alleles from the inherited parental pair is inactivated. This is usually achieved by histone/DNA modification, a process in which lncRNAs (such as Xist, Air, and H19) have been known to play major roles (Penny et al., 1996; Sleutels et al., 2002; Ilik et al., 2013). Another interesting mechanism of action of lncRNAs is as sponges, sequestering miRNA with complementary sequences and thereby disrupting their binding with associated targets; lncRNAs can also act as decoys binding to the target itself and leading to stabilization or destabilization of the target mRNA (Yoon et al., 2014; Bayoumi et al., 2016; Sun et al., 2019). LncRNAs also play crucial roles in the assembly, maintenance, and regulation of complex nuclear architectures comprising many subcompartments and domains with nuclear bodies and chromatin, which are the centers of various biological processes (Engreitz et al., 2016; Pisignano et al., 2019; Song Z. et al., 2021) (Figure 2).

## 3 Development of myeloid leukemia

Leukemia is a cancer of the early blood-forming cells. Although many leukemias are sporadic, most of them are acquired and typified by recurring chromosomal translocations and point mutations in the genes (Gilliland et al., 2004). Characterization of the leukemogenic genes has led to a two-hit model of pathogenesis. Most leukemias appear to be the consequence of collaborations between one class of mutations or gene rearrangements that confer proliferative and/or survival advantages to the hematopoietic progenitors and a second class of mutations that primarily impair the hematopoietic differentiation and subsequent apoptosis of cells (Kelly and Gilliland, 2002; Gilliland et al., 2004).

The AML phenotype characterized by proliferation and impaired differentiation is usually associated with chromosomal translocations resulting in loss of function in the transcription factors (TFs) along with mutations in the hematopoietic tyrosine kinases (like FLT3 and c-KIT, and in N-RAS and K-RAS) that confer proliferative advantages. This results in rapid accumulation of immature, non-functional blood cells in the bone marrow that

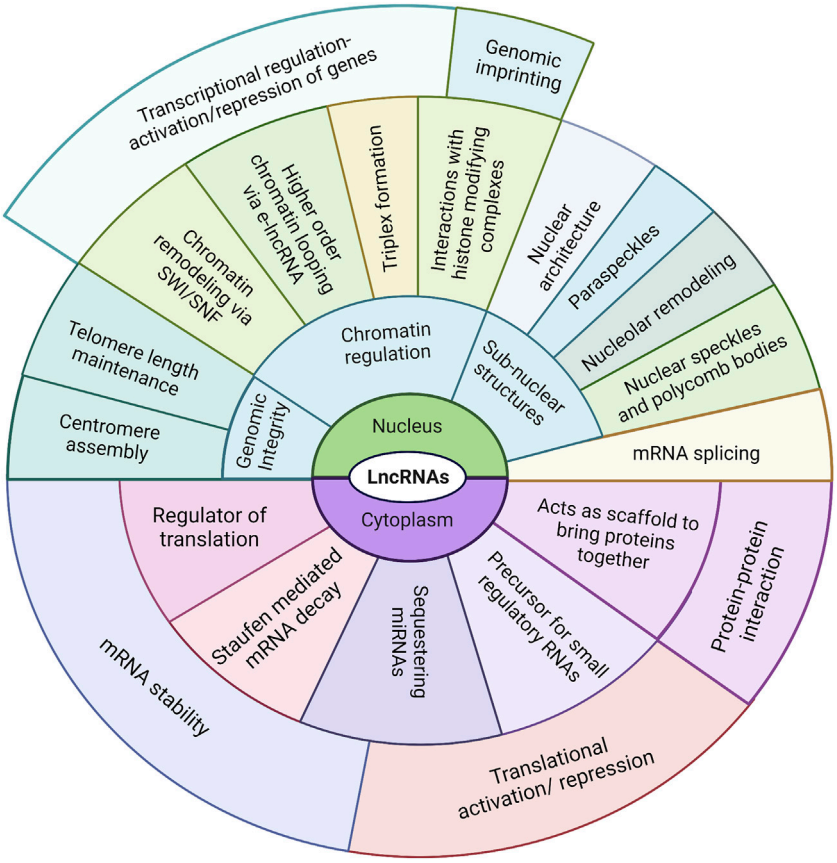


FIGURE 2
Compilation of known mechanisms employed by lncRNAs to regulate their targets. The regulatory techniques and targets (DNA, RNA, and proteins) vary widely depending on their subcellular localization.

later spills into the blood and other organs (Kantarjian et al., 2021; Padmakumar et al., 2021). CMLs are caused by constitutively activated tyrosine kinases, such as BCR/ABL, that confer proliferative and survival advantages to the hematopoietic progenitors but do not affect differentiation, thus resulting in the accumulation of relatively mature but still abnormal blood cells (Perrotti et al., 2010; Ochi et al., 2021).

## 4 LncRNAs in normal hematopoiesis and related malignancies

The continuous generation of specialized blood cells over the lifetime of an organism requires dynamic yet precise gene programming with tight coordination between the cell-lineage specifications, proliferation, and differentiation. Recent comprehensive genome-wide studies on hematopoietic stem cells (HSCs) and lineage-primed multipotent progenitors have revealed that hundreds of lncRNAs are expressed together with lineage-specific TFs that are required for hematopoietic differentiation and cell-fate decisions (Dahariya et al., 2019; Ghafouri-Fard et al., 2021). Luo et al. (2015) performed deep RNA sequencing of HSCs and identified low-expressing lncRNAs in rare HSC populations; they identified and annotated 159 HSC-specific lncRNAs (some involved in HSC self-renewal and differentiation by binding to hematopoietic TF binding sites) with high confidence scores. LncRNAs are perfect regulators for driving specific biological programs like hematopoiesis; this is attributable to the features of lncRNAs, such as their versatility of interactions with both nucleic acids and proteins, along with their highly specific temporal and spatial expressions. This topic has been explored in detail in reviews by Qiu et al. (2021) and Alvarez-Dominguez and Lodish (2017).

Over the past decade, increasing evidence has shown a close relationship between various lncRNAs and the pathophysiology of leukemia. The roles of lncRNAs in leukemia progression, both positive and negative, are attributed to their activities in terms of their specific roles in the differentiation, energy metabolism, malignant proliferation, apoptosis, and drug resistance of the leukemia cells (Gao J. et al., 2020). In a systemic review of 86 articles, Dieter et al. (2020) documented that 3,927 lncRNAs are differentially expressed in various leukemias; further analysis revealed that 12 lncRNAs were consistently dysregulated between leukemic cases and controls (CCAT1, CCDC26, CRNDE, HOTAIR, KCNQ5IT1, LINC00265, MALAT1, PVT1, SNHG5, TUG1, MEG3, and NEAT1).

Findings focusing on the detailed functions and mechanisms of the lncRNAs involved in leukemia pathogenesis are underway, and these specific lncRNAs are expected to serve as diagnostic biomarkers, novel therapeutic targets, and predictors in clinical

TABLE 1 Functional roles and action mechanisms of lncRNAs in the pathogenesis of AML.

| LncRNAs with oncogenic roles in AML | | | | | |
|---|---|---|---|---|---|
| S. No | LncRNA | Target of the lncRNA (DNA/RNA/protein) | Mechanism of action | Functional role in AML pathogenesis | References |
| 1 | HOXBLINC | -NPM1c + signature genes | - Gene regulation via MLL1 recruitment | - Enhances HSC self-renewal | Zhu et al. (2021) |
| | | | - Promoter H3K4me3 modification, both in cis and trans | - Expands myelopoiesis | |
| 2 | HOXA-AS2 | - LATS2 | - Epigenetic regulation of LATS2 by binding to EZH2 and suppressing its expression | - Supports cellular proliferation | Feng et al. (2020b), Qu et al. (2020) |
| | | - SOX4 | - Acts via the SOX4/PI3K/AKT pathway | - Constrains differentiation | |
| 3 | HOXB-AS3 | - rRNA | - Regulates rRNA transcription via an interaction with the EBP1 protein to guide it to the ribosomal DNA | - Promotes cell proliferation | Papaioannou et al. (2019b), Huang et al. (2019) |
| | | - Key factors in cell-cycle progression and DNA replication | | - Regulates *de novo* protein synthesis in blast cells | |
| 4 | HOTAIRM1 | - HOXA1-4 genes | - Epigenetic regulation in cis via recruitment of the UTX/MLL complex on promoters of the target HOXA genes | - Induces cell proliferation and inhibits apoptosis | Zhang et al. (2014), Wang and Dostie (2016), Chen et al. (2017b), Hu et al. (2019) |
| | | - Myeloid differentiation markers CD11b,c and CD18 | - Sponging microRNAs | - Regulates switching from proliferative phase to granulocytic maturation | |
| | | - miR-20a; ULK1, miR-106a; E2F1 and miR-125b; DRAM2 | | - Degrades the chimeric oncoprotein PML-RAR found in APL via autophagy | |
| | | - miR-148b | | | |
| 5 | HOTTIP | - Posterior *HOXA* genes | - Orchestrates CTCF-defined hematopoietic-associated TADs | - Enhances HSC self-renewal | Luo et al., 2018a (2019) |
| | | - Canonical Wnt/β-catenin pathway | | -Constrains differentiation of HSCs | |
| | | - Various key hematopoietic regulators | | | |
| 6 | HOTAIR | - p15 | - Epigenetic regulation represses p15 by H3K27 trimethylation of its promoter mediated by PRC2 in *trans* | - Induces cell growth, inhibits apoptosis, and increases the number of colony formation units | Gupta et al. (2010), Bhan and Mandal (2015), Xing et al. (2015), Portoso et al. (2017), Gao et al. (2018), Wang et al. (2019b), Hu et al. (2019, 2021a) |
| | | - p21 | Suppresses HOXA5 by DNMT3B recruitment to increase promoter methylation | - Regulates differentiation | |
| | | - HOXA5 | - Sponging microRNAs | - Clonogenic growth of AML cells | |
| | | - miR-193; p21 | | | |
| | | - miR-17-5p; c-KIT | | | |
| 7 | RUNXOR | RUNX1 | - Epigenetic regulation via recruitment of EZH2 and H3K27 modifications at the promoter | - Promotes RUNX1 translocation in AML, which is associated with 30–40% of the cases | Wang et al. (2014, 2015) |

