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Review Article

Unraveling the role of long non-coding RNAs in therapeutic resistance in acute myeloid leukemia: New prospects & challenges

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ABSTRACT

Acute Myeloid Leukemia (AML) is a fatal hematological disease characterized by the unchecked proliferation of immature myeloid blasts in different tissues developed by various mutations in hematopoiesis. Despite intense chemotherapeutic regimens, patients often experience poor outcomes, leading to substandard remission rates. In recent years, long non-coding RNAs (lncRNAs) have increasingly become important prognostic and therapeutic hotspots, due to their contributions to dysregulating many functional epigenetic, transcriptional, and post-translational mechanisms leading to alterations in cell expressions, resulting in increased chemoresistance and reduced apoptosis in leukemic cells. Through this review, I highlight and discuss the latest advances in understanding the major mechanisms through which lncRNAs confer therapy resistance in AML. In addition, I also provide perspective on the current strategies to target lncRNA expressions. A better knowledge of the critical role that lncRNAs play in controlling treatment outcomes in AML will help improve existing medications and devise new ones.

1. Introduction

Hematopoiesis is a highly regulated process of developing various blood cell lineages from hematopoietic stem cells (HSCs) that undergo multiple, intermediate stages of maturation [1]. Leukemia is a diverse family of life-threatening hematologic malignancies that manifest from an oligoclonal, unregulated proliferation of failed differentiated HSCs. According to the Canadian Cancer Society, cancer is the prime factor responsible for deaths in Canada, and of the 124,200 reported cases of cancer in Canadian males in 2023, approximately 3.14 % of cases accounted for leukemia while for the 114,900 female cancer cases, leukemia accounted for 2.17 % of all cases. The National Cancer Institute SEER predicted an estimated 59,610 new cases of leukemia in the general US population for 2023 with the predicted mortality rate at a staggering estimate of 39.7 % (23,710 deaths). While there exists a wide heterogeneity in the genetic abnormalities and risk factors that lead to leukemogenesis, with treatment options varying on a case-by-case basis, the general factors that increase the risk of leukemia include high/fatal doses of radiation; long exposure to carcinogenic species like Benzene, and workplace accidents/hazards [2]. Based on the diseases' rate of progression and cell lineage affected, the World Health Organization (WHO) has broadly classified leukemia into 4 unique subtypes namely acute myeloid leukemia (AML), chronic myeloid leukemia (CML), acute lymphoblastic leukemia (ALL), and chronic lymphoblastic leukemia (CLL) [3,4]. AML is a rare clonal malignancy stemming specifically from the abnormal development and uncontrolled proliferation of immature blood cells called myeloid blasts which subsequently infiltrate the bone marrow (BM), and other tissues, interfering with other healthy cells and preventing them from performing their biological functions [5]. The diagnosis of AML is based on a greater than or equal to 20 % threshold limit of the presence of immature, malignant myeloid blasts in the blood and other tissues [6,7]. While rarely diagnosed in children and youth, AML is the most common form of acute leukemia occurring in adults in the USA. The estimated general US population diagnosed with acute myeloid leukemia was 20,380 cases for 2023 with deaths estimated to be at a ghastly approximation of 11,310 (55.4 % for all diagnosed cases) [8]. Growing advances in hematological cancer research have dramatically improved therapy outcomes with most patients achieving complete remission (CR). Induction chemotherapy is the first treatment regimen to combat cancer with a single or a concoction of different chemotherapeutic reagents. An intense 7-day cytarabine (Cyt) + 3-day anthracycline regimen remains unchallenged as induction chemotherapy to treat AML for over 40 years [9]; but despite achieving a promising 60–80 % remission rate in the younger generation and 40–60 % in adults greater than 65 years of age [6,10], approximately 10–20 % of all patients fail to respond to induction chemotherapy and more than

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85 % patients experience relapse which diminishes the probability of survival after further treatment regimens [11]. The genomic, and molecular heterogeneity, of AML, is diverse and growing evidence suggests that strong therapeutic resistance in leukemic cells is strongly correlated to the observed high relapse and poor prognosis in patients [12,13]. The underlying mechanisms influencing leukemic cells to become more resistant to therapeutic effects have not yet been fully elucidated. Therefore, a greater mechanistic understanding of pathways mediating therapeutic resistance in AML is an urgent, indispensable need that will help open novel avenues for creating more effective and safe treatment procedures. lncRNAs are the group of non-coding RNAs (ncRNAs) greater than 200 nucleotides in length but lack appreciable protein translation [14–16]. Several studies have documented the significant contributions of lncRNAs in enhancing therapeutic resistance in various cancers including lung cancer [17–21], breast cancer [22–26], colorectal cancer [27–30], gastric cancer [31–34], and ovarian cancer [35–37]. In this review, I offer thorough insights into the numerous ways through which lncRNAs induce and support chemoresistance, self-renewal, and immortalization against programmed death in AML (Fig. 1). Knowing the critical roles played by different lncRNAs in AML will improve our awareness of the interactions between different underlying processes that result in heightened chemo refractory and

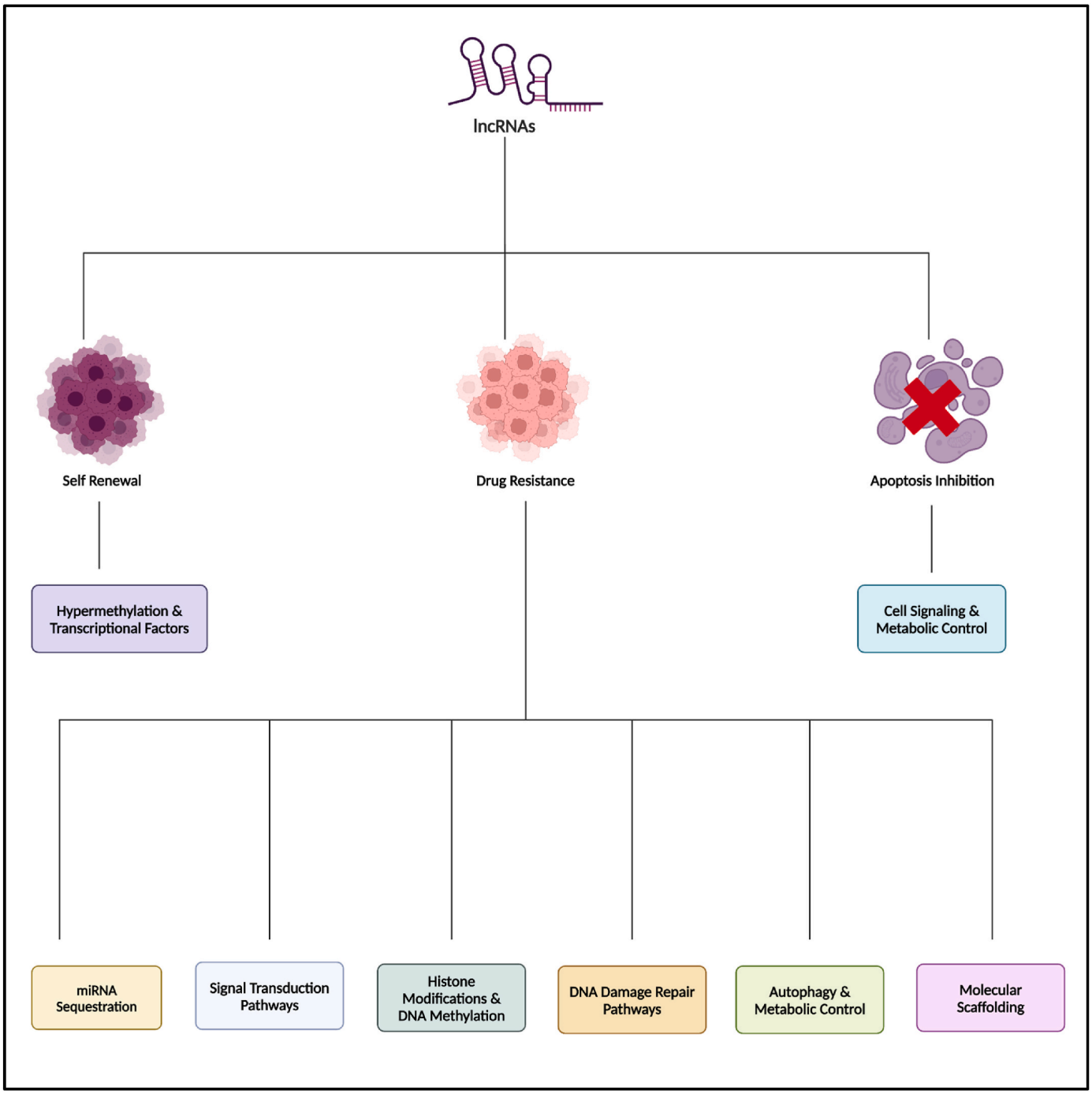

Fig. 1. Graphical Abstract
An illustration summarizing the different mechanisms through which lncRNAs regulate drug resistance, promote apoptosis inhibition, and enhance the self-renewal capacity of LSCs.

ultimately lead to the development of novel medicines, creating new avenues for the treatment of AML. Finally, I hope that the studies discussed herein will encourage the creation of brand-new questions and lines of inquiry that will have a significant influence on clinical practice.

