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# EXPLORING THE ROLE OF EPIGENETICS IN LEUKEMIA PROGRESSION AND THERAPY RESISTANCE

**Arshia Arooj[1,2,*3], Abbas Shahid[4], Ali Zafar[5], Muhammad Bilal[6],**
**Muhammad Abdullah[7], Sobia Nawaz[8]**

[1]*Department of Life Sciences (Biotechnology), University of Management and Technology*
[2]*Department of Biochemistry and Biotechnology, University of Veterinary and Animal Science*
[3]*School of Science Engineering and Environment, University of Salford*
[4,5]*Department of Basic and Applied Chemistry, Faculty of Science and Technology, University of Central Punjab, Lahore 54000, Pakistan.*
[6]*Department of Theriogenology, University of Veterinary and Animal Sciences Lahore, Pakistan*
[7]*MBBS/MD International Medical University Bishkek Kyrgyzstan, Department of Zoology, University of Lahore, Pakistan*

[*1]arshiaarooj957@gmail.com

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**Corresponding Author: ***
**Arshia Arooj**

## Abstract

*Leukemia remains one of the most pressing global health concerns, with therapy resistance posing a persistent challenge across chemotherapy, targeted therapy, and immunotherapy. Increasing evidence reveals that epigenetic abnormalities including DNA methylation, histone modifications, chromatin remodeling, and non-coding RNA dysregulation play crucial roles in leukemogenesis, disease progression, and the emergence of drug resistance. These modifications form intricate regulatory networks that reprogram transcriptional landscapes, sustain leukemic stem cell self-renewal, and foster clonal adaptability under therapeutic stress. While single-agent epigenetic therapies have demonstrated limited efficacy, their combination with conventional chemotherapy, molecularly targeted drugs, or immunotherapies shows promise in enhancing therapeutic response and reducing relapse rates. Moreover, the advent of integrative multi-omics and spatial multi-omics technologies has enabled the identification of leukemia-specific epigenetic drivers and illuminated the heterogeneity of the leukemic microenvironment, opening new avenues for precision medicine. This review synthesizes current insights into the role of epigenetic dysregulation in leukemia progression and therapy resistance, evaluates the clinical potential of epigenetic-based therapeutic strategies, and discusses future challenges and opportunities in translating these approaches into personalized leukemia care.*

## INTRODUCTION

Leukemia is a type of blood cancer that happens when immature or defective blood cells grow out of control and build up in the bone marrow, blood and other organs. The disease is often divided into two types: acute and chronic. It also has two subtypes: myeloid and lymphoid. Each type has its own molecular and clinical features. Leukemia is a global health issue despite breakthroughs in biology and targeted and immunotherapy treatments. The relapse and therapy resistance remain the primary obstacles for the cure

(Wouters & Delwel, 2016; Cruz-Rodriguez et al., 2018). The clinical issues show that the condition is more complecated than the genetics. Epigenetic issues are crucial to leukemia's formation, progression, and therapy resistance.

The epigenetics studies inheritable changes in gene expression that occur without changes to the underlying DNA sequence (Bernt & Armstrong, 2011). The most recognized epigenetic mechanisms involve DNA methylation, histone modifications, the movement of nucleosomes through chromatin remodeling and the regulation by non-coding RNAs. These processes are essential for normal blood cell development and for maintaining the delicate balance between self-renewal and differentiation in hematopoietic stem and progenitor cells. When these mechanisms are disrupted, it leads to significant changes in gene expression, driving malignant transformation and sustaining leukemic stem cell (LSC) populations. Unlike genetic mutations, which are permanent, epigenetic modifications are dynamic and reversible, making them promising targets for therapy (Dawson & Kouzarides, 2012).

In leukemia, anomalous DNA methylation patterns have been consistently identified across subtypes. Hypermethylation of promoter CpG islands often results in the silencing of tumor suppressor genes, whereas global hypomethylation leads to genomic instability and the activation of oncogenes. The recurrent mutations in DNA methylation regulators, including DNMT3A, TET2, and IDH1/2, further emphasize the significance of epigenetic dysregulation in leukemogenesis (Ley et al., 2010; Figueroa et al., 2010). Histone alterations constitute an additional regulatory layer, wherein post-translational modifications, including acetylation, methylation and phosphorylation, modify chromatin accessibility and transcriptional activity. The mutations in histone modifiers such as EZH2, ASXL1, and genes linked with the MLL/KMT2A complex, have been significantly correlated with leukemic development and unfavorable outcomes (Shih et al., 2012). In addition to DNA and histone modifications, non-coding RNAs like miRNAs and lncRNAs interact with chromatin regulators or directly affect messenger RNA stability and translation to alter transcriptional programs (Garzon et al., 2009).