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TABLE 1 (*Continued*) Functional roles and action mechanisms of lncRNAs in the pathogenesis of AML.

| LncRNAs with oncogenic roles in AML | | | | | |
|---|---|---|---|---|---|
| S. No | LncRNA | Target of the lncRNA (DNA/RNA/protein) | Mechanism of action | Functional role in AML pathogenesis | References |
| | | | - Facilitates long-range interchromosomal interactions with chromatin regions that are involved in multiple RUNX1 translocations | | |
| 8 | UCA1 | - METTL14; CXCR4 and CYP1B1 | - Affects stability of METTL14 by regulating post-translational m6A methylation of mRNA. | - Promotes migration, invasion, and cell proliferation, and reduces apoptosis in AML cells | Li et al. (2022a) |
| 9 | ANRIL | - miR-125a, miR-186 | - Sponging miRNAs, in turn regulating their downstream targets. For example, regulation of the miR-34a/HDAC1/E2F1/ASPP2 axis | - Increases malignant cell survival | Sun et al. (2018a), Wang et al. (2020b), Tao et al. (2021), Yin et al. (2021) |
| | | - miR-34a; HDAC1 | - Epigenetic regulation of the adiponectin receptor and hence the glucose metabolism | - Promotes AML cell proliferation, migration, and invasion | |
| | | - AdipoR1; Sirtuin1 | | | |
| 10 | CCAT1 | - miR-155; c-Myc | - Sponging miRNAs | - Represses monocytic differentiation and promotes cell growth | Chen et al. (2016), Wang et al. (2020a) |
| | | - miR-490-3p; c-Myc | | - Increases viability and metastasis of AML cells | |
| 11 | H19 | - miR-326; BCL-2 | - Sponging miRNAs, in turn regulating their downstream targets | - Sustains leukemic cell proliferation and limits apoptosis | Zhao et al. (2017), Zhao and Liu (2019), Mofidi et al. (2021) |
| | | - miR-19a-3p; IDH2 | | - Maintains the increased transcriptional level of the antiapoptotic gene BCL-2 | |
| | | - miR-29a-3p; Wnt/β cat | | | |
| 12 | SNHG16 | - CELF2 mRNA | - Causes mRNA instability (regulates CELF2/PTEN/PI3K/AKT axis) | - Enhances proliferative and migration capacity of AML cells | Yang et al. (2020b), Shi et al. (2021) |
| | | - miR183-5p; FOXO1 | - Sponging miRNAs | - Inhibits apoptosis | |
| 13 | PCAT1 | - FZD6 protein | - Regulates mRNA stability | - Enhances cell proliferation and inhibits apoptosis | Yuan et al. (2019) |
| | | | - Activates Wnt signaling via FZD6 | | |
| 14 | USP30-AS1 | - USP30 | - Epigenetic regulation | - Aids in cell proliferation | Zhou et al. (2022) |
| | | - ANKRD13A | - Translocation of HLA-I protein from cell membrane to cytoplasm | - Helps in tumor immune escape | |
| 15 | CD27-AS1 | - miR-224-5p; PBX3 | - Sponging miRNAs | - Promotes cell growth and malignancy in AML | Tao et al. (2021) |
| | | | - Positive regulation of MAPK signaling | | |
| 16 | SNHG5 | - miR-26b; CTGF/VEGFA | - Sponging miRNAs | - Contributes to angiogenesis in AML | Li et al. (2021b) |
| 17 | MAFG-AS1 | - miR-147b; HOXA9 | - Sponging miRNAs | - Induces cell growth and EMT | Yao et al. (2022) |

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TABLE 1 (*Continued*) Functional roles and action mechanisms of lncRNAs in the pathogenesis of AML.

| LncRNAs with oncogenic roles in AML | | | | | |
|---|---|---|---|---|---|
| S. No | LncRNA | Target of the lncRNA (DNA/RNA/protein) | Mechanism of action | Functional role in AML pathogenesis | References |
| 18 | SNHG1 | - miR-488-5p; NUP205 | - Sponging miRNAs | - Stimulates the Wnt signaling pathway leading to AML cell growth | Bao et al. (2019), Tian et al. (2019), Li et al. (2021a) |
| | | - miR-489-3p; SOX12 | | | |
| | | - miR-101 | | | |
| 19 | DUBR | - miRNA-142-3P | - Sponging miRNAs | - Contributes to survival, proliferation, and apoptosis inhibition in AML cells | Yin et al. (2021) |
| | | - FUS protein | - Details unexplored | | |
| 20 | LINC00641 | - miR-378a; ZBTB20 | - Sponging miRNAs | - Silencing inhibits proliferation, migration, invasion, and cell-cycle arrest, and induces apoptosis in AML cells | Wang et al. (2019a) |
| 21 | LINC00899 | - miR-744-3p; YY1 | - Sponging miRNAs | - Promotes cell proliferation and inhibits cell apoptosis | Dong et al. (2020a) |
| 22 | LINC00662 | - miR-340-5p; ROCK1 | - Sponging miRNAs | - Promotes cell growth and inhibits apoptosis | Liu et al. (2019) |
| 23 | LINC00265 | - miR-485; IRF2 | - Sponging miRNAs | - Inhibits apoptosis by promoting autophagy | Zhang et al. (2020a) |
| | | | | - Increases cell proliferation | |
| 24 | LOC285758 | miR-204-5p; E-cadherin, N-cadherin and Twist1 | - Sponging miRNAs | - Promotes cell viability and invasion abilities | Xue and Che (2020) |
| 25 | LINC00467 | miR-339; SKI pathway | - Sponging miRNAs | - Malignant phenotypes of AML cells | Lu et al. (2021) |
| LncRNA with tumor supressing role in AML | | | | | |
| 26 | PU.1-AS | eIF4A | - Competitively binds to the translation initiating factor | - Promotes leukemogenesis | Ebralidze et al. (2008) |
| | | | - Interferes with translational elongation | | |
| | | | - Suppresses translation of its parent gene *PU.1* | | |
| 27 | IRAIN | - IGF1R | - Involved in long-range intrachromosomal interactions between the IGF1R promoter and a distant intragenic enhancer | - Enhances proliferative capacities of AML cells | Sun et al. (2014) |
| | | - PI3K/Akt signaling pathway | - Activates in *cis* the expression of its parent gene IGF1R | - Augments treatment-resistance abilities of AML cells | |
| 28 | NEAT1 | - RUNX2 | - Epigenetic regulation via direct interactions with DNA and chromatin regulators | - Regulates AML cell differentiation | Zhao et al. (2019), Feng et al. (2020a), Miliara et al. (2022) |
| | | - Chromatin regulators KMT2A, KMT5B and CHD7 | - Sponging miRNAs | - Suppresses cell proliferation and enhances apoptosis | |
| | | - miR-338-3p; CREBRF | | | |

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TABLE 1 (*Continued*) Functional roles and action mechanisms of lncRNAs in the pathogenesis of AML

| LncRNAs with oncogenic roles in AML | | | | | |
|---|---|---|---|---|---|
| S. No | LncRNA | Target of the lncRNA (DNA/RNA/protein) | Mechanism of action | Functional role in AML pathogenesis | References |
| | | - miR-23a-3p; SMC1A | | | |
| 29 | H22954 | - PDGRA | - Reduces stability of mRNA by binding to its 3′ UTR. | - Inhibits angiogenesis in AML | Li et al. (2022b) |
| 30 | TP73-AS1 | - miR-21; PTEN | - Sponging miRNAs | - Affects cell proliferation | Yuan et al. (2021) |
| 31 | DUXAP8 | - Wnt5a, β-catenin, c-Myc, and cyclin-D1 | Unknown | - Overexpression results in inhibition of glycolysis and induces apoptosis in AML. | Zhai et al. (2021) |
| 32 | LINC01018 | - miR-499a-5p; PDCD4 | - Sponging miRNAs | - Suppresses AML cell proliferation and promotes apoptosis | Zhou et al. (2021) |
| 33 | NR-104098 | - EZH2 | - Directly binds and recruits E2F1 at the promoter of EZH2 to suppress its expression | - Inhibits proliferation and induces differentiation<br>- Additionally plays a main role in mouse xenografts | Feng et al. (2020c) |

outcomes. In this review, we summarize the updates on lncRNAs reported for myeloid leukemias (AML and CML), their mode of influence in leukemia progression via various mechanisms, and the methods by which scientists can exploit them as potential drug targets.

# 5 LncRNAs in AML

Although AML is fairly rare, accounting for only about 1% of all cancers, it is the most prevalent type of leukemia in adults and has an incidence rate of 4.1 per 100,000 individuals every year. The incidence of AML increases with age and constitutes 80% of all adult leukemias. AML is an extremely aggressive malignancy of the hematopoietic system, with a mortality rate of 2.7 per 100,000 individuals per annum (Deschler and Lübbert, 2006; Yi et al., 2020; Vakiti et al., 2021). The malignant transformations in AML can be attributed to chromosomal abnormalities for one group of patients, whereas recurrent somatic mutations in several oncogenes have been reported for the cytogenetically normal other groups (Meyer and Levine, 2014; Abelson et al., 2018; Kishtagari and Levine, 2021).

Numerous studies have characterized lncRNAs and demonstrated their roles in the pathogenesis of AML through the various mechanisms by which they exert oncogenic or tumor-suppressive effects. This review summarizes a few of the well-characterized lncRNAs in terms of functions and mechanisms with respect to AML pathogenesis (Table 1). Based on their mechanism of action in AML, the lncRNAs can be loosely categorized into two groups as those that are epigenetic regulators or/and chromatin modifiers and those that are associated with microRNA sponging to indirectly regulate downstream targets. The lncRNAs may also exert both mechanisms or/and completely different ones. Irrespective of the mechanism, lncRNAs have been found to impact one or multiple cancer phenotypes of AML cells, such as cell survival, proliferation, and differentiation.