2. Significance of lncRNA expressions in AML

With great strides being accomplished in cancer research, it has been found that the dysregulation of various lncRNA expressions is an important factor responsible for leukemogenesis. Indeed, a diverse spectrum of evidence suggests that lncRNAs can be exploited as important prognostic and therapeutic targets [15,38–41]. lncRNAs are involved in regulating cellular proliferation, myeloid differentiation, drug resistance, leukemic cell metabolism, RNA modifications, and inhibition of apoptosis in AML [42]. Illustriously, in addition to enhancing m^6A methylation, the lncRNA UCA1 also increases the stability of CXCR4 and CYP1B1 by binding to and then upregulating the expression of the METTL14 protein. METTL14 is substantially overexpressed in AML patients with t(11q23), t(15; 17), and t(8; 21) cytogenetic abnormalities [43], and studies also suggest that both CXCR4 and CYP1B1 play an important role in AML pathogenesis and represent promising therapeutic targets [44–46]. Given that METTL14 is a crucial component of UCA1-modified m^6A methylation and that m^6A methylation levels are likewise considerably expressed in AML, the significance of the UCA1-mediated METTL14/CXCR4/CYP1B1 axis becomes important [47]. Various studies highlight how lncRNAs upregulate various signal transductions to facilitate AML metastasis and restrain apoptosis. A prominent example is the lncRNA SNHG16 which is substantially expressed in several cancers and is essential for tumorigenesis as it is involved in the growth and proliferation of cancer cells, as well as enhancing chemoresistance, metastasis, and preventing cell apoptosis [48]. Little is known about this lncRNA's function, specifically in AML. Recently, it was shown that SNHG16 regulates oligoclonal proliferation and advocates aggressive cell migration in AML. SNHG16 directly binds to the CELF2 protein and overexpression of SNHG16 down-regulates CELF2 expression levels since their interaction gives SNHG16 an authoritative control over the regulation of CELF2 protein to its mRNA target, inherently reducing the stability of the CELF2 mRNA. Since PTEN's main function is to negatively regulate the PI3K/AKT signal pathway, whose overexpression is a major contributor to carcinogenesis, enhanced SNHG16 expression decreases PTEN activity, leading to an increase in PI3K/AKT signaling [49]. The role of lncRNAs as competing endogenous RNAs (ceRNAs) has garnered increasing attention in recent times. Patients with M5 subtype AML are reported to have significant levels of HOTTIP expression. The microRNA-608 (miRNA-608) gene is the main target of HOTTIP, and M5, U-837, and THP-1 AML cell lines with increased HOTTIP expression exhibited significantly lower levels of miRNA-608. As a ceRNA, HOTTIP traps miRNA-608 inside of itself. CCK-8 and flow cytometry demonstrated that this encapsulation upregulates DDA1 expression, which is normally tightly downregulated by miRNA-608. This increase in DDA1 is responsible for increasing the proliferative potential of AML. As a result, the HOTTIP/miRNA-608/DDA1 axis is discovered to hasten AML pathogenesis [50]. The lncRNA SBF2-AS1 is overexpressed in AML. The active tumor suppressor miR-188-5p is sequestered by SBF2-AS1, which acts as a ceRNA to promote ZFP91 expression and boost AML proliferation. ZFP91 is an active tumorigenesis promoter, and miR-188-5p inhibits ZFP91 mRNA expression by binding to its 3′-UTR. Since high levels of ZFP91 are linked to poor prognosis in AML patients, its elevation by SBF2-AS1 through the/miR-188-5p/ZFP91 axis is clinically valuable since evidence further suggests G0/G1 cell cycle arrest and greater apoptosis in AML cells on SBF2-AS1 knockdown [51]. Conspicuously, in the case of AML, lncRNAs are known for being significantly involved in metabolic reprogramming [52]. For instance, ANRIL accelerates AML advancement by modulating glucose metabolism. The Adiponectin receptor 1 (AdipoR1) expression level is found to be positively correlated with ANRIL, evident from knockdown studies demonstrating that silencing AdipoR1 boosts cell apoptosis and lessens proliferation like the results observed on ANRIL knockout. Aberrant glucose metabolism is an important component of leukemogenesis [53]. Mechanistically, the expressions of pAMPK, SIRT1, GLUT1, and LDHA are increased when ANRIL expression is increased in AML cells. Taken in tandem, these results highlight that ANRIL functions as an important marker in AML by mediating uncontrolled proliferation through the AdipoR1/-AMPK/SIRT1 axis [54].

3. Significance of lncRNAs in regulating chemoresistance

The development of both intrinsic and acquired forms of chemoresistance continues to be the biggest impediment to improving the lives of cancer patients [55]. Intrinsic chemoresistance refers to the cancer cells' natural capacity to fend off the effects of anti-cancer medications even before the patient is administered them. Causes for the emergence of intrinsic multidrug resistance in cancers are explained by ingrained genetic mutations in tumor microenvironments (TMEs), decreased responsiveness brought on by cancer stem cells, and the development of defense mechanisms to counteract the cytotoxic effects of chemotherapeutic agents. A progressive decrease in the medicine's effects during or after the completion of the chemotherapeutic regimen, on the other hand, indicates acquired drug resistance. Similar to its intrinsic counterpart, acquired chemoresistance is caused by many circumstances, including the activation of multiple oncogenes, physiochemical changes in the drug target, and finally, advancements in the TMEs post-treatment [56]. Cancer cells fight drug effects by a variety of strategies, which can be broadly categorized in a dichotomic sense as physical and metabolic responses. Physical features such as extracellular matrix (ECM) architecture, TME matrix stiffness, and cell adhesion-mediated drug resistance (CAM-DR) all contribute to chemoresistance in various carcinomas. The biochemical pathways that contribute to the enhancement of drug-resistant characteristics in cancers include effects of tumor-associated macrophages (TAMs), hypoxia, glycolysis, intercellular communication, cytokine-cancer cell communication, and secretion of exosomes by cancer cells [57]. Other mechanisms include overexpression of specific ABC transporter proteins [58,59], increased autophagy [60,61], and lysosomal sponging in cellular alcoves [15,62,63]. While many miRNAs, transcription factors, and histone complexes have been well known to modulate chemoresistance in cancers [64–71], how lncRNAs contribute to and control chemoresistance in malignancies is an ongoing research subject of significant importance. To rephrase this question, it would be more useful to consider what precise pathways lncRNAs use to increase drug resistance in cancer cells. Many attempts have been made to address this question. For instance [26], showed that the lncRNA DDX11-AS1 promoted doxorubicin (DOX) resistance in breast cancer cells by interacting with and upregulating levels of the LIN28A protein. Consequently, this resulted in enhanced stability of mRNA expressions of ATG7 and ATG12 proteins leading to DOX resistance. In another study by [34] it was found that the lncRNA EIF3J-DT stabilized the mRNA expression of the ATG14 protein by interacting with it directly while also simultaneously sponging the miRNA MIR188-3p to prevent ATG14 degradation to induce chemoresistance in gastric cancer. Besides breast and gastric cancer, lncRNAs play an active role in mediating drug resistance in various other malignancies like lung cancer [72,73], ovarian cancer [74,75], osteosarcoma [76,77], lymphoma [78], and other hematological malignancies [79,80]. The processes by which lncRNAs regulate chemoresistance include but are not restricted to, post-translational histone modifications, mRNA stabilization, miRNA sequestration, anti-apoptotic signaling, and interactions with transcription factors [81,82]. I would like to point out that despite an abundance of evidence pointing to the multifaceted role of lncRNAs in AML [83–87], the specific actions taken by lncRNAs for mediating drug resistance in AML have not been clearly explained. Moreover, while scientific research over the past five years has answered some

questions, it has also opened doors to new potential research frontiers, as I will discuss ahead.

3.1. Mechanism 1: lncRNA mediated miRNA sequestration

Since some lncRNAs have miRNA binding sites, they regulate gene expression by inhibiting the quantity of miRNA available to its corresponding downstream target's mRNA. This process is known as sequestration or molecular sponging. Interactions between miRNAs and lncRNAs play an important role in the development of chemoresistance in AML. For instance, the overexpression of the lncRNA SATB1-AS1 causes desensitization of AML cells towards Adriamycin (ADR or DOX) and Cytarabine (Cyt). Principally, miR-580 functions as a tumor suppressor in AML, and SATB1-AS1 sponges miR-580 to boost levels of the 2'-5'-oligoadenylate synthetase 2 (OAS2) protein. Furthermore, the SATB1-AS1/miR-580/OAS2 axis is itself regulated by the GSK3β/β-catenin signaling pathway. This signal transduction is identified by the increased expressions of β-catenin in AML cells exhibiting greater resistance to Adr/Cyt chemotherapeutic treatment. SATB1-AS1 therefore has been identified as a novel lncRNA intricately involved in mediating drug resistance in AML cells and can be exploited as a therapeutic target [88]. BM samples extracted from patients receiving DOX treatment overexpress the lncRNA HOXA-AS2. In addition, miR-520c-3p levels are markedly substandard in both the THP-1/ADR and U937/ADR cell lines, and knocking out HOXA-AS2 enhances miR-520c-3p expression. Furthermore, miR-520C-3p binds to several putative locations on the 3′-UTR of S100A4 mRNA to inhibit its expression. Remarkably, S100A4 is an oncogene that is essential for the development of chemoresistance in a variety of malignancies [89]. Therefore, in tandem, the HOXA-AS2/miR-520c-3p/S100A4 axis is a lucrative target that can be targeted to overcome DOX resistance in AML [90]. lncRNA NEAT2, also known as MALAT1 is an 8.7 knt lncRNA transcript localized in the nucleus at the 11q13.1 chromosomal region in humans that exhibits extensive evolutionary conservation relative to most other lncRNAs [91]. Numerous studies have demonstrated how it affects chemoresistance in different cancers via miRNA sponging including gastric cancer [92–94], lung cancer [95], bladder cancer [96], and breast cancer [97,98]. MALAT1 enhances Ara-C resistance in AML cells by retarding miR-96 expression. It is observed that MALAT1 expression is significantly elevated in the HL60, and THP-1 cell lines exhibiting strong resistance towards Ara-C. On the other hand, there is a marked downregulation of miR-96, suggesting that MALAT1 functions in opposition to miR-96. MALAT1 expression in AML cells is negated by miR-96 overexpression, and conversely, decreasing miR-96 expression eliminates these effects [99]. Lysine Demethylation 4C (KDM4C), an oncogene frequently discovered to be overexpressed in a variety of malignancies contributes to the course of these diseases as well as their resistance to radiation and medication [100–103]. Interestingly, KDM4C plays a critical role in regulating MALAT1 expression in AML cells. Mechanistically, KDM4C demethylates the MALAT1 promoter region to boost MALAT1 expression in the HL60/Ara-C cell line. Apart from the previously discussed miR-96, another miRNA target of MALAT1 is miR-328-3p. Downregulated miR-328-3p levels are the consequence of MALAT1 overexpression, indicating a negative correlation between the two. Cyclin D2 (CCND2) is a cyclin-dependent kinase that is involved in promoting chemoresistance in various cancers [104,105]. As CCND2 is a target of miR-328-3p in AML, upregulating miR-328-3p reduces CCND2 expression levels, helping AML cells become more sensitive to Ara-C treatment [106]. Therefore, KDM4C's epigenetic regulation of MALAT1 and its subsequent control over the miR-328-3p/CCND2 axis constitutes a unique mechanism for MALAT1-mediated AML chemoresistance. To mitigate Ara-C resistance in AML, therapeutics that oppose and stifle the expression of either or both MALAT1 and KDM4C can be developed. The activation of the myelocytomatosis (MYC or c-MYC) oncogene is considered an important hallmark of cancer due to its role in upregulating self-renewal capacity [107,108], and chemoresistance [109,110]. Interestingly lncRNAs have been known to regulate c-MYC expression to moderate chemoresistance in different cancers [32,111,112]. The lncRNA XIST is involved in mediating drug resistance and metastasis in various cancers [113]. Compared to normal BM samples, XIST is substantially expressed in KG-1 BM cell lines derived from AML patients. Reduction in XIST expression in KG-1 cell lines positively correlates with enhanced susceptibility to DOX therapy. Furthermore, XIST specifically targets the tumor suppressor miR-29a to block its expression, which in turn increases the expression of the MYC oncogene, leading to heightened DOX resistance in AML cells. Thus, inhibiting XIST expression to limit MYC activity via the XIST/miR-29a/MYC axis may provide a useful therapeutic approach to combating DOX resistance [114]. Almost all eukaryotes contain a class of biological molecules called tetraspanins (Tspans), which are key players in the construction and regulation of the plasma membrane. Tspans act as molecular scaffolds that assemble and attract proteins to specific areas of the cell membrane to form functional units that emit signal pathways [115]. Despite evidence suggesting their importance in the regulation of various cellular processes, Tspans also play important roles in the proliferation and chemoresistance of various carcinomas [116–119]. Interestingly, HL60/ADR and K562/ADR resistant cell lines overexpress the lncRNA KCNQ1OT1, and miR-193a-3p remains repressed as a direct target of KCNQ1OT1. Tspan3 is a downstream target of miR-193a-3p and is shown to be raised in both the ADR-resistant cell lines. Together, KCNQ1OT1 sequesters miR-193a-3p to upregulate Tspan3 and mediate ADR resistance in AML cells. Thus, it is worthwhile to develop strategies to selectively target the KCNQ1OT1/miR-193a-3p/Tspan3 axis to diminish ADR resistance in AML [120]. Surprisingly, abnormal MEG3 lncRNA expressions are linked to a worse prognosis and higher ADR resistance in AML cells. ADR resistance in AML cells can be increased by mutating MEG3 to downregulate the expression of miR-155 and increase the expression of mannosyltransferase ALG9 [121]. In azacitidine-resistant AML cell lines THP1-/Aza, another lncRNA, NRF2-AS1, is overexpressed. Its expression is positively associated with that of insulin-like growth factor-1 (IGF1), which is also overproduced in the same cell line. Aza resistance results from NRF2-AS1's inhibition of miR-483-3p expression, which in turn adversely affects IGF1 expression in AML [122]. When looked at from a broader perspective, it is axiomatic to say that the important role played by lncRNAs in modulating drug resistance by inhibiting their miRNA targets is an important mechanism that holds significant therapeutic importance for clinicians.