## 5.1 LncRNAs as epigenetic regulators, chromatin modifiers, and genomic organizers in AML

### 5.1.1 Regulatory lncRNAs arising from the HOX cluster

Epigenetic regulation, chromatin modifications, interactions, and conformations, are the most well-understood functions of lncRNAs. For example, lncRNAs have been transcribed from the HOX cluster, and HOX gene dysregulations have been widely documented in AML. Many lncRNAs like HOTAIR, HOTAIRM1, HOXB-AS3, HOXA-AS2, and HOXBLINC originating from the HOX cluster are involved in transcription regulation via the epigenetic phenomenon. Silencing and overexpression studies by Feng et al. (2020b) have validated the role of the lncRNA HOXA-AS2 in supporting the cellular proliferation and restraining the differentiation of AML cells. HOXA-AS2 was also shown to epigenetically regulate the expression of its downstream target *LATS2* via EZH2 binding

(Feng et al., 2020b). LATS2 is a component of the Hippo signaling pathway that regulates cell-cycle progression and apoptosis to inhibit the growth and development of tumors. HOXA-AS2 acts as a modular scaffold for histone-modifying complexes by directly binding with EZH2 and triggering H3K27me3 trimethylation at the promoter of *LATS2*, thereby suppressing its expression (Feng et al., 2020b).

The HOXA-AS2 lncRNA is also shown to directly regulate *SOX4* expression and modulate its downstream target PI3K/AKT pathway (Qu et al., 2020). Given its restricted expression in myeloid cells, the lncRNA HOTAIRM1 transcribed from the intergenic and antisense region of the HOXA gene cluster is one of the most studied lncRNAs in relation to myeloid leukemias (Zhang et al., 2014; Wang and Dostie, 2016); it was found to act as an activator of the proximal *HOXA* genes in the NB4 cell line and as a repressor of the more distant *HOXA 4/5/6* genes in NT2-D1 cells. HOTAIRM1 was found to accomplish these through three-dimensional chromatin organizational changes for interactions with either UTX/MLL or PRC2 complexes; it was shown to delay recruitment of the histone demethylase UTX and transcription of the central *HOXA* genes by participating in the physical dissociation of the chromatin loops at the proximal end of the cluster (Wang and Dostie, 2016).

Overexpression of HOXBLINC, a HOX-B locus-associated lncRNA, was shown to enhance HSC self-renewal and expand myelopoiesis, leading to the development of AML in mice. Mechanistically, HOXBLINC establishes aberrant expression signatures of the genes found in NPM1 mutants through various mechanisms like MLL1 recruitment, chromatin domain, and *cis* and *trans* promoter accessibility; it activates the anterior HOX-B genes by recruiting the MLL1/Setd1a complex at its promoter and maintaining a 3D interactome between the enhancer and promoter (Zhu et al., 2021). The posterior HOX-A locus-associated lncRNA HOTTIP was found to activate the posterior *HOXA* genes, in addition to the canonical Wnt/β-catenin pathway and various key hematopoietic regulators by coordinating CTCF-defined hematopoietic-associated TADs leading to leukemic transformation (Luo H. et al., 2018, 2019). The HOTAIR lncRNA expressed from the HOX-C locus is recognized as a *trans*-acting epigenetic repressor of the HOX-D locus genes (Gupta et al., 2010; Bhan and Mandal, 2015). Epigenetic regulation seems to be the primary mechanism of HOTAIR, for which multiple targets have been identified in several studies; it represses p15 expression in *trans* to maintain leukemogenesis via H3K27 trimethylation of its promoter mediated by PRC2 (Gao et al., 2018). HOTAIR also recruits DNMT3B to increase *HOXA5* promoter methylation, causing its suppression as well as leading to increased proliferation and reduced apoptosis of the AML cells (Wang S. L. et al., 2019). The lncRNA HOXB-AS3 transcribed from the *HOXB* cluster was found to be overexpressed in AML (Papaioannou et al., 2019b); by dissecting the functional aspects of HOXB-AS3, Papaioannou et al. (2019b) showed its interactions with the ErbB3-binding protein 1 (EBP1) and guiding of EBP1 to the ribosomal DNA locus to regulate rRNA expression, facilitating adequate protein production in rapidly proliferating leukemic blasts cells.

### 5.1.2 Roles of lncRNAs not associated with the HOX cluster

In addition to the lncRNAs arising from the HOX cluster, several other lncRNAs have been reported to adopt similar mechanisms of action. For example, the lncRNA USP30-AS1 was found to promote AML pathogenesis by epigenetically regulating USP30 and ANKRD13A in *cis*, which are known to aid cell proliferation and translocation of the HLA-1 protein from the cell membrane to cytoplasm, leading to tumor immune escape (Zhou et al., 2022). The lncRNA NEAT1 acts as a tumor suppressor and is downregulated in AML. Recently, Miliara et al. (2022) investigated the genome-wide RNA and DNA interactions using RADICL sequencing and showed that NEAT1 binds to the genomic loci of key hematopoietic regulators like *RUNX2, SOX6,* and *FOSL2* while interacting with chromatin regulators KMT2A, KMT5B, and CHD7 to influence AML cell differentiation.

RUNXOR is an unspliced RUNX1-intragenic lncRNA transcribed from an upstream overlapping promoter; translocation of RUNX1 is associated with almost 30–40% of the AML cases. Wang et al. (2015) confirmed that RUNXOR epigenetically regulates RUNX1 in AML via recruitment of EZH2 and H3K27 methylation; they additionally revealed that RUNXOR utilizes its 3′-region to directly interact with the RUNX1 promoters and enhancers, facilitating long-range interchromosomal interactions with the chromatin regions involved in multiple RUNX1 translocations (Wang et al., 2014). Another lncRNA involved in chromatin dynamics to regulate chromatin architecture and status is IRAIN, whose low expression in AML was first identified by Sun et al. (2014) using the RNA-guided chromatin conformation capture (R3C) method and described as a paternally imprinted lncRNA regulating the expression of its parent gene *IGF1R* in AML in *cis*. IGF1R is a receptor tyrosine kinase that is abundantly activated in leukemic cells, giving them proliferative and treatment resistance capacities through IGF1R receptor-mediated activation of the PI3K/Akt signaling pathway. IRAIN was found to promote *IGF1R* expression by allowing long-range intrachromosomal interactions between the *IGF1R* promoter and a distant intragenic enhancer (Sun et al., 2014). However, the detailed mechanisms and effects of this chromosomal looping remain unexplored.

## 5.2 microRNA-associated lncRNAs in AML

The number of lncRNAs listed in the microRNA sponging group has increased in recent times, as sponging is one of the common mechanisms of gene regulation (Sun et al., 2022). For example, the lncRNA H19 that is otherwise known for its epigenetic regulation acts as a sponge for miR-326, miR-19a-3p, and miR-29a-3p in the hematopoiesis and AML context (Zhao et al., 2017; Zhao and Liu, 2019; Mofidi et al., 2021). Overexpression of H19 in AML is negatively correlated with miR-326, causing increased transcription of the antiapoptotic gene *BCL-2* (Mofidi et al., 2021). H19 was reported to sustain leukemic cell proliferation and limit apoptosis by regulating the expressions of *IDH2* and Wnt/β cat effectors by limiting the availabilities of miR-19a-3p and miR-29a-3p, respectively (Zhao et al., 2017; Zhao and Liu, 2019). Recently, HOTAIR was found to regulate AML differentiation via the CEBPBβ/HOTAIR/miR-17-5p/p21 pathway (Hu L. et al., 2021). Utilizing the mechanism of sponging microRNA, HOTAIR was shown to titrate miR-193a, which modulates the expression of its target c-KIT, thus affecting the clonogenic growth of AML cells (Xing et al., 2015).

Several reports have experimentally confirmed the sponging activity of CCAT1 in AML, where it is overexpressed (Chen et al., 2016; Izadifard et al., 2018; Wang C. et al., 2020); it reduces the availability of miR-155 and miR-490-3p, eventually resulting in the upregulation of c-Myc (Chen et al., 2016; Wang C. et al., 2020). CCAT1 represses monocytic differentiation and promotes cell growth via miR-155 while markedly increasing the viability and metastasis of AML cells via the CCAT1/miR-490-3p/MAPK1/c-Myc positive feedback loop (Chen et al., 2016; Wang C. et al., 2020). Very recently, elevated levels of the lncRNA MAFG-AS1 were shown to induce cell growth and epithelial–mesenchymal transitions (EMTs) in AML cells via sponging miR-147b and promoting the expression of HOXA9 indirectly (Yao et al., 2022). Given its repressed expression in AML, the lncRNA TP73-AS1 was revealed to sponge miR-21 and hence upregulate its downstream target PTEN to affect cellular proliferation in AML (Yuan et al., 2021). High expression of the lncRNA DUBR was linked with AML pathogenesis in a recent report by Yin et al. (2021); this study revealed that DUBR sequesters miRNA-142-3P and interacts with FUS protein, increasing their expressions and contributing to cell survival, proliferation, and apoptosis inhibition in AML cells. However, further details regarding these regulations by DUBR remain unexplored (Yin et al., 2021).

Studies have demonstrated that the lncRNA NEAT1 affects the cellular behaviors of AML cells by directly repressing the sponging targets miR-338-3p and miR-23a-3p, consequently modulating the levels of their downstream targets CREBRF and SMC1A, respectively (Zhao et al., 2019; Feng S. et al., 2020). Cancer-associated ANRIL is an antisense lncRNA in the *INK4* locus that is transcribed from the short arm of chromosome 9 on p21.3 (Pasmant et al., 2011). In a thorough analysis using experiments on loss and gain of functions Wang C. H. et al. (2020) showed that ANRIL accelerates AML pathogenesis by negatively regulating miR-34a and causing *HDAC1* overexpression that in turn inhibits E2F1 recruitment to suppress *ASPP2*; inhibition of *ASPP2* expression restrains apoptosis, promoting aberrant proliferation of the AML cells (Wang C. H. et al., 2020). Upregulation of the lncRNA SNHG1 is correlated with poor prognosis of AML and is associated with the mechanism of sponging microRNAs in AML cells; it has been shown to promote the development of AML through the miR-488-5p/NUP205 axis (Bao et al., 2019). The role of SNHG1 as a competing endogenous lncRNA in the inhibition of the antitumor miR-101 has also been demonstrated (Tian et al., 2019). Downregulating the lncRNA HOTAIRM1 was shown to inhibit proliferation and induce apoptosis in AML cells by negatively regulating miR-148b (Hu et al., 2019). The lncRNA SNHG16 has been reported to have an oncogenic role in AML; it sequesters miR183-5p and causes upregulation of its target gene *FOXO1*, which is a known promoter of cell proliferation and apoptosis inhibition (Yang R. et al., 2020).

## 5.3 Other mechanisms adopted by lncRNAs in AML

Owing to their ability to bind with both proteins and nucleic acids (DNA and RNA), lncRNAs can coordinate gene regulation at multiple levels through various mechanisms of action, such as regulating the stability of protein/RNA, glucose metabolism, autophagy, signaling pathways, and angiogenesis.

LncRNAs can affect the stability of mRNA or proteins through direct interactions with them; for example, the lncRNA SNHG16 that is overexpressed in AML binds directly to the CELF2 mRNA, resulting in its instability (Shi et al., 2021). *CELF2* enhances PTEN activity under normal physiological conditions, which in turn affects PI3K/AKT signaling; under the influence of SNHG16, this pathway is disrupted, endowing proliferative and migration capacities to the AML cells (Shi et al., 2021). Yuan et al. (2019) found that the lncRNA PCAT-1 interacts directly with the FZD6 protein, regulating its stability. FZD6 belongs to a family of G-protein-coupled receptors that are essential components of the Wnt signaling pathway, and its high expression in AML has been identified as a biomarker (Yang et al., 2022). PCAT1 thus enhances cell proliferation and inhibits apoptosis by activating Wnt signaling via FZD6, thus contributing to the pathogenesis of AML (Yuan et al., 2019). In a recent study, the lncRNA UCA1 was shown to indirectly regulate the post-translational m6A methylation of mRNA, in turn upregulating the expressions of CXCR4 and CYP1B1 by affecting the stability of METTL14 in AML (Li J. et al., 2022); it was also found to be involved at the translational level through titration of the hnRNP1 protein, which facilitates translation of $p27^{kip1}$ (Hughes et al., 2015). Both mechanisms promote migration, invasion, and cell proliferation as well as reduce apoptosis in AML.

Another mechanism by which ANRIL promotes malignant cell survival is by regulating the expression of the key glucose metabolism regulator, i.e., adiponectin receptor (AdipoR1) (Sun L. Y. et al., 2018). Additionally, silencing ANRIL and the adiponectin receptors inhibits the phosphorylation of AMP-activated protein kinase/sirtuin 1 to substantially decrease glycolysis and proliferation of the AML cells (Sun L. Y. et al., 2018). HOTAIRM1 was reported to cause degradation of the chimeric oncoprotein PML-RARA found in AML via autophagy; this process is induced when HOTAIRM1 sponges miR-20a, miR-106a, and miR-125b, affecting their downstream targets ULK1, E2F1, and DRAM2, respectively (Chen Z.-H. et al., 2017).

Recently, the lncRNA SNHG1 was reported to enhance AML pathogenesis via activation of Wnt/β-catenin signaling; SNHG1 sequesters miR-489-3p, resulting in overexpression of SOX12 to stimulate the Wnt signaling pathway and cause AML cell growth (Li C. et al., 2021). The lncRNA DUXAP8, which is downregulated in both AML bone-marrow tissues and cell lines, has been shown to stimulate the expressions of the Wnt/β-catenin pathway proteins, namely, Wnt5a, β-catenin, c-Myc, and cyclin-D1, to inhibit glycolysis and induce apoptosis in AML (Zhai et al., 2021). The antisense lncRNA CD27-AS1 was found to have positive effects on MAPK signaling, leading to cell growth and malignancy in AML; mechanistically, it was found to sponge miR-224-5p, thus increasing the PBX3 levels that are responsible for regulating MAPK signaling (Tao et al., 2021).

The lncRNA SNHG5 was found to be upregulated by YY1 in AML; downstream, SNHG5 was shown to regulate AML angiogenesis by activating the connective tissue growth factor (CTGF)/vascular endothelial growth factor A (VEGFA) by directly targeting miR-26b (Li Z.-J. et al., 2021). Another lncRNA that regulates angiogenesis in AML is H22954, which was found to

TABLE 2 Functional roles and action mechanisms of lncRNAs in the pathogenesis and/or IM resistance of CML.

| LncRNAs promoting oncogenic properties and/or IM resistance in CML | | | | | |
|---|---|---|---|---|---|
| S. No | LncRNA | Target of the lncRNA (DNA/RNA/protein) | Mechanism of action | Functional role in CML pathogenesis | References |
| 1 | HMRHL | - Genes- ZIC1, PDGRFβ and TP53 | - Direct regulation of the target gene via triplex formation at the promoter | - Promotes cell proliferation, migration, and invasion<br>- Association with perturbed expression of several crucial TFs and cancer-related genes in CML | Fatima et al. (2019), Choudhury et al. (2021) |
| 2 | HULC | - miR-200a; c-Myc and Bcl-2 | - Sponging microRNAs | - Promotes oncogenesis in CML<br>- Loss of function of HULC results in IM-induced apoptosis and suppressed phosphorylation of PI3K and AKT. | Lu et al. (2017) |
| 3 | MALAT1 | - miR-328 | - Sponging microRNAs | - Contributes to cancer phenotypes and IM sensitivity in CML | Wen et al. (2018) |
| 4 | ADORA2A-AS1 | - miR-665; TGFBR1 and ABCC2 | - Sponging microRNAs | - Promotes tumorigenesis and reduces IM sensitivity | Liu et al. (2022b) |
| 5 | PLIN2 | - GSK3<br>- Wnt/β-catenin signaling pathway | Unknown | - Promotes CML progression | Sun et al. (2017) |
| 6 | SNHG5 | - miR-205-5p; ABCC2 | - Sponging microRNAs | - Promotes IM resistance in CML | Gao et al. (2019) |
| 7 | UCA1 | - miR-16; MDR1 | - Sponging microRNAs | - Promotes IM resistance in CML | Xiao et al. (2017) |
| 8 | HOTAIR | - MRP1 | - Regulates PI3K/AKT-dependent MRP1 expression | - Associated with multidrug-resistant CML | Wang et al. (2017) |
| 9 | CCAT2 | Unknown | Unknown | - Promotes IM resistance in CML | Shehata et al. (2022) |
| 10 | HOTTIP | - PTEN | - Epigenetic regulation via recruitment of EZH2 | - Promotes IM resistance in CML | Liu et al. (2022a) |
| 11 | OIP5-AS1 | - miR-30e-5p; ATG12 | - Sponging microRNAs | - Promotes autophagy-related IM resistance in CML | Dai et al. (2021) |
| 12 | PANTR1 | - MDR and stem-cell marker | Unknown | - Promotes IM resistance in CML | Gao et al. (2020a) |
| LncRNAs with tumor suppressing role and/or IM sensitivity in CML | | | | | |
| 13 | MEG3 | - miR-21 | - Sponging microRNAs | - Overexpression decreases cell growth and survival, reverses IM resistance, and reduces expression of multidrug-resistant transporters, including MRP1, MDR1, and ABCG2 | Zhou et al. (2017), Li et al. (2018a, 2018c, 2018b) |
| | | - miR-147 | - Regulates STAT3 by inhibiting the phosphorylation of JAK/STAT | - Modulates cell proliferation, survival, and apoptosis | |
| | | - miR-184 | - Regulates expression of PTEN | | |
| 14 | HAND2-AS1 | - miR-NA-1275 | - Sponging microRNAs | - Regulates cell proliferation and apoptosis | Yang et al. (2019) |
| 15 | H19 | - PCBP1 and FUS protein<br>- miR-19a-3p and miR-106b-5p | - Sponging microRNAs | - Affects viability and apoptosis of CML cells | Yang et al. (2020a) |
| 16 | NEAT1 | - miR-766-5p; CDKN1A | - Sponging microRNAs | - Alters the progression of CML | Zeng et al. (2018), Yao et al. (2021) |
| | | - c-Myc<br>- SFPQ | - Regulation of IM-induced apoptosis via directional interactions with c-Myc and SFPQ | - Regulates cell growth and IM-induced apoptosis | |

target the 3' untranslated region (UTR) of *PDGFRA* and reduce its half-life, thus inhibiting angiogenesis in AML (Li X. et al., 2022). Another interesting mechanism by which lncRNAs regulate gene expression is at the translational level, such as in the antisense lncRNA PU.1-AS that originates from an intronic promoter in *PU.1*. As an essential requirement for normal hematopoiesis, *PU.1* encodes a key TF and suppresses myeloid leukemia (Cook et al., 2004). PU.1-AS interferes with the translation of PU.1 by competitively binding to the translation initiating factor eIF4A; it was also found to interrupt translational elongation, although the exact mechanism remains unknown (Ebralidze et al., 2008).

We have attempted to include the majority of documented and experimentally validated lncRNAs in the context of AML. Some of the remaining lncRNAs are mentioned in Table 1, along with their functional targets, mechanisms, and references for the convenience of readers (Wang J. et al., 2019; Liu et al., 2019; Dong X. et al., 2020; Zhang F. et al., 2020; Feng et al., 2020c; Xue and Che, 2020; Lu et al., 2021; Zhou et al., 2021).