3.2. Mechanism 2: Signal transduction pathways regulated by lncRNAs

Several signaling pathways play important roles in leukemogenesis and multidrug resistance [123–125]. Interestingly, a wide range of evidence suggests that lncRNAs are also capable of altering certain signaling pathways, resulting in more drug-resistant cells [126–128]. Illustriously, the overexpression of HOTAIR facilitates chemoresistance in AML cells by mediating the AKT/NOTCH1 signaling pathway. p21 and p53 are well-studied biomarkers known for their role in suppressing cancer metastasis [129,130]. HOTAIR is highly expressed in the K562 and A02 ADR drug-resistant cell lines. Selectively inhibiting HOTAIR expression sensitizes AML cells to ADR therapy. Mechanistically, HOTAIR upregulates NOTCH1 gene expression to induce chemoresistance in AML cells and functions as a negative regulator of p21. HOTAIR inhibition leads to an increase in p21 expression levels and a stark decrease in AKT phosphorylation that sensitizes K562/A02 cells to ADR [131]. The lncRNA CRNDE was discovered to be substantially expressed in AML cells with strong ADR resistance in a recent study by [132]. The expression of p-glycoprotein (P-gp) and multidrug resistance protein 1 (MDR1) was significantly elevated in ADR-resistant AML cells. Abolishing CRNDE expression significantly decreased MDR1/P-gp levels and HL60/ADR cells were re-sensitized to ADR. At the molecular level, β-catenin, c-MYC, and cyclin D1 were among the key components that

were inhibited because of downregulating CRNDE, which suppressed the Wnt/β-catenin pathway. Cytoplasmic lncRNA UCA1 facilitates the desensitization of AML cells to daunorubicin (DNR) by stimulating the PI3K/AKT signaling pathway. The primary miRNA target of UCA1 in the HL60 and U937 AML cell lines is miR-613. Furthermore, in both AML cell lines UCA1 overexpression enhanced the levels of p-PI3K/PI3K and *p*-AKT/AKT. When combined, these findings suggest that the PI3K/AKT pathway was activated because of UCA1-mediated silencing of miR-613. Therefore, UCA1 increases DNR resistance in AML cells by blocking miR-613, which activates the PI3K/AKT signaling pathway [133]. LINC00239 is overexpressed in KG-1 and HL60 AML cell lines and inhibits the effects of DOX by upregulating the PI3K/AKT/mTOR signaling pathway. Elevated expression of LINC00239 caused greater phosphorylation of mTOR and AKT, resulting in higher resistance of AML cells to DOX in the HL60 AML cell line. This impact was confirmed by pretreatment with their respective dual inhibitor, NVP-BEZ235, which suppressed the expression levels of mTOR and PI3K/AKT respectively leading to a considerable reduction in the phosphorylation levels enhanced by LINC00239 [134]. lncRNA HOTAIRM1 is highly expressed in AML cells that are resistant to glucocorticoids (GC). ChIP-seq data indicates that the acute myeloid leukemia-1 (AML1) oncogene directly binds to H3K4me3 and H3K27ac sites on HOTAIRM1's promoter region causing increased histone methylation and acetylation, heightening HOTAIRM1 expression. The AML1-HOTAIRM1 molecular scaffold facilitates the repression of the ARHGAP18 gene by sequestering AML1 from the accessible, open chromatin region of ARHGAP18. Reduced ARHGAP18 expression eventually triggers the RHOA/ROCK1 signaling pathway by producing greater amounts of the RhoA-GTP protein complex. This, in turn, causes the BCL-2 gene to be overexpressed, which increases GC chemoresistance in AML [135]. A remarkable work by [136] discovered that the lncRNA GAS6-AS2 plays a significant role in strengthening Ara-C resistance in AML. GAS6-AS2 is overexpressed in the K562/Ara-C line alongside AXL protein and reducing GAS6-AS2 expression declined AXL mRNA levels, effectively sensitizing K262 AML cells to Ara-C treatment. Mechanistically, GAS6-AS2 in-trans interacts with DNMT1 and DNTM3A at the promoter region of AXL to reduce methylation on its upstream CpG sites that consequently enhances AXL transcription. Additionally, the effects of GAS6-AS2 were confirmed in NSG mice *in-vivo* and the MOLM14 AML cell line *in-vitro*. It was found that GAS6-AS2 expedites the activation of the GAS6/TAM signaling axis, which in MOLM14 cells imparts the observed Ara-C resistance.

3.3. Mechanism 3: Regulation of histone modifications & DNA methylation

Previously, I discussed how HOTAIR participates in the Wnt/β catenin pathway to enhance chemoresistance in AML. HOTAIR further imparts chemoresistance in AML through another pathway. The Phosphate and tensin homolog (PTEN) is a tumor suppressor gene that negatively regulates the expression of the PI3K/AKT/mTOR signaling pathway, a major pathway involved in the development of many cancers including AML [137]. Under-expressed or mutated forms of PTEN expression have been identified in various malignancies [138–140]. It was recently found that the HL60/ADM cell line showed heightened levels of HOTAIR while PTEN was starkly downregulated due to a heavily methylated promoter region. Silencing HOTAIR resulted in a marked downregulation of DNMT3b while rescuing its expression had the opposite effect. Therefore, the overexpression of HOTAIR enhances DNMT3b levels which diminishes PTEN and culminates in increased ADM resistance [141]. It is noteworthy that additional research is necessary to delve deeper into the function of HOTAIR in controlling AML chemoresistance, as this work did not identify any additional downstream target of PTEN or precisely annotate a mechanism that controlled HOTAIR expression in AML. The tumor suppressor gene located at the chr5q31.1 chromosomal region - Zinc finger CCHC-type containing 10 (ZCCHC10) plays an active role in downregulating various cancers [142]. However, it is often under-expressed or mutated in various cancers causing carcinogenesis [143]. According to [144] the lncRNA SNHG1 epigenetically silences ZCCHC10 expression in AML cells allowing them to develop resistance towards venetoclax. Briefly, in a similar mechanism adopted by HOTAIR to suppress PTEN in ADM-resistant AML cells, lncRNA SNHG1 functions as a guide molecule to bind directly to both DNMT1 and DNMT3b and aid them to the promoter of ZCCHC10 to inhibit its expression. Venetoclax functions as a BCL-2 inhibitor [145] and enhanced ZCCHC10 mediated apoptosis of AML cells in ML2 and ALM3 cell lines and in mice incubated with MOLM-13-Vec and MOLM13-Zh10 xenograft models. Therefore, the SNHG1/ZCCHC10/p53 apoptosis pathway can serve as a valuable therapeutic target for AML therapy. Enhancer of zeste homolog 2 (EZH2), the enzymatic catalytic component of PRC2, increases the H3K27 methylation of its target genes to affect their expression [146]. Chemoresistance in malignancies, including leukemias, is caused by hypermethylated CpG islands and anomalous DNA methylation records at CpG-deprived areas [147,148]. Moreover, it's also thought that elevated H3K27me3 can facilitate chromatin remodeling, which drives the target genes' chromatin into a more docile state to minimize DNA-drug interactions [149] as a means to increase drug resistance in tumors. EZH2 positively regulates H3K27me3 expression to confer chemoresistance in neoplastic diseases. The role of EZH2-mediated H3K27me3 chemoresistance remains enigmatic in AML. Intriguingly, the lncRNA TUG1 directly binds to EZH2 to epigenetically limit the expression of miR-34a as observed in HL60 and HL60/ADR cell lines. TUG1 improves EZH2 recruitment on miR-34a to enrich H3K27me3 levels on the miR-34a promoter region which substantially reduces AML cells susceptibility to ADR treatment. Taken together, these findings imply that TUG1 promotes chemoresistance in AML by downregulating miR-34a through EZH2 recruitment [150]. The TUG1/miR-34a/EZH2 regulatory axis is a useful therapeutic target to improve ADR sensitization in AML cells. The antisense lncRNA USP30-AS1 is located on the chr12(q24,11) on the USP30 gene's opposite strand [151]. [40] discovered that the lncRNA USP30-AS1 regulates USP30 gene expression to enhance survival and inhibit apoptosis in HL60 AML cells. Mechanistically, USAP30-AS1 enriched USP30's promoter region with both H3K4me3 and H3K27ac marks while the former histone mark was enhanced partially by binding to the protein complex ASH2L.

3.4. Mechanism 4: lncRNAs participate in DNA damage repair pathways

Chemotherapy and radiotherapy treatments currently offered to cancer patients can elicit various unwarranted immunogenic reactions and induce injuries in various tissues causing genomic instability. Irregularities in the human genome are also a direct cause of the development and recurrence of various cancers [152]. lncRNA-mediated DNA damage repair induces chemoresistance in various malignancies [153–155]. Therefore, a greater understanding of the pathways regulated by lncRNAs leading to DNA damage repair might reveal new insights about how AML cells become resistant to external drug and radiation influence. Recently [156], identified that the nuclear factor kappa B subunit (RELA), an important component of DNA repair pathways, modulates the transcription of lncRNA uc002jit. In their previous study, the authors proved that RELA also regulated the transcription of poly (ADP-ribose) polymerase 1 (PARP1) and dual silencing of both PARP1 and RELA resulted in elevated levels of DNA damage in AML cells [157]. Accumulating evidence suggests that PARP1 upregulation is associated with greater resistance to anti-cancer treatment [158–160]. Interestingly, blocking uc002jit directly lowers PARP1 mRNA stability and levels, making AML cells more susceptible to DNR therapy. Hence the RELA/uc002jit/PARP1 pathway holds significant value for researchers to manufacture drugs aimed at inhibiting uc002jit in cancer cells to activate and elevate levels of DNA repair. LINC00152 is a large intergenic lncRNA of length 828 bp located on the 2p11.2 chromosome.