## 6 LncRNAs in pediatric AML

Although AML occurs in all age groups, children constitute a very small percentage of AML patients. Most of the known lncRNAs in AML were first reported in adults, but there are several recent studies that describe functional lncRNAs in pediatric AML. Schwarzer et al. (2017) reported subtype-specific lncRNA signatures for six major cytogenetic subgroups of pediatric AML: Down syndrome (DS), non-DS acute megakaryoblastic leukemia (AMKL), inv [16], t [8; 21], and AML with KMT2A rearrangements (t [9; 11] and t [10; 11]); furthermore, they defined the core lncRNA stem-cell signature in normal HSCs and pediatric AML blasts, which were significantly correlated with poor survival in an independent cohort of AML patients (Schwarzer et al., 2017). In another study by Porcù et al. (2021), CDK6-AS1 was found to be overexpressed in pediatric AML, leading to an immature phenotype as well as activation of mitochondrial biogenesis in healthy HSCs and primary AML blasts; this study also uncovered the potential role of the CDK6-AS1/CDK6 axis in phenotype differentiation through downregulation of RUNX1 signaling. The UCA1 lncRNA has been studied in pediatric and adult AML cell lines and shown to be oncogenic in function, wherein UCA1 knockdown affects the viability, migration, and invasion of leukemic cells through titrating miRNAs like miR-126, miR-204, miR96-5p, and miR296-3p (Sun M. D. et al., 2018; Li J. J. et al., 2020; Li et al., 2020 J.; Liang et al., 2020). In a more clinically relevant scenario, UCA1 knockdown was shown to suppress the chemoresistance of pediatric AML by inhibiting glycolysis through direct binding with miR-125a (Zhang Y. et al., 2018). There are several examples of lncRNAs that have been characterized in pediatric AML that show correlations to patient prognosis and survival; such examples were summarized in a recent review by Neyazi et al. (2022). In a recent comprehensive study, Vanhooren et al. (2022) performed a miRNA-lncRNA network analysis in leukemic stem cells (LSCs) and leukemic blasts (L-blasts) from pediatric AML patients; this study identified several novel lncRNAs and miRNAs in pediatric AML that could become new biomarkers for risk stratification and targeted therapy in the future. Using RNA-seq data from normal bone marrow and *de novo* AML pediatric patient samples, followed by regularized Cox proportional hazards modeling of the event-free survival (EFS), Farrar et al. (2022) calculated a 37-gene lncScore that showed a significant correlation with patient survival. Similarly, Guo et al. (2020) proposed a lncRNA risk scoring system based on the expressions of 14 lncRNAs for effectively predicting the prognosis of pediatric AML patients. Tao et al. (2022) constructed a ferroptosis-related lncRNA-mRNA coexpression network to investigate the prognostic roles of ferroptosis-related lncRNAs in pediatric AML patients. Accordingly, a model of 22 ferroptosis-related signatures (lncRNAs and mRNAs) was proposed as an independent prognostic factor of pediatric AML. It would be of interest in the future to look for common lncRNAs in these studies to correlate lncRNA expression signatures to pediatric AML patient survival and prognosis.

## 7 LncRNAs in CML

In 2018, the global incidence of CML was approximately 1 in 100,000 (Höglund et al., 2015; Hu Y. et al., 2021), accounting for about 15% of newly diagnosed cases of leukemia. Considering that CML is a late-developing disease, the average age range at diagnosis is 57–60 years. Clinically, CML is divided into three phases: an initial chronic phase (CP), an accelerated phase (AP), and a blast phase (BP). CML is usually diagnosed in the CP, which quickly progresses to a blast crisis without effective medical intervention and can lead to death (Sandberg et al., 1971; Zalcberg et al., 1986).

CML is a myeloproliferative disorder originating in the HSC compartment and is predominantly caused by the formation of the chimeric oncogene BCR-ABL1, which is also known as the Philadelphia (Ph) chromosome. The formation of the Ph chromosome is a result of reciprocal translocation between the long arms of chromosomes 9 and 22 t (9; 22) (q34; q11). ABL1 encodes a ubiquitously expressed non-receptor tyrosine kinase responsible for regulating cell-cycle progression, proliferation, DNA repair, and differentiation, among others. Fusion with BCR endows ABL with the ability to become constitutively active, which is a sufficient cause for the development of CML (Sandberg et al., 1971; Chen et al., 2010).

Since the introduction of tyrosine kinase inhibitor (TKI) therapy with imatinib (IM) in 2001 (Goldman, 2000; Kantarjian, 2001) and second-generation TKI in 2007 (Swords et al., 2007), CML has transformed from a life-threatening disease to a manageable chronic condition (Bower et al., 2016). Nevertheless, there are constant search efforts for new treatment strategies and therapeutic targets, especially for the BP and drug resistance as well as BCR-ABL1-independent CML. LncRNAs are emerging as promising candidates in this regard and are expected to serve as diagnostic biomarkers, predictors of clinical outcomes, and therapeutic targets.

Note to readers: Compared to AML, the number of lncRNAs reported and experimentally validated for CML is far fewer. Categorizing them on the basis of mechanism was not suitable; hence, we broadly categorized the studies on lncRNAs in CML into two groups, with the first group focusing on the implications of lncRNAs for drug-resistant CML and tackling the problem of mutations acquired during the treatment course of patients that allow them to escape TKI therapy. The second group focuses on

BCR-ABL1-independent CML and/or the general biology behind the pathogenesis of CML (Table 2).

## 7.1 Implications of lncRNAs in IM resistance

The first line of treatment for CML with the identified BCR-ABL1 oncogene is a competitive TKI like IM that binds to the BCR-ABL1 protein and restrains downstream signal transduction. This drug has greatly improved the 5-year survival rates of CML patients from 34.2% to 80–90% (Kantarjian et al., 2012). However, there are challenges owing to the development of IM resistance, which can be attributed to several mechanisms such as the high copy number of mutant BCL-ABL1 genes, acquired mutations, aberrant expressions of drug transporters, and/or epigenetic alterations. However, the underlying mechanism is still largely unknown. Given the evidence of the involvement of lncRNAs in key biological processes, scientists are now trying to explore the roles of lncRNAs in this regard. For example, the lncRNA SNHG5 was found to be overexpressed in CML patients and IM-resistant cell lines; the study further demonstrated that SNHG5 acts as a competitive endogenous RNA (ceRNA) to sponge away miR-205-5p, upregulating its downstream target ABCC2 and promoting IM resistance in CML (Gao et al., 2019).

Another lncRNA that employs the same mechanism is UCA1, which competitively binds with miR-16, repressing the expression of MDR1 and contributing to IM resistance in CML (Xiao et al., 2017). The lncRNA MEG3 was also found to contribute to IM resistance through possible regulation of miR-21 (Zhou et al., 2017); it was found to be downregulated in CML, and miR-21 expression was observed to have an inverse correlation with MEG3 expression. The study further showed that ectopic expression of MEG3 decreases cell growth and survival, reverses IM resistance, and reduces the expressions of multidrug-resistant transporters, such as MRP1, MDR1, and ABCG2. However, the underlying regulatory mechanisms were unexplored in these works (Zhou et al., 2017; Li et al., 2018b). The role of the overexpressed lncRNA HOTAIR in multidrug-resistant CML was also explored and found to regulate MRP1 expression in a PI3K/AKT-dependent manner (Wang et al., 2017). Recently, the overexpression of another lncRNA, HULC, has been linked with an increase in IM resistance, while the opposite effect was observed for HULC depletion. Mechanistically, HULC was found to regulate the PI3K/AKT pathway by depleting miR-150-5p and thereby modulating MCL1 expression (Han and Ma, 2021). The lncRNA CCAT2 was found to be highly expressed in CML patients and was linked to IM resistance, suggesting that it is a reliable molecular marker for predicting IM responses in CML patients in the CP (Shehata et al., 2022).

Liu J. et al. (2022) have shown that the lncRNA HOTTIP, which is highly expressed in IM-resistant patients and cell lines, recruits EZH2 to suppress the expression of the *PTEN* gene contributing to IM resistance. A recent report highlighted that autophagy is associated with drug resistance in CML cells; the study revealed that the lncRNA OIP5-AS1 promotes autophagy-related IM resistance in CML by sponging miR-30e-5p and modulating ATG12 levels (Dai et al., 2021). The lncRNA PANTR1 was found to mediate IM resistance by promoting the expressions of MDR and stem-cell markers in CML cell lines (Gao J. J. et al., 2020).

## 7.2 Role of lncRNAs in the general biology of CML

In addition to their association with IM resistance, the roles of lncRNAs in CML pathobiology have been explored widely. This gives us insights into the functional mechanisms involved and potential drug targets, especially in Ph-chromosome-independent CML. For example, several studies have verified the downregulation of the lncRNA MEG3 in CML patient samples as well as cell lines, promoting it as a possible prognostic marker (Zhou et al., 2017; Li et al., 2018c; 2018b); MEG3 was found to modulate cell proliferation, survival, and apoptosis in CML cells. Suppressed expressions of MEG3 by histone deacetylase (HDAC1) and DNA methyltransferases (DNMT1, DNMT3A, DNMT3B) have been reported, indicating the potential clinical applications of demethylation drugs and HDAC inhibitors in the treatment of CML (Li et al., 2018b, 2018c). The expression patterns of numerous microRNAs were found to be correlated with MEG3 expression in CML; for example, MEG3 and miR-147 were observed to be directly correlated, while the expressions of miR-184 and miR21 were inversely correlated (Zhou et al., 2017; Li et al., 2018b, 2018c; Li J. et al., 2018). By deciphering the mechanisms of MEG3 in CML, Li et al. (2018c) showed that MEG3 could regulate STAT3 at least partly by inhibiting the phosphorylation of JAK/STAT through a possible negative feedback loop between MEG3 and STAT3. Direct correlation between the expression patterns of MEG3 and PTEN in CML are also suspected to be involved in the pathogenesis (Li et al., 2018b). Recently, HOTAIR was reported to accelerate CML progression by regulating PTEN; the study confirmed high expression of HOTAIR in the bone-marrow samples from CML patients and showed DNMT1 recruitment to regulate methylation of the *PTEN* promoter (Song H. et al., 2021).

The expression of the lncRNA HAND2-AS1 was reported to be low in CML patients, which was interestingly also found to decrease further with disease progression from AP to CP. Mechanistically, HAND2-AS1 was found to regulate cell proliferation and apoptosis by sequestering miRNA-1275 (Yang et al., 2019). Increased expression of the lncRNA HULC was also found to be positively correlated with the clinical stages of CML; results from the corresponding study showed that HULC promotes oncogenesis in CML by modulating the expressions of c-Myc and BCL-2 through sponging of miR-200a. The loss of function of HULC resulted in IM-induced apoptosis and suppressed phosphorylation of PI3K and AKT (Lu et al., 2017).