Extensively studied, this specific lncRNA has been known to regulate chemoresistance in many malignancies [161–164]. Recently [165], identified that LINC00152 was highly expressed in CD34+CD38− leukemic stem cells (LSCs), and silencing LINC00152 resulted in substandard PARP1 expression which was also significantly elevated in $CD34^{+}CD38^{-}$ cells which further sensitized LSCs to DOX treatment. Although a detailed mechanism is still unknown, nonetheless, since both LINC00152 and PARP1 were found to be highly expressed in signaling pathways associated with DNA damage repair, future research should be directed towards investigating the exact mechanistic action of LINC00152 in DNA damage repair in AML.

3.5. Mechanism 5: Autophagy regulation by lncRNAs

Autophagy is a self-destructive process in which defective cells and organelles are eliminated. Often, they are also recycled to preserve cellular functioning during endogenous or external nutritional stress. Changes in various autophagy processes play a significant role in the genesis of several deadly diseases, including cancer [166]. The mechanisms regulating autophagy in malignant neoplasms remain an active topic of scientific investigation. Interestingly, lncRNA-mediated autophagy-related pathways play an active role in promoting resistance to anti-cancer drugs [17,34,167,168]. The lncRNA DANCR is overexpressed in Ara-C-resistant AML cell lines. It imparts drug resistance by restricting miR-874-3p expression. Downregulating miR-874-3p decreases its inhibitory effect on ATG16L1, a significant autophagy-related protein that promotes autophagosome formation [169] whose upregulation is linked to enhanced drug resistance. As a result, DANCR-mediated autophagy serves as an anti-apoptotic route through which AML cells increase their survival in response to medication effects. The DNAJ family is a class of proteins associated with heat shock protein 70s (Hsp70s); that are essential matrons involved in various structural and protein activities like folding and degradation. DNAJB9 is a newly discovered member of this protein family; responsible for stimulating ATPase enterprises by interacting with binding immunoglobulin protein (BiP) in the endoplasmic reticulum (ER) lumen, where it is localized [170]. The lncRNA SNHG5 has miR-32 as its proximate target and inhibits its expression. DNAJB9 shares a positive correlation with SNHG5 and conversely, a negative correlation exists between miR-32 and DNAJB9. SNHG5 modulates the SNHG5/miR-32/DNAJB9 axis to directly target autophagy for enhancing drug resistance in AML cells [171].

3.6. Mechanism 6: Metabolic control - The Warburg effect & lncRNAs in AML

Changes in metabolic pathways in cancer cells are crucial distinguishing features that set them apart from other normal cells in the body. Cancer cells frequently modify their metabolic pathways to maintain survival and growth, and a better understanding of these pathways will surely contribute to the development of more effective treatments [172]. New evidence suggests that lncRNAs play an active role in regulating cancer metabolism through signaling pathways and post-transcriptional and epigenetic modifications that are associated with increased drug resistance and poor prognosis [173–177]. The alarmingly high rate of glucose uptake by cancer cells to enhance aerobic glycolysis and lactate generation is known as the Warburg effect [178]. A discussion on the mechanisms regulating the Warburg effect is herein not elucidated, however, for a further academic understanding, I direct the readers to a review by [179]. This effect plays an important role in imparting chemoresistance to various cancers [180–182] including AML. The overexpression of the lncRNA UCA1 is directly responsible for reversing the inhibition of hypoxia-inducible factor 1-alpha (HIF-1α) reliant glycolysis in HL60 and HL60/ADR cell lines. Mechanistically, UCA1 binds to miR-125a, thereby restraining its functionality and upregulating its target gene, HK2 expression, responsible for elevated glycolysis in AML. In this way, UCA1 increases the chemoresistance in pediatric AML, and the UCA1/miR-125a/HK2 axis commands therapeutic importance [183]. The lncRNA TUG1 is highly expressed in HL60/ADR AML cell lines and unsurprisingly silencing TUG1 enhances the apoptotic effects of ADR. Curiously, the Warburg effect is also upregulated; characterized by aberrant uptake of glucose due to upregulated mRNA expression levels of HK2 and PKM2 in the HL60/ADR cell line. The enhanced levels of the PI3K/AKT signaling pathway are involved in intricately regulating the Warburg effect to induce chemoresistance in various carcinomas [184–186]. Recently a study by [187] corroborates the results from previous studies since downregulating TUG1 reduced AKT levels through reduced phosphorylation whilst hyperactivating AKT signaling reversed the ADR cytotoxic effects on abrogating TUG1 expression. Therefore, TUG1 enhances ADR resistance in AML by elevating the Warburg effect via enhancing AKT signaling [188].

3.7. Mechanism 7: Transcriptional regulation by lncRNAs as scaffolding domains

lncRNAs can regulate gene expression by functioning as molecular scaffolds for the assembly of various ribonucleic complexes (RNPs) and transcription factors [189]. Thus, lncRNAs can exercise precise genetic control by directly binding to multiple effector molecules for regulating the spatiotemporal dynamics of complex cellular events. lncRNA scaffolding is gaining increased attention due to its important role in the development of chemoresistance in various cancers [27,190]. A better understanding of the role of such scaffolding effects in cancer will allow researchers to change cell fate by using strategies to boost or suppress the expression of various molecular species involved in the design and assembly of such domains, which are quite complex [191]. Recently, a novel lncRNA AC026150.8 has been reported to function as a molecular scaffold for regulating chemoresistance in AML. In KG-1 and K562 cells, heightened levels of AC026150.8 led to stronger desensitization to Ara-C, while dampening its expression eliminated the consequences of drug resistance. Western blotting and bioinformatics research verified that the splicing factor, poly(rC)-binding protein 1 (PCBP1), is recruited by AC026150.8. Therefore, it is proposed that the PCBP1 - AC026150.8 scaffold controls atypical splicing in AML cells to increase their resistance to Ara-C [192]. However, since the precise mechanism of AC026150.8 - PCBP1 scaffold is only suggested to be able to mediate splicing in AML cells, more confirmation is needed. If validated, it would be interesting to know if any additional effector molecules outside the PCBP1 factor can attach to AC026150.8 to control splicing in AML cells. Since it is evident that this interaction does promote Ara-C resistance in AML cells, it is also vital to ascertain the specific mechanism of the AC026150.8 - PCBP1 scaffold. 40–160 nm wide extracellular vesicles inscribed within a lipid bilayer in eukaryotic species are known as exosomes [193]. Exosomes harbor various important molecular species including but not limited to RNAs, metabolites, and proteins [194], and are now considered to be crucial components of various aspects of cell communication, and signaling for mediating biological processes like wound healing [195–198], cell differentiation [199], and immune responses [200–202]. Interestingly lncRNAs transmitted by exosomes (exosomal lncRNAs) also regulate chemoresistance in various cancers and are important therapeutic targets [177,203–207]. In a fantastic study recently by [208], for the first time, a relationship between exosomes and lncRNAs to promote chemoresistance in AML has been established. The $m^{6}A$ demethylase FTO was overexpressed in bone marrow-derived mesenchymal stem cell exosomes (BM-MSCs-Exo). AML cells treated with FTO-exosomes (FTO-exo) in high levels were particularly unresponsive to Ara-C treatment. Mechanistically, FTO-exo boosted lncRNA GLCC1 expression in THP-1 and Kasumi-1 AML cell lines by demethylating the promoter of lncRNA GLCC1 to improve GLCC1-HuR binding. In addition, GLCC1 served as a scaffold between the oncogene c-MYC and insulin-like growth factor 2 mRNA binding

protein (IGF2BP1) and FTO-exo strengthened GLCC1/c-MYC signaling axis, making AML cells more resistant to Ara-C. It's vital to remember that this study solely confirmed the findings in an *in-vitro* environment and *in-vivo* modeling is still warranted to truly comprehend how GLCC1 scaffolding influences AML chemoresistance. The findings nonetheless offer compelling new insights (Table 1) (Fig. 2).

4. lncRNAs control apoptosis resistance pathways in AML

Achieving high amounts of cellular apoptosis of cancer cells is the primary goal of cancer treatment. In short, apoptosis is a type of planned cell death brought on by the dissolution of the cell membrane caused by caspase 6 (CAS6), which shreds down DNA into primitive structures [209]. The human genome is vulnerable to endogenous stresses caused by chemotherapy medications. These stresses result in the recruitment of BCL-2 and Bak to the mitochondria and the release of cytochrome *c* into the cytosol. The apoptosome protein complex is then generated through the interplay amongst procaspase-9, Apaf-1, and cytochrome *c*. Apoptosomes cause caspase-9 (CAS9) and caspase-3 (CAS3) to become activated, which leads to apoptosis and therapeutic resistance in AML cells [210]. In contrast, the extrinsic pathway is regulated by the cellular communications between ligands and multiple cell death receptors like FAS [211]. Interestingly, pro-apoptotic gene downregulation, self-renewal of cancer cells, and abnormal expression of genes like BCL-2 are all significant contributors to greater chemoresistance in malignancies that protect cancer stem cells (CSCs) from apoptosis-mediated death. lncRNAs are known to regulate anti-apoptosis pathways to confer drug resistance in various malignancies. For instance, lncRNA SNHG6 upregulated BCL-2 expression through sequestering miR-127 to induce cisplatin resistance in gastric cancer [212]. Another lncRNA H19 prevented apoptosis in multiple myeloma cells by sponging miR-29b-3p expression to mediate and upregulate the translation of anti-apoptotic myeloid leukemia cell differentiation protein (MCL-1) that subsequently enhanced bortezomib resistance [213]. Recently the role of

Table 1
lncRNAs Regulate Chemoresistance in AML.

lncRNA	Molecular Target	Mechanism of Action	Cell Line Used	Modeling Environment	Drugs Used	References
SATB1-AS1	miR-580	Sequesters miR-580 to upregulate OAS2 expression	HL-60/ADR OCI-AML5/Cyt	Both *in-vitro* and *in-vivo*	ADR and Cyt	[88]
HOXA-AS2	miR-52C-3p	Downregulates miR-52C-3p expression to upregulate S100A4	U937/ADR and THP-1/ADR	*In-vitro*	ADR	[90]
MALAT1	miR-96 and miR-328-3p	Suppresses both miR-328-3p and miR-96. Under expression of miR-328-3p results in upregulation of CCND2	HL60 and THP-1	*In-vitro*	Ara-C	[99,106]
XIST	miR-29a	Upregulates c-MYC expression by antagonizing miR-29a	KG-1 BM	Both *in-vitro* and *in-vivo*	DOX	[114]
KCNQ1OT1	miR-193a-3p	Promotes Tspan3 expression by repressing miR-193a-3p	HL60/ADR and K562/ADR	*In-vitro*	ADR	[120]
MEG3	miR-155	Reduces expression of miR-155 to increase ALG9 levels	U937/ADR and THP-1/ADR	*In-vitro*	ADR	[121]
NRF2-AS1	miR-483-3p	Silences miR-483-3p expression to enhance IGF1 mRNA levels	THP-1/Aza	*In-vitro*	Aza	[122]
HOTAIR	p21/NOTCH signaling	Suppresses p21 expression and enhances NOTCH1 expression levels	K562/ADR	*In-vitro*	ADR	[131]
CRNDE	β-catenin, c-Myc, cyclinD1/Wnt/β-catenin pathway	Upregulates β-catenin, c-Myc, and cyclinD1 to enhance the Wnt/β-catenin pathway	HL60/ADR	*In-vitro*	ADR	[132]
UCA1	miR-613/PI3K/AKT/mTOR pathway	Suppresses miR-613 to enhance levels of p-PI3K/PI3K and *p*-AKT/AKT	HL60 and U-937	*In-vitro*	DNR	[133]
LINC00239	mTORC1	Increased mTORC1 activity by upregulating phosphorylation of mTOR and AKT	HL60	*In-vitro*	DOX	[134]
HOTAIRM1	ARHGAP18	Sponges AML1 away from ARHGAP18 to activate RHOA/ROCK1 signaling	HL60/ADR and K562/ADR	*In-vitro*	ADR	[120]
HOTAIR	DNMT3b	Suppresses PTEN expression by enhancing DNMT3b expression levels	HL60/ADM	*In-vitro*	ADM	[141]
SNHG1	ZCCHC10	Recruits DNMT1 and DNMT3b to ZCCHC10 promoter to downregulate its expression	ML2 and ALM3 cell lines and MOLM-13-Vec and MOLM13-Zh10 xenograft models	*In-vitro and in-vivo*	Venetoclax	[144]
TUG1	miR-34a	Suppresses miR-34a by enhancing EZH2 recruitment on miR-34a to enrich H3K27me3 levels on its promoter region	HL60/ADR	*In-vitro*	ADR	[150]
USP30-AS1	USP30	Enriches promoter region of USP30 with both histone methylation (H3K4me3) and acetylation (H3K27ac) marks	HL60	*In-vitro*	N/A	[40]
uc002jit.1	PARP1	Enhances PARP1 expression levels and stability	KG1α xenograft model and Kasumi-1, and HEK293 cell lines	Both *in-vitro* and *in-vivo*	DNR	[156]
LINC00152	PARP1	Potentially regulates PARP1 expression (no specific mechanism discovered)	$CD34^{+}CD38^{-}$ LSCs	*In-vitro*	DOX	[165]
DANCR	miR-874-3p	Raises ATGL16 protein levels by repressing miR-874-3p	HL60, U937, and KG1α cell lines	*In-vitro*	Ara-C	[296]
SNHG5	miR-32	Inhibits miR-32 expression to upregulate DNAJB9 levels	HL60, HL60/ADR	*In-vitro*	ADR	[171]
UCA1	miR-125a	Inhibits miR-125a expression to upregulate HK2 levels	HL60, HL60/ADR	*In-vitro*	ADR	[183]
TUG1	AKT	Enhances AKT signaling	HL60/ADR	*In-vitro*	ADR	[188]
AC026150.8	PCBP1	The AC026150.8 - PCBP1 scaffold mutates alternative splicing in AML cells	KG-1 and K562 cell lines	*In-vitro*	Ara-C	[192]
GLCC1	c-MYC and IGF2BP1	Functions as a bridge to assemble c-MYC and IGF2BP1 on its domain	THP-1 and Kasumi-1 cell lines	*In-vitro*	Ara-C	[208]

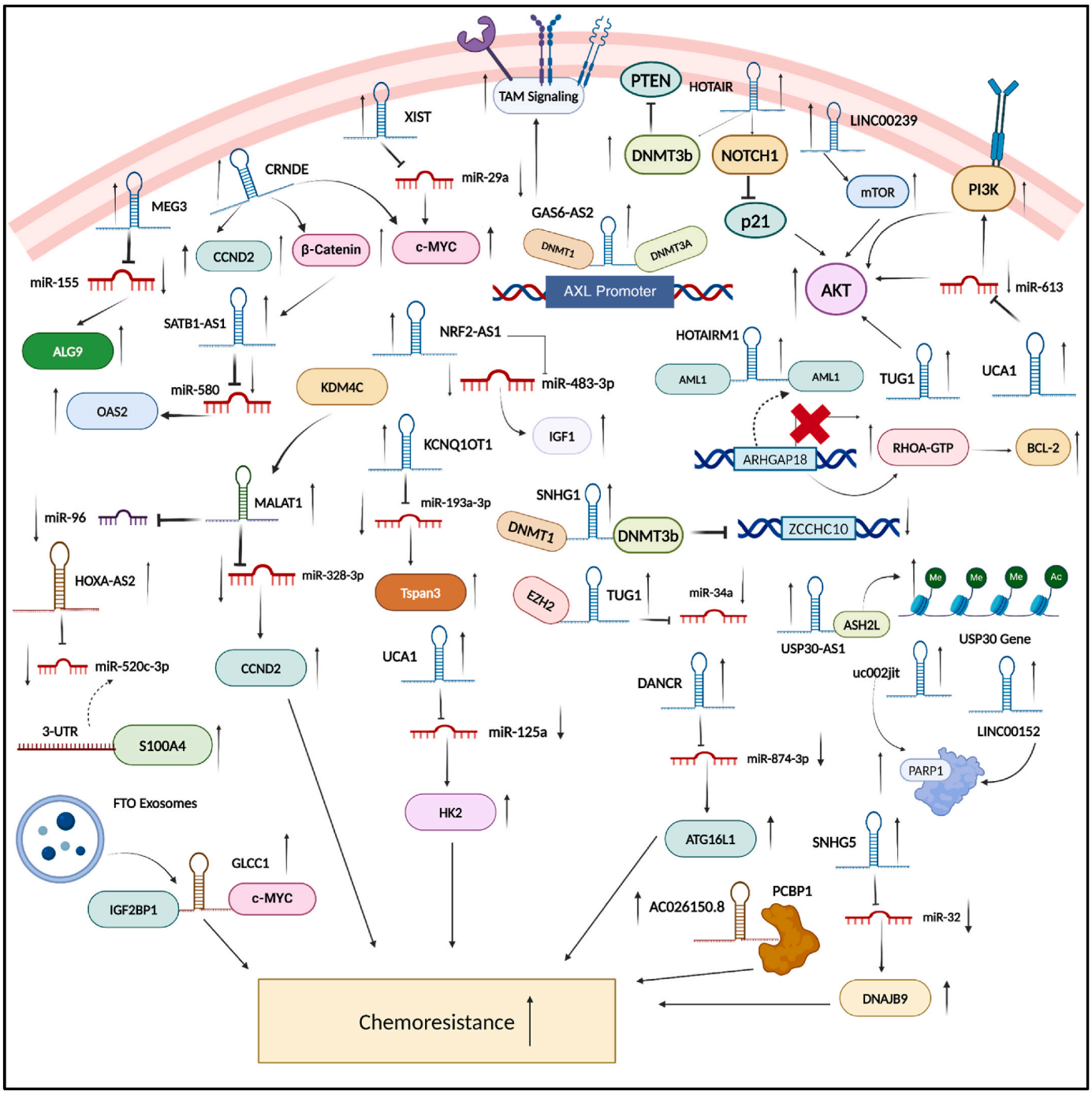

Fig. 2. lncRNAs regulate chemoresistance in AML
Schematic illustration summarizing the mechanisms by which lncRNAs regulate drug resistance in AML. The major molecular mechanisms through which lncRNAs enhance chemoresistance are A) miRNA sequestration, B) signal transduction pathways, C) histone modifications and DNA methylation, D) DNA damage repair pathways, E) autophagy and metabolic reprogramming, F) molecular scaffolding.

lncRNA HOTTIP in regulating FAS signaling to prevent apoptosis in various AML cell lines was examined. In detail, on knocking out HOTTIP in WT MOLM3 cells it was observed that the expression of FAS, CAS3, and CAS9 were significantly upregulated, and a similar effect was observed in CBS7/9$^{+/-}$ and OCl-AML13 cell lines while the latter two cell lines also exhibited repressed HOXA gene expressions. It is proposed that at a transcriptional level, HOTTIP upregulates the expression of miR-196b that directly represses FAS expression as was observed with the increased apoptosis of AML cells on miR-196b downregulation in the MOLM13 cell line [214]. Although more research is necessary to fully understand this mechanism, these findings demonstrate that HOTTIP controls the FAS signaling axis to prevent cellular apoptosis in AML cells. Boosting the lncRNA SLED1 expression in Kasumi and U937 AML cells resulted in diminished apoptosis when administered DOX treatment. In addition, flow cytometry studies confirmed increased apoptosis on abolishing SLED1, and it is postulated that SLED1 affects AML cell survival via two different mechanisms. First, as shown by KEGG pathway analysis, by participating in the PI3K/AKT signaling pathway; and second, by elevating BCL-2 expression. Although SLED1's mode of action is merely speculated, it is an intriguing point to consider with evident

therapeutic significance for subsequent research into investigating the potential of lncRNAs in mediating anti-apoptosis in AML [215]. Hepatocyte nuclear factor 4α (HNF4α) is an important transcription factor that plays an instrumental part in gene regulation by attracting cofactors to the promoter regions of its target genes [216] to facilitate metabolism and cellular development. Abnormal expressions of HN4Fα are associated with chemoresistance and metastasis in various cancers [217–219]. Recently it was demonstrated that LINP1 controlled HN4Fα expression to positively affect leukemic cells' capacity to survive. Moreover, a drop in the expression levels of lactate dehydrogenase A (LDHA) and glucose transporter 1 (GLUT1) was caused by silencing both LINP1 and HN4Fα, which reduced the uptake of glucose by AML cells. Lastly, overexpressing HN4Fα and LINP1 led to a considerable increase in pAMPK and WNT5A levels, suggesting that LINP1 regulates glucose metabolism in AML cells through the HN4Fα/AMPK/WNT5A metabolic pathway to enhance cell survival [52].