Although scarcely expressed in CML, the lncRNA H19 was found to be a tumor suppressor that affects the viability and apoptosis of CML cells. Using computational and experimental techniques, Yang J. et al. (2020) identified the proteins PCBP1 and FUS as well as microRNAs miR-19a-3p and miR-106b-5p as the targets of H19 in CML. METTL3-mediated m6A modification was found to be responsible for the low expression of the lncRNA NEAT1 in CML; NEAT1 was also found to alter the CML progression through downstream regulation of the miR-766-5p/CDKN1A axis (Yao et al., 2021). However, in another study, NEAT1 was shown to be regulated by c-Myc, and its role in IM-induced apoptosis through interactions with SFPQ (which regulates cell growth and death pathway related genes) was confirmed (Zeng et al., 2018). Overexpression of the protooncogene lncRNA

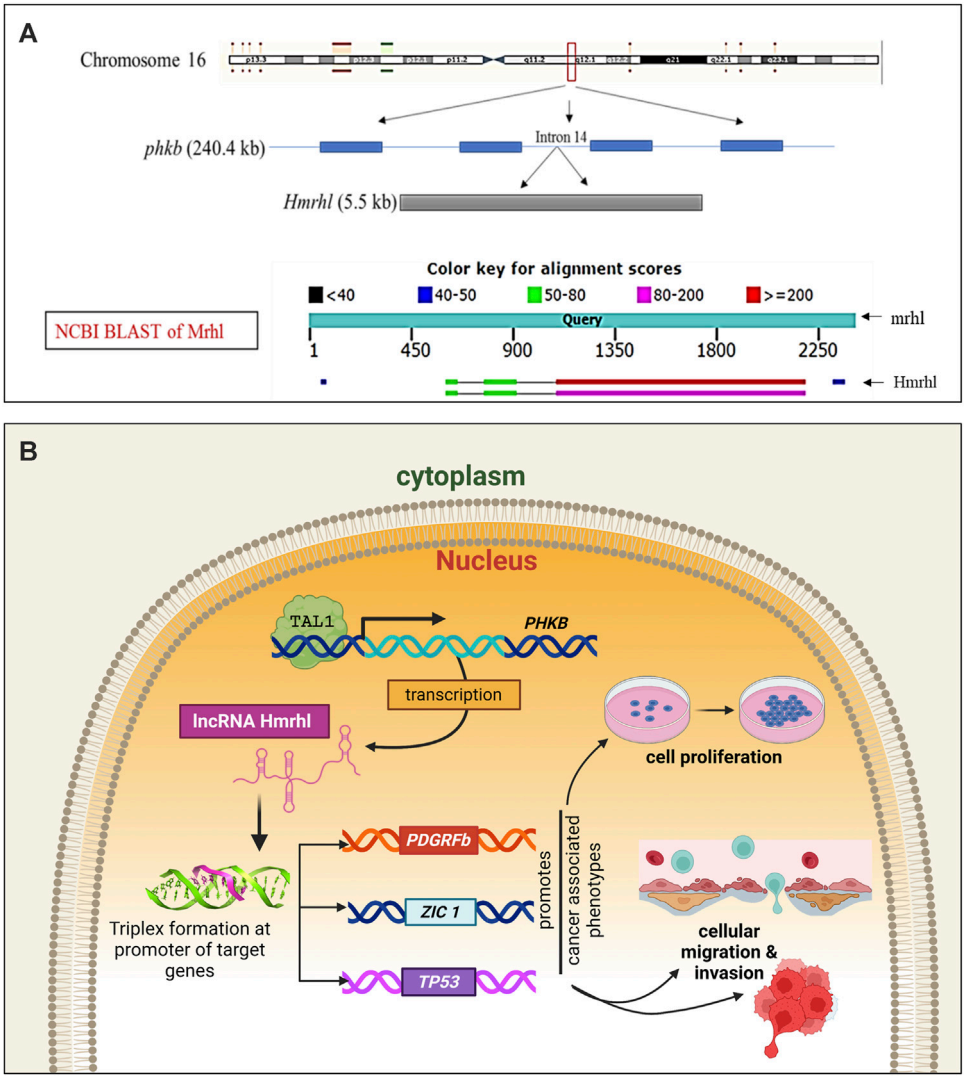


FIGURE 3
Human meiotic recombination hot spot locus (Hmrhl) lncRNA. **(A)** Genomic context with respect to its mouse homolog "mrhl" with which it shares 65% sequence homology and syntenic location within the intron of the *PHKB* gene. **(B)** Graphical model representing its regulatory mechanism and targets for promoting leukemogenesis of CML in K562 cells. The nuclear-restricted Hmrhl is the only reported lncRNA that acts at the chromatin level in CML by directly interacting with the target genes via triplex formation at their promoter and thereby regulating expression.

MALAT1 was reported to contribute to cancer phenotypes and IM sensitivity of CML cells via miR-328 targeting (Wen et al., 2018). The lncRNA ADORA2A-AS1 was also found to be overexpressed in CML; using the loss of function study, this lncRNA was shown to exert tumor-promoting activities and reduce IM sensitivity via sponging miR-665 and thereby regulating TGFBR1 and ABCC2 (Liu Y. et al., 2022). The lncRNA PLIN2 was found to promote CML progression via regulation of the GSK3 and Wnt/β-catenin signaling pathways both *in vitro* and *in vivo*; high levels of PLIN2 were shown to be the result of regulation by CEBPA, which is also upregulated in CML (Sun et al., 2017).

Lastly, a recent finding by our research group shows high expression of the lncRNA Hmrhl in the CML cell line K562 (Fatima et al., 2019; Choudhury et al., 2021). Hmrhl was discovered as a human homolog of the mouse lncRNA meiotic recombination hot spot locus (mrhl), which was also first reported by our group and has been studied extensively thereafter (Nishant et al., 2004; Ganesan and Rao, 2008; Arun et al., 2012; Akhade et al., 2014; Kataruka et al., 2017; Pal et al., 2021; 2022; Kayyar et al., 2022). With restricted expressions in the testes, liver, kidneys, and spleen, mrhl was found to be a negative regulator of Wnt signaling and a regulator of *SOX8* at the chromatin level in mouse spermatogonial cells (Arun et al., 2012; Akhade et al., 2014). The role of mrhl as a chromatin regulator of cellular differentiation and development genes along with its probable importance in the maintenance of the stemness in mouse embryonic stem cells was also established (Pal et al., 2021); the key role of mrhl in neuronal differentiation has also been reported recently (Pal et al., 2022). The lncRNA Hmrhl shares 65% homology with its mouse counterpart mrhl and an identical syntenic locus within the *PHKB* gene (Figure 3A). Unlike the restricted expressions of mrhl in a few organs,

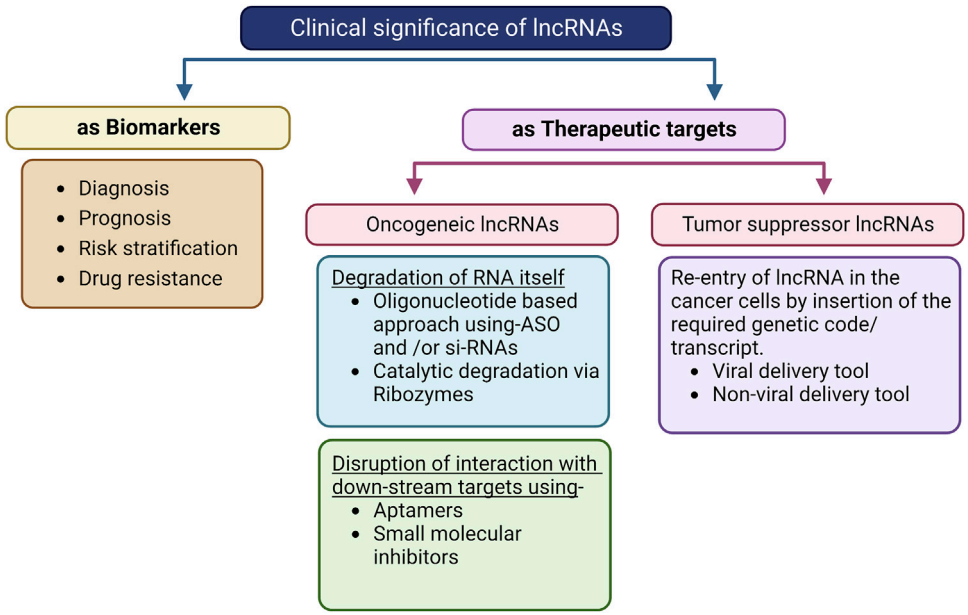


FIGURE 4
Flowchart depicting the clinical significance of lncRNAs and their incorporation into therapeutics. The presence of some lncRNAs in body fluids like serum, blood, plasma, and urine along with their specific expressions makes them suitable for use as biomarkers using non-invasive detection methods. For example, high levels of the lncRNAs LINC00899, FBXL19-AS1, LINC00460, and LINC00265 in the serum have been suggested as early diagnostic and prognostic biomarkers for AML patients. This method is limited by the stability of the RNA as well as lack of easy, robust, and economical detection methods for clinical use. Oligonucleotide- and catalytic-based approaches are promising for targeting and degrading oncogenic lncRNAs. siRNAs and ASO are already under phase I/II/III clinical trials for some lncRNAs in other diseases. The same approach can be applied in case of AML with targets like HOTAIR, DANCER, and UCA1, and is limited by the stability, delivery method, interferon-induced effects, and binding efficiency of the ribozyme. Aptamer and small-molecular inhibitors can also be used to inhibit the oncogenic effects of lncRNAs by disrupting their interactions with downstream targets. Tumor-suppressive lncRNAs like HOTAIRM1 can be repressed in AML cells to reverse carcinogenic effects using both viral and non-viral delivery channels.

Hmrhl was shown to be ubiquitously expressed in all the organs studied. With a transcript length of 5.5 kb, Hmrhl was found to be larger than mrhl (2.4 kb), which was achieved by acquiring seven different repeat elements (L2b, L2c, MIR, Charlie 15a, AluY, L1PA3, and AluSx) that flank the highly conserved central region. The expression profile of Hmrhl confirmed its deregulation in several cancers. In the CML cell line, Hmrhl was shown to act as an enhancer RNA for its host gene *PHKB* (Fatima et al., 2019).

Our recently published study (Choudhury et al., 2021) verified the enrichment of Hmrhl within the nucleus and its association with chromatin; this study shows the influence of Hmrhl in promoting cancer-related phenotypes, such as proliferation, migration, and invasion in the CML cell line K562, using gene silencing techniques. By adopting transcriptome-based methods, this report further revealed the association between Hmrhl and the perturbed expressions of several crucial TFs as well as cancer-related genes, highlighting its significance in CML pathobiology. Additionally, the genome-wide occupancy study of Hmrhl indicated its association with several loci throughout the genome, particularly at the intergenic and repetitive element sites along with the other regions. The study further intersected data from RNA-seq and ChIRP-seq, resulting in the identification and selection of *TP53, PDGFRβ,* and *ZIC1* as the possible targets of Hmrhl. Triplex formation at the promoter sites of the target genes was postulated to be the probable regulatory mechanism of Hmrhl (Choudhury et al., 2021) (Figure 3B). Furthermore, the study showed significant rescue effects on cancer-associated cellular phenotypes by overexpression of one of the target genes *PDGFRβ* in Hmrhl-silenced K562 cells. It was also verified that Hmrhl is regulated by TAL1, a key TF involved in hematopoiesis, in CML (Figure 3B).