5. Mechanisms of leukemic stem cell self-renewal by lncRNAs

The ability of CSCs to self-renew remains one of the main obstacles to fighting chemoresistance. The ability of CSCs to differentiate and develop into various lineages is known as "self-renewal," and it is essentially limitless [220]. This unique ability of CSCs to protect themselves against apoptosis-mediated cell death is one of the main causes of patients' poor response to chemotherapy regimens and poor prognosis due to relapses [221–223]. A growing body of research indicates that lncRNAs actively mediate the ability of CSCs to undergo self-renewal and that they can both stimulate [224–227] and impede [41,226,228] this process. Pediatric AML patients with MLL-type leukemia, a very aggressive subtype of AML, have a dismal prognosis even with intensive use of cutting-edge chemotherapy treatments [229]. One of the main causes of these results is that the disease can reappear after drug exposure, which lowers the survival rate [230,231]. DOT1-like (DOT1L) methyltransferase protein uniquely interacts with the H3K79 histone site to regulate H3K79me/H3K79me2/H3K79me3 histone methylation in human genes [232] and its aberrant expression is associated with many facets of carcinogenesis [233,234]. Recently [235] investigated the role of lncRNA LAMP5-AS1 in regulating DOT1L in MLL leukemia. H3K79me3/H3K29me2 levels were dramatically reduced at loci of HOXA9, HOXA10, CDK6, and MEIS1 cancer stem genes situated in the HOXA cluster on LAMP5-AS1 knockdown in THP-1 and MOLM13 MLL patient cell lines. The methyltransferase activity of DOT1L was significantly affected by downregulating LAMP5-AS1, which markedly downregulated the expressions of cancer stemness genes preventing MLL recurrence. Consequently, LAMP5-AS1 might be a valuable therapeutic target to further abrogate self-renewal in AML. It is underestimated how transcription factors control the expression of lncRNAs, which in turn drives cancer development. Due to their interactions with many transcription factors, numerous studies have shown the carcinogenic relevance of lncRNAs as co-transcriptional regulators of gene expression [236–238]. Research indicates transcription factors actively contribute to chemoresistance induction in malignancies by affecting the expression of lncRNAs. For example, to impart oxaliplatin resistance in colorectal cancer cells, the transcription factor MYBL2 (B-MYB) stimulates the production of the lncRNA CCAT1, which downregulates the expression of the suppressor of cytokine signaling 3 (SOCS3) [67]. In urothelial cancer, another lncRNA TUG1, whose expression is boosted by the transcription factor nuclear factor erythroid 2 (Nrf2), increases DOX resistance [239]. Intriguingly [240], have reported that the lncRNA HOXB-AS3 plays a critical role in elevating the self-renewal capacity of LSCs. YTH domain-containing protein 1 (YTHDC1) is an important m^6A reader that plays a crucial role in promoting chemoresistance in breast cancer [241,242], bladder cancer [140], colon cancer [243], ovarian cancer [244], and prostate cancer [245]. Inhibiting YTHDC1 expression in $CD34^+CD38^-$ LSCs accelerates the AML cell's demise. Mechanistically, YTHDC1 interacts with the m^6A alteration of the HOXB-AS3 RNA precursor to upregulate the expression of the spliceosome NR_033205.1. It appears that the YTHDC1/HOXB-AS3 circuit is a new and significant target that can be used to prevent LSCs from regenerating themselves, hence enhancing drug efficacy and patient health. The p15 tumor suppressor gene is frequently downregulated due to elevated methylation on its promoter region, and this facilitates leukemogenesis [246]. *In-vitro* studies using the U937 and Kasumi-1 AML lines, as well as *in-vivo* modeling using the U937 mouse xenograft model, demonstrated that HOTAIR increased methylation at the promoter of the p15 gene by enlisting the PRC2 complex to upregulate H3K27me3 trimethylation, which continued the maintenance of LSCs [247] (Table 2) (Fig. 3).

6. Therapeutic relevance of tumor suppressor lncRNAs in AML

lncRNAs are often categorized as either oncogenic or tumor suppressors based on whether they play an important role in promoting carcinogenesis or inhibiting it. Often tumor suppressor expressions are significantly downregulated in cancers and upregulating their expressions can potentially counteract or abrogate altogether oncogenic effects like chemoresistance and self-renewal of CSCs. The importance of a lncRNA's fundamental nature in defining its activity is rather surprising, given that a lncRNA can retain oncogenic capabilities in one form of cancer while exhibiting tumor-suppressive features in another. Take for instance the case of the lncRNA NEAT1. It facilitates cancer cell proliferation, growth, and metastasis in various malignancies [248–251]. Unexpectedly, contrary to its oncogenic nature, lncRNA NEAT1 serves as a tumor suppressor in AML [252]. demonstrated that the expression of lncRNA NEAT1 was starkly downregulated in the K652 and THP-1 AML cell lines. Enhancing NEAT1 expression in both cell lines greatly sensitized AML cells to treatment by Alisertib and Bortezomib chemotherapeutic drugs. As previously mentioned, ABC proteins play a crucial role in desensitizing cancer cells to treatment, and overexpressing NEAT1 expression in both cell lines leads to a decrease in ABCG2 protein expression effectively reducing drug resistance. Furthermore, NEAT1 (specifically, NEAT1_1 isoform) is under-expressed in $CD34^+$ LSCs. NEAT1_1 reduces the ability of LSCs to renew themselves by inhibiting the Wnt/β signaling cascade and quickening the degradation of the DVL2 protein by interacting with the Trim56 E3 ubiquitin ligase [253]. Another unique lncRNA, MAGI2-AS3, possesses therapeutic significance since it reduces the ability of LSCs to reincarnate themselves by inducting the TET2 DNA methylase on the promoter of the LRIG1 protein that it targets. Additionally, it attaches to the LRIG1 protein directly and boosts demethylation on LRIG1's promoter [41]. Remarkably, a single lncRNA can function inside the same cancer as both an oncogene and a tumor suppressor. The lncRNA MEG3 is renowned evidence of this paradox. MEG3 can promote cellular death as well as the development of chemoresistance. Research carried out *in-vitro* on WT MOLM13 and U937 AML cell lines, as well as *in- vivo* on NSG mice, proved that overexpression of MEG3 inhibited the formation of tumors by ceasing the G0/G1 cell cycle phase. MEG3 has an intriguing dual mechanism of action as a tumor suppressor. Firstly, MEG3 stabilizes p53 to increase the level of RB protein, which subsequently lowers the expression of the DNMT3A DNA demethylase. Furthermore, TET2 and WT1 collaborate to control and improve MEG3 expression, which further suppresses tumor growth [254]. Additionally, it is noted that MEG3 expression is positively associated with miR-493-5p and that MEG3 is present in HL60/Ara-C AML at substandard levels. Raising MEG3 levels increases the production of miR-493-5p, which post-transcriptionally silences METTL3, preventing the activation of the MYC gene which consequently re-sensitizes AML cells to Ara-C therapy [255]. Nevertheless, because MEG3 sequesters miR-155 to raise ALG9 levels, which confers ADR resistance in AML cells, aberrant expression of MEG3 is also linked to the onset of chemoresistance [121]. Tumor suppressor lncRNAs typically work by inhibiting the expression of oncogenes, resulting in increased apoptosis. Illustriously, the lncRNA transcript H22954 proves to be an

Table 2
lncRNAs Modulate Apoptosis Resistance & Self Renewal in AML.

lncRNA	Molecular Target	Mechanism of Action	Cell Line Used	Modeling Environment	Drugs Used	References
HOTTIP	miR-196b	Potentially elevates miR-196b to control FAS signaling (more confirmation needed)	MOLM3, CBS7/9$^{+/-}$ and OCl-AML13 cell lines	Both *in-vitro* and *in-vivo*	N/A	[214]
SLED1	Proteins in PI3K/AKT signaling and BCL-2	Potentially targets PI3K/AKT signaling and also elevates BCL-2 expression (more confirmation needed)	U937, Kasumi cell lines	*In-vitro*	DOX	[215]
LINP1	HN4Fα	Elevates HN4Fα Expression to further increase pAMPK and WNT5A levels	KG-1, THP-1, and NOD/SCID (NSG) mice models	*In-vitro* and *in-vivo*	N/A	[52]
LAMP5-AS1	DOT1L	Directly interacts with DOT1L to upregulate H3K79me3/H3K29me2 histone methylation at HOXA9, HOXA10, CDK6, and MEIS1 genes	THP-1, MV4-11, RS4-11, HEK293T, MOLM13 MLL cell lines and NOD/SCID mice models	Both *in-vitro* and *in-vivo*	N/A	[235]
HOXB-AS3	N/A	YTHDC1 regulates HOXB-AS3 expression by enhancing its spliceosome NR_033205.1 levels	CD34^{+}CD38^{-} LSCs (THP-1 cell line isolated) and NSG mice	Both *in-vitro* and *in-vivo*	N/A	[240]
HOTAIR	p15	Recruits PRC2 on the promoter of p15 to increase methylation on its promoter	U937 and Kasumi-1 AML lines and U937 mouse xenograft model	Both *in-vitro* and *in-vivo*	N/A	[247]