An extensive literature search shows that most of the lncRNAs associated with CML exert their functions via microRNA sponging. To the best of our knowledge, Hmrhl is the only lncRNA reported so far that acts via direct interactions with chromatin to regulate its target genes, contributing to the pathobiology of CML.

# 8 Clinical significance of lncRNAs in myeloid leukemia: prognostic markers and possible treatment strategies

## 8.1 LncRNAs as biomarkers in myeloid leukemia

In addition to studies on the functional and biological significances of lncRNAs in the pathology of myeloid leukemia, several works have focused on translational research to explore the significance of lncRNAs as prognostic biomarkers or drug targets in patients (Figure 4). Many lncRNAs with altered expressions in AML

TABLE 3 Prognostic and clinical significance of documented lncRNAs in myeloid leukemia (AML and CML).

| LncRNAs with prognostic significance in AML | | | | |
|---|---|---|---|---|
| S. No. | LncRNA | Expression level | Clinical significance | References |
| 1 | ANRIL | High | - Associated with low CR and OS | Gamaleldin et al. (2021) |
| | | | - Linked with FLT3 mutation | |
| 2 | HOXBLINC | High | - Critical for leukemogenesis in NPM1-mutant AML | Zhu et al. (2021) |
| 3 | HOXA-AS2 | High | - Negative prognosis of AML patients | Feng et al. (2020b), Qu et al. (2020) |
| 4 | HOXB-AS3 | High | - Predicts poor prognosis in AML patients | Papaioannou et al. (2019b), Huang et al. (2019) |
| | | | - Linked with NPM1-mutant AML | |
| 5 | HOTAIRM1 | High | - Association with shorter OS, shorter leukemia-free survival, and higher cumulative incidence of relapse | Díaz-Beyá et al. (2015) |
| | | | - Correlated with 33 microRNA signatures | |
| | | | - Diagnostic marker for stratification of patients into high, intermediate, and low risk groups | |
| 6 | HOTAIR | High | - Linked with poor OS and relapse-free survival (RFS) | Hao and Shao (2015), Wu et al. (2015), Saad et al. (2021), Salah et al. (2021) |
| | | | - Associated with higher WBC and BM blast counts as well as lower hemoglobin and platelet counts | |
| | | | - Linked with FLT3-ITD and NPM1 mutations | |
| 7 | RUNXOR | High | - Associated with t (8; 21) translocation in AML | Wang et al. (2014) |
| 8 | IRAIN | Low | - Associated with shorter OS, disease-free survival (DFS), and high WBC count. | Pashaiefar et al. (2018), Hussein et al. (2023) |
| | | | - Linked with relapse | |
| 9 | PVT-1 | High | - Linked with APL and t (8; 21) | Izadifard et al. (2018), El-Khazragy et al. (2019) |
| | | | - Associated with shorter OS and DFS | |
| | | | - Acts as miR-200 sponge to regulate c-Myc | |
| 10 | CCAT1 | High | - Associated with M4-M5 subtypes | Izadifard et al. (2018), El-Khazragy et al. (2019) |
| | | | - Regulates c-Myc via miR-155 sponging | |
| 11 | SNHG3 | High | - Predicts poor outcomes in AML | Peng et al. (2020) |
| | | | - Modulates SRGN expression (which plays an important role in granule-mediated apoptosis) by competitively binding with miR-758-3p | |
| 12 | GAS5 | High | - Adverse prognosis in AML patients | Ketab et al. (2020), Pavlovic et al. (2021), Qin et al. (2022) |
| | | | - Along with its target miRNA-222 and NR3C1, could be used as a dual biomarker for prognosis of AML in young and adult patients, respectively | |
| | | | - Inhibits Nrf2 expression to regulate cell apoptosis and proliferation | |
| 13 | PANDAR | High | - Associated with low CR and OS rates | Yang et al. (2018) |
| | | | - Linked with higher AML blasts, older patients, and poor karyotypes | |
| 14 | H19 | High | - Lower CR and OS rates along with WBC count | Zhang et al. (2018a) |
| | | | - Intermediate karyotype classifications of recurrent mutations, FLT3/ITD, and DNMT3a | |
| 15 | CASC15 | Low | - Associated with RUNX1-rearranged AML and t (8; 21) | Fernando et al. (2017) |
| | | | - Associated with good prognosis | |
| | | | - Activates SOX4 expression via YY1 regulation | |

(Continued on following page)

TABLE 3 (*Continued*) Prognostic and clinical significance of documented lncRNAs in myeloid leukemia (AML and CML).

| LncRNAs with prognostic significance in AML | | | | |
|---|---|---|---|---|
| S. No. | LncRNA | Expression level | Clinical significance | References |
| 16 | MEG3 | Low | - Poor risk stratification, worse treatment response, and unfavorable survival data | Yao et al. (2017), Sellers et al. (2019), Gao (2021a), Pei et al. (2022) |
| | | | - Has hypermethylated promoter in AML | |
| 17 | TUG1 | High | - Associated with monosomal karyotype/FLT3-ITD mutations | Wang et al. (2018a), Luo et al. (2018b), Qin et al. (2018), Li et al. (2019), Zhang et al. (2020a, 2020c) |
| | | | - Correlated with shorter OS, lower CR, and high WBC count | |
| | | | - Acts by sponging microRNAs (miR-370-3p/MAPK1, miR-193a-5p/Rab10, miR-221-3p/KIT, and miR-185) | |
| | | | - Activates ERK1/2 signaling and regulates glycolysis | |
| 18 | CCDC26 | High | - Linked with childhood AML | Chen et al. (2019) |
| | | | - Correlated with age, anemia, risk stratification, remission, and shorter OS | |
| | | | - Repress c-Kit expression | |
| 19 | LINC00899 | High | - Associated with shorter OS | Wang et al. (2018b) |
| | | | - Positively associated with French–American–British (FAB) classification and cytogenetics | |
| | | | - Suggested as a serum biomarker for early detection and prognosis of AML | |
| 20 | FBXL19-AS1 | High | - Unfavorable prognosis and shorter OS | Sheng et al. (2021) |
| | | | - Associated with FAB classification and cytogenetics | |
| | | | - Suggested as a serum biomarker for AML | |
| 21 | LINC00460 | High | - Unfavorable prognosis and shorter OS | Zhuang et al. (2021) |
| | | | - Associated with FAB classification and cytogenetics | |
| | | | - Suggested as a serum biomarker for AML | |
| | | | - Acts via the miR-320b/PBX3 axis to regulate viability, cell-cycle distribution, and apoptosis of AML cells | |
| 22 | LINC00909 | High | - Associated with FAB classification, cytogenetics, and poor prognosis | Ma et al. (2020) |
| | | | - Sponges miR-625 and suppresses the Wnt/β-catenin signaling pathway | |
| 23 | LINC00265 | High | - Unfavorable prognosis and shorter OS | Ma et al. (2018) |
| | | | - Associated with FAB classification and cytogenetics | |
| | | | - Suggested as a serum biomarker for AML | |
| | | | - Activates PI3K/AKT signaling | |
| 24 | KCNQ1OT1 | High | - Associated with NCCN risk grade and shorter OS | Jia et al. (2018) |
| 25 | CD27-AS1 | High | - Unfavorable prognosis and shorter OS | Tao et al. (2021) |
| | | | - Acts via miR-224-5p/PBX3/MAPK signaling | |
| 26 | PCAT18 | High | - Linked with NPM1 mutation in AML | Zhang et al. (2020b) |
| 27 | LINC00152 | High | - Associated with FAB classification, cytogenetics, and poor prognosis | Zhang and Tao (2019) |
| | | | - Promotes leukemogenesis through the miR-193a/CDK9 axis | |
| 28 | LINC01268 | High | - Associated with poor prognosis | Chen et al. (2020) |
| | | | - Acts via the miR-217/SOS1 axis | |

(Continued on following page)

TABLE 3 (*Continued*) Prognostic and clinical significance of documented lncRNAs in myeloid leukemia (AML and CML).

| LncRNAs with prognostic significance in AML | | | | |
|---|---|---|---|---|
| S. No. | LncRNA | Expression level | Clinical significance | References |
| 29 | NORAD | High | - Associated with poor OS and RFS<br>- Linked with non-M3 AML patients | Masoud Eslami et al. (2021) |
| 30 | RPPH1 | High | - Predicts worse overall survival | Lei et al. (2019) |
| 31 | MORRBID | High | - Associated with FLT3ITD mutations<br>- Predicts poor prognosis | Cai et al. (2019) |
| 32 | KIAA0125 | High | - Directly related to RUNX1 mutation<br>- Inversely correlated with t (8; 21) and t (15; 17) karyotypes<br>- Associated with lower CR rate, shorter OS, and DFS. | Wang et al. (2021) |
| LncRNAs with prognostic significance in CML | | | | |
| 33 | MEG3 | Low | - Associated with AP and BP of CML.<br>- High degree of methylation of MEG3 found in patents<br>- Potential biomarkers for early diagnosis of BP along with its targets miR-147 and miR-21 | Li et al. (2018b, 2018c) |
| 34 | CCAT2 | High | - Potentially reliable molecular marker for predicting IM responses in CP CML patients | Shehata et al. (2022) |
| 35 | HAND2-AS1 | Low | - Expression level decreases with disease progression<br>- Can be used for stratification of patients into AP, BP, and CP | Yang et al. (2019) |
| 36 | HOTAIR | High | - Linked with IM resistance | Wang et al. (2017), Song et al. (2021a) |
| 37 | DLEU2 | Not known but high in related disease CLL | - Biomarker for AP in CML | Xu et al. (2020) |
| 38 | SNHG5 | High | - Biomarker for CP in CML<br>- Promotes IM resistance through miR-205-5p/ABCC2 | He et al. (2020), Xu et al. (2020), Shahpouri-Arani et al. (2022) |
| 39 | SNHG3+SNHG5 | High | - Biomarker for BP in CML | Xu et al. (2020) |

and CML patients have been suggested as prognostic markers for early diagnosis (Table 3) (Wang et al., 2014; Wang X. et al., 2018; Díaz-Beyá et al., 2015; Hao and Shao, 2015; Wu et al., 2015; Fernando et al., 2017; Yao et al., 2017; Ma et al., 2020, 2018; Zhang T. et al., 2018; Zhang W. et al., 2020; Zhang X. et al., 2020; Zhang F. et al., 2020; Luo W. et al., 2018; Izadifard et al., 2018; Jia et al., 2018; Pashaiefar et al., 2018; Qin et al., 2018, 2022; Yang et al., 2018; Papaioannou et al., 2019b; Cai et al., 2019; Chen et al., 2019; El-Khazragy et al., 2019; Huang et al., 2019; Lei et al., 2019; Li et al., 2019; Sellers et al., 2019; Zhang and Tao, 2019; Feng et al., 2020b; Chen et al., 2020; Ketab et al., 2020; Peng et al., 2020; Qu et al., 2020; Tan et al., 2020; Xu et al., 2020; Gao, 2021a; Saad et al., 2021; Gamaleldin et al., 2021; Masoud Eslami et al., 2021; Pavlovic et al., 2021; Salah et al., 2021; Zhu et al., 2021; Pei et al., 2022; Hussein et al., 2023).