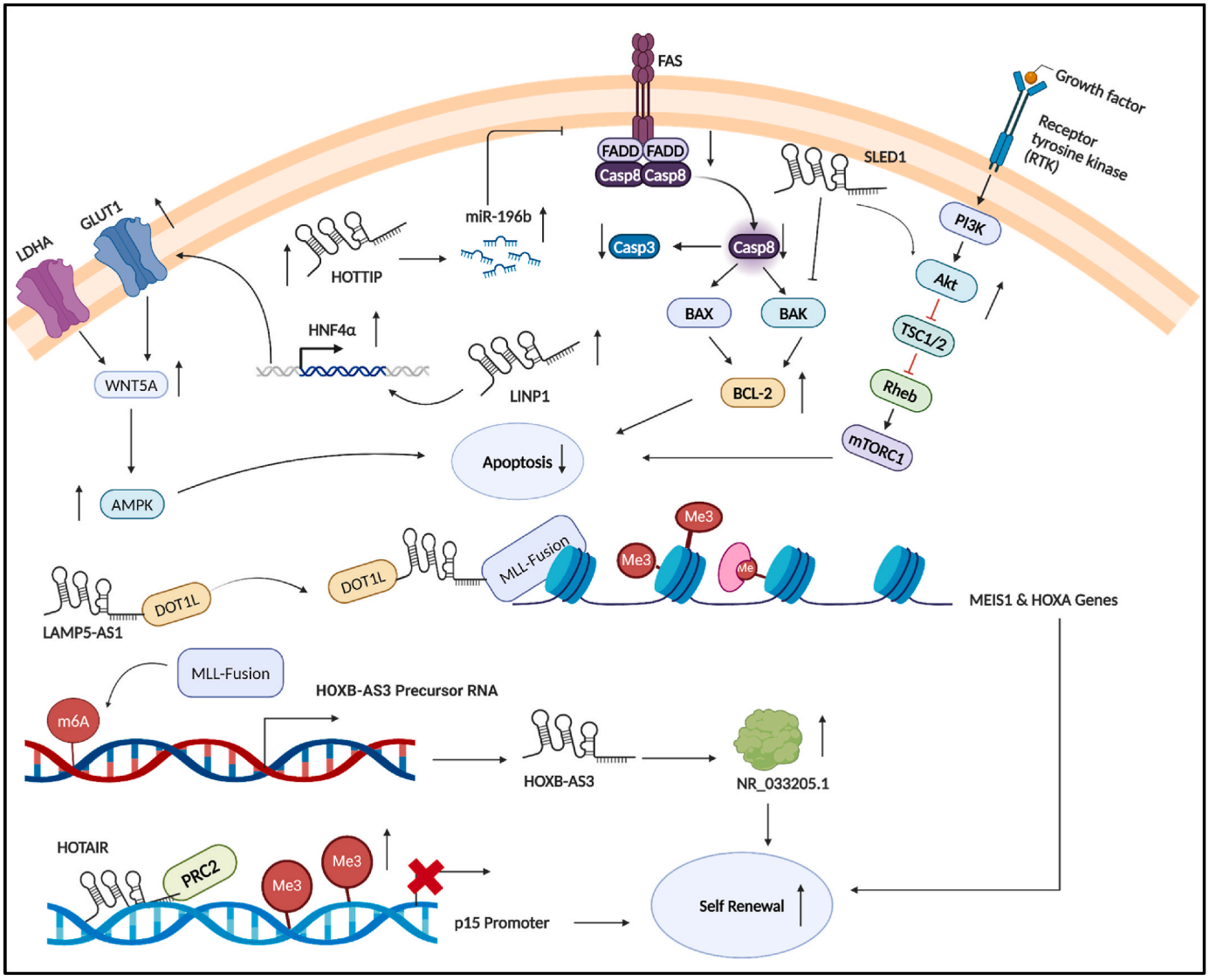

Fig. 3. lncRNAs Regulate Apoptosis Resistance & LSC Self Renewal Pathways in AML
Diagrammatic representation of the processes by which lncRNAs support the prevention of apoptosis and improve LSCs' ability to renew themselves. lncRNAs possess the ability to subvert pro-apoptotic gene expressions, rewire metabolism, and even aberrantly upregulate transduction pathways like the PI3K/AKT signaling to impede apoptosis. Furthermore, lncRNAs increase H3K79me/H3K79me2/H3K79me3 histone methylation at their target gene's promoter region and interact directly with transcription factors, consequently enhancing LSC self-renewal potential.

important therapeutic target for overcoming BCL-2-mediated drug and extrinsic apoptosis resistance, as it lowered BCL-2 expression to enhance the expression of CAS9, CAS7, and PARP, while all effects of H22954 were reversed on rescuing BCL-2 expression [256]. In another case, the lncRNA LINC00998 has been found to increase the synthesis of the RNA-binding protein ZFP36 by binding directly to its promoter. As a result, ZFP36 binds to the 3′ UTR of its target mTORC2 gene, compromising its expression by accelerating the process of mTORC2 mRNA degradation [257]. The data from the preceding research provides some significant insights and perspectives that further emphasize the need to create lncRNA-based treatments to counteract chemoresistance and enhance apoptosis levels in AML.

7. Perspectives & future directions

The largest barrier to improving AML patients' health remains chemoresistance. The resistance of AML cells to therapeutic effects is caused by a multitude of causes, but this review intends to highlight the role that lncRNAs play in controlling this process. It is important to understand that there is a great deal of variation in the chemotherapeutic medications employed, the pathways annotated, and the experimental modeling methodology across all the research reviewed. While most of the research examined in this review only contains *in-vitro* results, the absence of *in-vivo* verification makes it difficult to apply the results to valuable clinical settings. Therefore, using animal or patient-derived xenograft-based *in-vivo* modeling, future studies should examine and validate the mechanisms and effects revealed in the discussed publications. Validating the mechanistic actions of the lncRNAs GLCC1, AC026150.8, SLED1, TUG1, UCA1, SNHG5, DANCR, LINC00152, USP30-AS1, HOTAIR, HOTAIRM1, LINC00239, CRNDE, KCNQ1OT1, MEG3, NRF2-AS1, and MALAT1 is still warranted. To fully understand several of the above-discussed mechanisms, additional experimental validation is needed. For example, in the case of lncRNA AC026150.8, it is merely hypothesized that, in comparison to healthy control cells, splicing in AML cells may be altered by AC026150.8 due to the scaffold that exists between AC026150.8 and PCBP1. In another case, it was only speculated that LINC00152 would promote chemoresistance in AML through DNA repair pathways since both PARP1 and LINC00152 were significantly expressed in these pathways. It is evident that further research is necessary, and these are promising areas to investigate for the next studies. Briefly, more experimental work is required to fully understand the mechanisms of lncRNAs AC026150.8, LINC00152, SLED1, HOTTIP, and HOTAIR. The processes by which lncRNAs in AML enhance chemoresistance are remarkably intricate and go beyond straightforward interactions between lncRNAs and miRNAs. It's important to note whether any new downstream target genes and proteins exist in a mechanism where lncRNAs may have an impact on their expression in the processes previously mentioned. For instance, it's unclear if there are any further downstream targets for the lncRNA HOTAIR than PTEN that HOTAIR downregulates to regulate chemoresistance. Investigating these possibilities can improve our comprehension of lncRNAs' functioning mechanisms. Therapeutic resistance in AML is regulated by several other routes that have not yet been thoroughly investigated. Recent research has shed light on the impact of lncRNAs on mitochondrial dynamics [258]. It would be beneficial to investigate which lncRNAs influence mitochondrial processes to help AML cells escape therapeutic interference.

8. Challenges & strategies to target lncRNAs in AML

Tremendous developments in genomic technologies have afforded novel perspectives into the structural intricacies and functioning of the human genome. This has opened a vast expanse of fascinating and valuable information about lncRNAs that previously remained oblivious. Despite their inability to code for functional proteins, lncRNAs play a significant role in regulating gene expression and are the subject of close attention and scrutiny. However, despite the swift technological advancement, our awareness of lncRNAs remains minimal. This is largely due to their low conservation compared to other mRNA species, which makes it challenging to investigate, comprehend, and compare their roles across multiple species. Furthermore, the lack of noticeable expression of lncRNAs makes it difficult to accurately measure their population in both cells and tissues. Lastly, the impact of a particular lncRNA's subcellular localization on its function is something we are just beginning to understand [259]. lncRNAs are often classified according to where they are in a cell and are heavily compartmentalized into subcellular domains including but not limited to the nucleus and cytoplasm. A great majority of lncRNAs, known as nuclear lncRNAs, are known to preferentially localize in the nucleus. Through chromatin remodeling and transcriptional mechanisms, they largely influence gene expression [260]. On the other hand, cytoplasmic lncRNAs play a crucial role in mediating post-transcriptional processes such as translation and mRNA degradation. They also operate as effector molecules in cell signaling pathways and interact with ribonucleic proteins (RBPs) to affect their gene expression [261]. It is evident that the subcellular habitat of lncRNAs directly influences the way they differ in function. Consequently, targeting lncRNAs in the human genome has proven to be difficult and represents a substantial obstacle for clinical studies. Interestingly, because lncRNAs do not code for well-conserved and functional proteins, they have long been regarded as "undruggable" macromolecules. This is one of the reasons why the present treatment regimen does not include any specific drugs aimed solely at regulating lncRNA expressions in AML patients. Nonetheless, fresh developments are paving the road to alter this paradigm as I discuss below.

8.1. Small interfering RNAs

Small interfering RNAs (siRNAs) have proven to be a game changer in the treatment of cancer patients. They work on the principle of RNA interference (RNAi), which is a method of gene silencing that uses a double-stranded RNA (dsRNA) to mandate the targeting of complementary mRNA to inhibit its expression through either transcriptional suppression or by inducing decay [262]. Illustriously, it was determined that siRNA (si-SNHG4) mediated silencing of the lncRNA SNHG4 in colorectal cancer cell line SW1116 appreciably reduced BCL-2 expression while also increasing CAS3 and BAX expression to enhance pro-apoptotic signaling [263]. Numerous other investigations have confirmed that siRNA-mediated lncRNA silencing is effective in boosting apoptosis and making cancer cells more susceptible to anti-cancer therapies [264–266]. Despite the progress, there are still a few issues that need to be resolved before siRNA therapies can be effectively applied in clinical settings. The biggest challenge is to deliver siRNA nanoparticles systemically to special target areas to initiate RNAi. To overcome this obstacle and increase the pharmacological effectiveness of siRNA treatments, lipid nanoparticle (LNP)-based delivery systems are currently being developed. These systems enable the integration of siRNAs into their supramolecular polymer matrix, optimizing the delivery mechanism by improving the drug encapsulation rate and boosting cellular uptake at the target site. Lipid nanoparticles embedded with siRNAs have been proposed to be viable therapies for an array of malignancies through rigorous testing both *in-vitro* and *in-vivo* models [267–270]. siRNAs are now being explored progressively more for applications in AML treatment. [271] investigated that in the t(8; 21) cytogenetic AML type, the lncRNA LINC01257 is significantly expressed. To block the expression of LINC01257, they created a Patisiran (FDA--validated) formulation containing an LNP-si-LINC01257 vessel. After being administered, the vessel was remarkably able to concentrate on and decrease LINC01257 expression, and cell count the Kasumi-1 AML cell line by 55 %. Whilst the study only validated the effects within *in-vitro* setting and *in-vivo* modeling in animal xenograft models is still warranted, nonetheless, this study indeed has set the wheels in motion for future studies to investigate the therapeutic application, safety, and

efficacy of using LNP-siRNA systems to target AML cells.

8.2. Antisense oligonucleotides

Antisense oligonucleotides (ASOs) are unit-stranded oligodeoxynucleotides that can influence protein expression through RNAi reminiscent of siRNAs [272]. Mechanistically, ASOs can manipulate the expression of genes, modify transcriptional and post-transcriptional processes, or sterically obstruct molecule-to-molecule interactions. ASO therapeutics are receiving more attention and are being evaluated in several clinical trials, which has aided in their entry into the pharmaceutical industry. While chemotherapeutic and radiotherapeutic intervention plays a major role in the current AML treatment regimen, novel possibilities for the development of more individualized treatment options, such as ASO therapies, can be launched as we keep discovering additional details about AML's molecular mechanisms. What's more assuring is that several ASO treatments have already been designed to treat AML, and a few of them are presently going through extensive clinical trials. Studies have primarily concentrated on developing strategies that directly target particular protein expressions that serve as surface biomarkers [273,274] or that play a role in anti-apoptotic pathways [275]. Developing and studying the sustainability of ASO treatments that target lncRNA expressions is crucial for achieving greater synergistic anti-cancer behaviors since lncRNAs are indispensable for AML cell self-renewal, chemoresistance, and prevention of apoptosis. While oligonucleotide-based therapies are beneficial, they have limitations that must be addressed before they can be further developed for clinical trials. For instance, incorporating foreign RNA molecules into the body might trigger undesirable immunogenic responses, which may reduce the quantity of medication endocytosed by the cells, further limiting the intended RNAi effects of such treatments [276,277]. Furthermore, such therapies need to minimize any harmful non-target effects to ensure that cells beyond the intended target ones remain in good health. Chemically conjugating glycoprotein molecules to siRNAs has proven effective in selectively targeting hepatocytes and is seen as a significant advancement in overcoming the body's natural biological barriers to nucleic acid medication delivery [278]. Future research can be devoted to potentially developing protein-conjugated siRNA delivery engines or investigating techniques to chemically modify oligonucleotide structures to enhance selectivity towards oncogenic lncRNA expressions in AML cells.