For example, an expression study of HOTAIRM1 in 241 AML patients revealed its association with shorter overall survival, shorter leukemia-free survival, and higher cumulative incidence of relapse (Díaz-Beyá et al., 2015); its expression was also correlated with 33 microRNA signatures, which can be combined and used as a diagnostic marker for stratifying patients into high, intermediate, and low risk groups (Díaz-Beyá et al., 2015). Two separate studies analyzing bone-marrow samples from 178 and 100 AML patients found ANRIL overexpression compared to healthy donors (Tan et al., 2020; Gamaleldin et al., 2021). ANRIL is also associated with low rates of complete remission (CR) and overall survival (OS) along with FLT3 mutation, implying that it could be a valuable prognostic marker for AML (Tan et al., 2020; Gamaleldin et al., 2021). In a study on 119 AML patients, higher PANDAR expression was associated with poor clinical outcomes with low CR and OS rates (Yang et al., 2018). The prognostic value of H19 expression was confirmed in AML patient samples and was correlated with lower CR and OS rates. High levels of H19 are also associated with WBC count and recurrent mutations, FLT3/ITD and DNMT3a in AML. These results were further validated by data analyses on TCGA and GEO (Zhang T. et al., 2018). Low levels of IRAIN are associated with high-risk AML patients, with an adverse prognosis of higher WBC and blast counts, shorter OS, and relapse-free survival (RFS). Resistance to chemotherapy with subsequent relapse was also observed in patients with low IRAIN expressions (Pashaiefar

et al., 2018; Hussein et al., 2023). Recently, lower GAS5 expressions during diagnosis have been related to adverse prognosis in AML patients (Ketab et al., 2020; Pavlovic et al., 2021; Qin et al., 2022). Separate studies have associated the expression pattern of GAS5 with the expression profiles of its targets, miRNA-222 and NR3C1, as dual biomarkers for prognosis in young and adult AML patients, respectively (Ketab et al., 2020; Pavlovic et al., 2021). At the molecular level, GAS5 was found to inhibit Nrf2 expression, thereby regulating cell apoptosis and proliferation while further inhibiting the progression of AML (Qin et al., 2022). The tumor suppressor MEG3 is widely reported to have a hypermethylated promoter in AML, and its low expression is correlated with poor risk stratification, worse treatment responses, and unfavorable survival data (Yao et al., 2017; Sellers et al., 2019; He et al., 2020; Gao, 2021a).

Low expression of the lncRNA MEG3 is also linked with the prognosis of CML patients in the AP and BP (Li et al., 2018b, 2018c). These patients also showed higher degrees of methylation of the MEG3 promoter (Li et al., 2018c). The expression patterns of MEG3 and its targets miR-147 and miR-21 could thus be used as potential biomarkers for early diagnosis of CML blast crisis (Li et al., 2018c, 2018b). A study on peripheral blood mononuclear cells from 43 newly diagnosed CML patients showed that enhanced expression of CCAT2 was associated with IM resistance (Shehata et al., 2022); the authors concluded that CCAT2 can therefore be used as a reliable molecular marker for predicting IM responses in CP CML patients. Expression of HAND2-AS1 in the bone-marrow samples of 30 CML patients showed a gradual decline in its level with disease progression from AP to BP to CP; an inverse correlation between HAND2-AS1 and miR-1275 was also shown in the study (Yang et al., 2019). High levels of HOTAIR have been reported in CML patients and are linked with IM resistance (Wang et al., 2017; Song H. et al., 2021); however, the role of HOTAIR as a biomarker has not been suggested yet. Using dynamic network biomarkers (DNBs) and KEGG enrichment analysis, Xu et al. (2020) identified three lncRNAs functioning as ceRNA as potential biomarkers for CML; the authors suggested DLEU2, SNHG3+SNHG5, and SNHG5 as effective biomarkers for AP, BP, and CP owing to their key roles in the pathogenesis of CML (Xu et al., 2020).

Note to readers: For better navigation and searchability, a consolidated supplementary excel sheet (Supplementary File S1) is provided and contains the list of all lncRNAs grouped under various topics based on their roles in AML and CML.

## 8.2 Treatment strategies using lncRNAs

The inherent properties of cell/tissue/disease-specific expressions of lncRNAs make them ideal candidates for diagnosis and prognostic stratification of patients depending on disease progression as well as possible responses to drug resistance. Some of the lncRNAs are reported to be present in bodily fluids (like the blood, plasma, serum, urine, and saliva). This allows non-invasive collection and easy detection of lncRNAs for screening as biomarkers (Badowski et al., 2022; Beylerli et al., 2022; Khawar et al., 2022; Aprile et al., 2023; Li et al., 2023). For example, high levels of the lncRNAs LINC00899, LINC00460, and FBXL19-AS1 in the serum have been suggested as biomarkers for the early clinical detection and prognosis of AML (Wang Y. et al., 2018; Sheng et al., 2021; Zhuang et al., 2021). Developments in transcriptomics technologies offer many techniques like qRT-PCR, RNA sequencing, and microarrays that can be used to detect lncRNAs (Wang et al., 2022). However, there is a need for developing robust and economical assays that are sensitive enough to detect lncRNAs readily and accurately for clinical applications.

For well-characterized lncRNAs, several strategies can be used for targeted treatment. Advanced techniques like the CRISPR/Cas9 for knock-in/-out of specific lncRNAs are under investigation (Sakuma and Yamamoto, 2018). si-RNAs as antisense oligonucleotides (ASOs) can be used in oligonucleotide-based techniques to target overexpressed oncogenic lncRNAs, where they can bind specifically with lncRNAs, initiating their degradation via RNA-induced silencing complex (RISC) or RNase H (Kole et al., 2012; Raguraman et al., 2021; Scharner and Aznarez, 2021; Zhang and Zhang, 2023). Investigations on improved delivery methods, stability of the oligonucleotide, and their long-lasting effects on patients are underway (Glazier et al., 2020; Shadid et al., 2021; Zhu et al., 2023). Another therapeutic strategy to inhibit lncRNA is catalytic degradation using ribozymes. However, their efficiency and specificity to the target are under investigation (Kruger et al., 1982; Pavco et al., 2000; Fedor and Williamson, 2005). Another method of tackling oncogenic lncRNAs is to disrupt their interactions with the targets using aptamers and small molecular inhibitors (Pedram Fatemi et al., 2015; Vitiello et al., 2015; Yang et al., 2017). The use of viral or non-viral delivery tools has also been proposed for tumor suppressor lncRNAs. Whole specific transcripts can also be delivered and re-expressed with functional rescue effects (Nayerossadat et al., 2012; Ibraheem et al., 2014).

Although none of the abovementioned therapeutic strategies were intended for use in myeloid leukemia, many of these are under clinical trials for other cancers, and some are already approved by the USFDA (Pavco et al., 2000; Parker et al., 2009; Smaldone and Davies, 2010; Nguyen et al., 2012; Coelho et al., 2013; Mansoori et al., 2014; Fatima et al., 2015; Liu et al., 2016; De Clara et al., 2017; Titze-de-Almeida et al., 2017; Papaioannou et al., 2019a). Studies on lncRNAs in myeloid leukemia are still in their early stages, but more ongoing research on the functional mechanisms as well as detailed characterizations along with data on the patients, disease progression, and chemoresistance are expected to enable application of these therapeutic strategies to myeloid leukemia.

# 9 Conclusion

It can be easily inferred from this review that lncRNAs play crucial roles in the occurrence and progression of myeloid leukemias, AML, and CML. Studies reported thus far have provided valuable insights into the regulatory mechanisms by which lncRNAs control the differentiation patterns, proliferative capacities, and apoptosis abilities of cells in both AML and CML. However, further in-depth studies on the functional mechanisms and regulatory targets of lncRNAs are needed in the context of myeloid leukemias to fully understand the complex pathobiology of the disease and identify promising therapeutic targets. Moreover, more numbers of studies on patient samples with large cohorts are essential to establish the clinical significance of lncRNAs and use them as potential biomarkers for diagnosis, risk stratification, and prognosis. Translation of the present knowledge from bench to bedside still presents a tremendous

challenge; however, with the fast pace of ongoing research on lncRNAs and advancements in detection techniques, there is great scope for lncRNAs to provide solutions to the current limitations, which is crucial for precision medicine in myeloid leukemia.

## Author contributions

SD: conceptualization, investigation, supervision, validation, visualization, writing–original draft, and writing–review and editing. VA: writing–review and editing. SC: writing–review and editing. MR: conceptualization, funding acquisition, project administration, supervision, validation, writing–original draft, and writing–review and editing.

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## In memoriam

This work was conceived by the late Prof. Manchanahalli Rangaswamy Satyanarayana Rao, a SERB Distinguished Fellow and SERB-YOS Professor. The remaining authors would like to dedicate this article to the memory of Prof. Rao, who was not only an exemplary scientist and mentor but also an exceptional human being.

## Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

## Publisher's note



## Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/frnar.2024.1334464/full#supplementary-material

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