8.3. Plant-based compounds

Currently, compounds found naturally in plants are being significantly reviewed for potential anti-cancer properties. Numerous such compounds isolated from plants, such as Taxol, have served as the basis for the development of blockbuster chemotherapeutic medications, such as paclitaxel, which is extensively used to treat malignancies [279]. There is a growing body of research [280–284] investigating the extraction and engineering of plant-based molecules to create more effective anti-cancer drugs, and these studies may ultimately lead to effective treatments [285]. Accumulating evidence suggests that plant metabolites appear to have promising potential to progress the treatment of AML [286–289]. Studies published recently additionally indicate that such compounds could potentially target lncRNAs in AML and thus accelerate cellular death. For instance, it has been shown that Naringenin (Nar) increases programmed cell death by downregulating the expression of the lncRNA XIST, which was shown to be overexpressed in the HL60 AML cell line. Greater resistance to apoptosis resulted from the overexpression of miR-34a′s downstream target HDAC1, which was caused by XIST suppressing miR-34a expression. Transfecting HL60 AML cells, with Nar, restrained XIST expression which facilitated apoptosis. This suggests that Nar-mediated control of the XIST/miR-34a/HDAC1 axis can be further clinically assessed using *in-vivo* models [290]. Matrine, an alkaloid derived from plants, was shown to target the long noncoding RNA LINC01116 and impede its expression to elevate the levels of miR-592. This, in turn, eliminated the JAK/STAT3 signaling pathway and culminated in greater cellular apoptosis and lowered tumor growth [291]. Even though the aforementioned studies have demonstrated the potential for using plant-based compounds to specifically target lncRNAs in AML, more research is still needed to determine the precise mechanisms of action of these natural molecules. Additionally, greater *in-vivo* tests in animal xenograft models and clinical trials are necessary to effectively translate these findings to beneficial ends.

8.4. Future possibilities for targeting lncRNAs in AML

Transcriptional interference has made it feasible to target genes precisely and efficiently, thanks to the development of revolutionary genetic engineering technologies. However, significant difficulties arise when lncRNA expressions are ablated using ASO and siRNA treatments, such as low knockdown levels and a higher chance of off-target effects [292]. The more complicated a particular lncRNA transcriptional machinery is, the more difficult it is to target it. In such cases, CRISPR/CAS9 positions itself as a unique method with distinct benefits over other available therapeutics. While CRISPR/CAS9-mediated AML treatments have not yet been converted into clinical practice for treating patients, various studies have used the CRISPR/CAS9 system to selectively knock down lncRNAs, and this can potentially lead to novel therapeutic strategies in the future [214,293,294]. Furthermore, as I have detailed above, lncRNAs can directly interact with a variety of protein complexes to boost drug resistance and restrict apoptosis. Consequently, it may be possible to create synthetic morpholino oligomers that will deliberately obstruct and sterically impair such types of interactions between lncRNAs and proteins [295] (Fig. 4).

9. Conclusions

AML is a rare and deadly form of leukemia with a high death rate. Therefore, developing new therapies is crucial to helping those suffering from this difficult, uncommon cancer. I outlined the key mechanisms by which lncRNAs in AML bestow therapeutic resistance in this review. It follows naturally that more investigation is required to fully understand the immunological role of oncogenic lncRNAs. In addition, current research also needs to focus on how tumor suppressor lncRNAs can be programmed to target pathways that confer drug and apoptosis resistance in AML for the design of more efficient therapies. I support additional research into novel pathways and treatment targets to hasten the creation of more effective medications. Many novel strategies, such as oligonucleotide therapeutics, are being developed and expanding rapidly to selectively target and alter lncRNA expressions. While there are still many challenges to overcome before they become commonplace clinical treatments, they are exciting areas for future research due to their success in pre-clinical studies.

Outstanding questions

1. What are the fundamental processes by which lncRNAs control mitochondrial dynamics to evade therapeutic impact in AML patients?
2. How do lncRNAs regulate DNA damage repair pathways?
3. To comprehend the relationships between lncRNAs and other macromolecules, how can we effectively build novel genomic and proteomic approaches?
4. How can strategies be created to increase the expression of tumor suppressor lncRNAs?
5. How might the integration of human line xenograft models or patient tumor organoid models help us better understand how lncRNAs regulate AML?

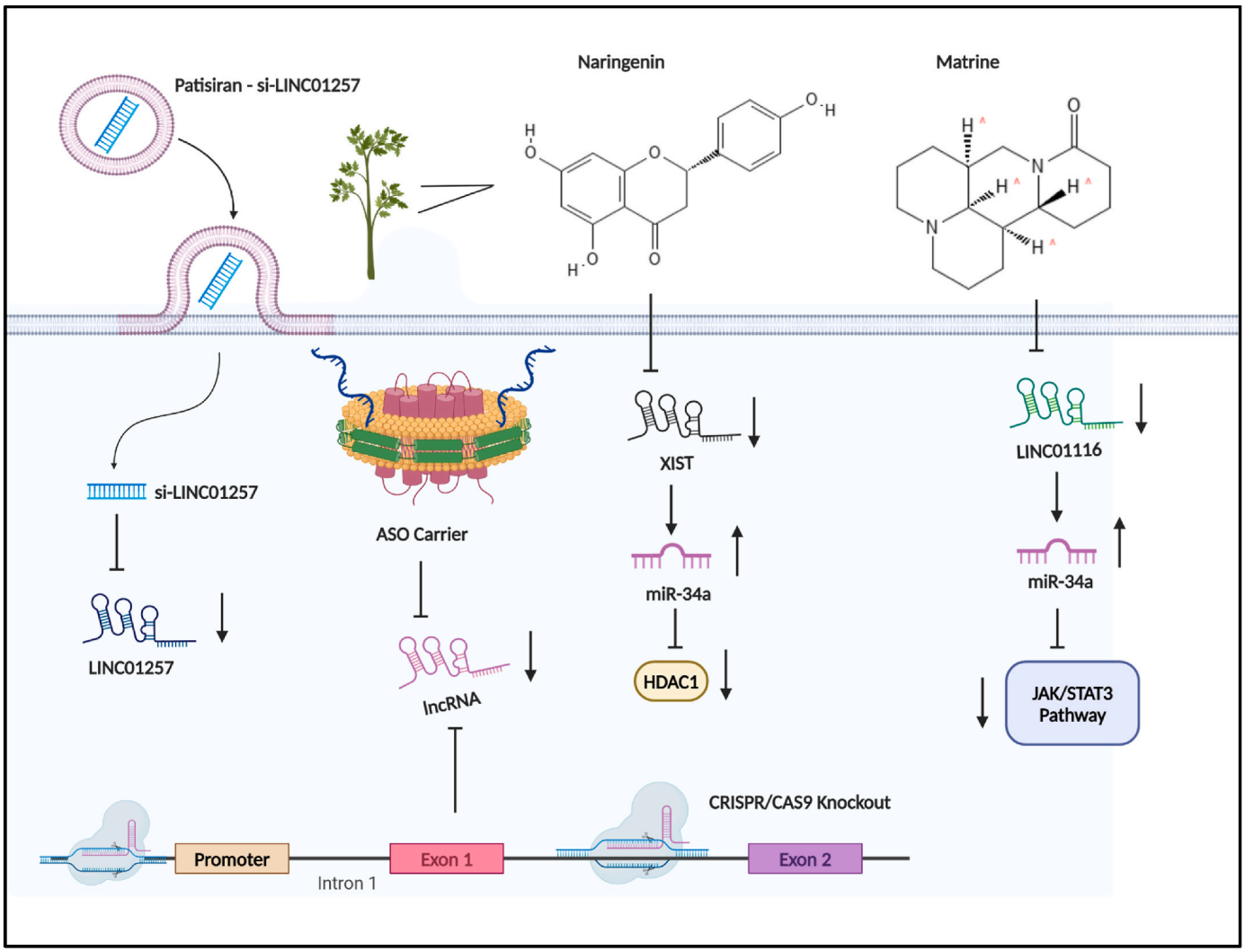

Fig. 4. Strategies to Target lncRNAs in AML
Figure highlighting strategies to target and inhibit the expression of oncogenic lncRNAs in AML. Currently, LNP-siRNA vehicles are the gold standard for targeting lncRNA expressions in various cancers and the LNP-si-LINC01257 vessel has been shown to inhibit the expression of the lncRNA LINC-1257 in AML. Plant metabolites like Nar and Matrine have proved to be clinically valuable as their heightened expression has been shown to decrease the expression of the lncRNAs XIST and LINC01116 leading to greater apoptosis levels in AML. Although CRISPR/CAS9 has been widely employed in several investigations to specifically knock down lncRNA expressions, it is yet unclear how this ground-breaking technology will be applied to actual clinical settings. Potential avenues for targeting lncRNAs in the future include the synthesis of ASO therapies and the use of morpholino oligomers to sterically obstruct lncRNA-protein complex interactions.

6. How can we enhance the systemic release of oligonucleotide therapies to target AML cells through the development of novel delivery systems?
7. How can we create delivery systems based on the CRISPR/CAS9 technology or morpholino oligomers to specifically knock down or block the interactions between oncogenic lncRNAs and proteins?
8. What plans of action can we build to reduce or eliminate the side effects of the new nucleic acid-based medicines and the present chemotherapeutic treatments?
9. How can we include more *in-vivo* modeling to better comprehend the mechanistic actions of oncogenic lncRNAs to create more potent treatments?
10. What methods do natural compounds use to specifically target and suppress the production of oncogenic lncRNA in AML? How may we apply that knowledge to create cutting-edge treatment plans that improve patient outcomes?

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Availability of data and material

Data sharing does not apply to this article as no new data was created or analyzed in this study.

Competing interests

There are no competing interests that I declare.

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CRediT authorship contribution statement

Siddhant Sharma: Writing – review & editing, Writing – original draft, Visualization, Validation, Investigation, Formal analysis, Conceptualization.

Declaration of competing interest

I (Siddhant Sharma) declare that I have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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