The living leukemic stem cells are a hallmark of leukemia. These cells can regenerate and resist treatment. These cells need epigenetic modifications to maintain stem-like behaviour and prevent differentiation (Kreso & Dick, 2014). LSCs are protected against hazardous treatments by their dormancy and ability to adapt to their surroundings and treatment. This adaptability enables them to endure treatment and experience disease recurrence. The findings suggest that treatment resistance in leukemia results from genetic and epigenetic factors related to alterations in chromatin structure and transcriptional networks under selection pressure (Shlush, 2018).

Epigenetic modifications are progressively associated with resistance to chemotherapy, targeted therapy and contemporary immunotherapy. Leukemic cells exhibit reduced susceptibility to cytotoxic agents, potentially attributable to hypermethylation of genes associated with apoptosis. Histone modifications can influence the accessibility of DNA repair genes, thereby enhancing cellular resistance to toxins (Garcia-Manero & Fenaux, 2011). The dysregulation of ncRNA can alter drug removal pumps, cell death pathways, and signaling systems, thereby enhancing resistance (Li et al., 2017). These adaptive strategies enable leukemic clones to evade drug-induced mortality without the necessity of acquiring new mutations. The epigenetic modifications needed to overcome resistance.

Recurrent mutations in epigenetic regulators give genetic evidence for epigenetics importance in leukemia. The DNMT3A mutations, frequent in AML, indicate poorer outcomes and occur early in pre-leukemic blood stem cells. This indicates their role in starting the disease (Ley et al., 2010). TET2 mutations disrupt DNA demethylation which skews blood cell development towards abnormal self-renewal (Ko et al., 2010). The mutant IDH1/2 produces the oncometabolite 2-hydroxyglutarate, inhibiting TET2 and histone demethylases. This results in extensive changes in epigenetics and disrupted cell development (Figueroa et al., 2010). Additionally, ASXL1 mutations interfere with the Polycomb repressive complex 2 (PRC2). This causes abnormal histone methylation and changes in transcription linked to negative outcomes (Shih et al., 2012). These findings have identified epigenetic regulators as crucial in leukemia development and emphasized their importance as treatment targets. In addition to DNA and histone modifications, non-coding RNAs like miRNAs and lncRNAs interact with chromatin regulators or directly affect messenger RNA stability and translation to alter transcriptional programs (Garzon et al., 2009).

The epigenetic modifications are being employed as biomarkers for diagnosis, prognosis and disease monitoring. Patient risk and treatment outcomes can be determined by DNA methylation patterns. Histone alterations and ncRNA expression levels are being studied as prognostic indicators (Bullinger et al., 2010). To better understand leukemia biology, researchers are merging epigenetic profiling with genomic and transcriptome data in multi-omics frameworks. Single-cell and spatial epigenomic methods allow tumor variety and leukemic cell-environment interactions to be studied. This illuminates medication resistance and relapse (Nam et al., 2021). Therapeutic implications arise from these findings. The hypomethylating medications like azacitidine and decitabine can treat AML and myelodysplastic syndromes. This is especially true for older patients who cannot tolerate rigorous therapy (Garcia-Manero & Fenaux, 2011).

Histone deacetylase inhibitors (HDACis) and inhibitors of mutant IDH enzymes have broadened the treatment arsenal, whilst BET bromodomain inhibitors and EZH2 inhibitors are currently undergoing clinical trials (Dawson & Kouzarides, 2012). However, epigenetic network redundancy and adaptability limit single-agent epigenetic therapy's efficacy. Combining epigenetic drugs with chemotherapy, targeted drugs, or immunotherapies to boost efficacy and overcome resistance is becoming more common (DiNardo et al., 2020). The incorporation of epigenetic therapies into precision medicine frameworks is anticipated to enhance outcomes and diminish relapse rates.

Recent studies have highlighted the therapeutic potential of natural plant extracts in combating pathogenic conditions and their secondary complications. For instance, (Shahid et al., 2023) demonstrated the antimicrobial and antiparasitic efficacy of *Salvadora persica* extracts against *Sarcoptes scabiei var. hominis*, suggesting that bioactive compounds from natural sources may also influence epigenetic pathways involved in disease modulation.

The animal microbiome plays a pivotal role in maintaining physiological balance, immunity, and overall health. Disruptions in microbial communities are increasingly linked to various infectious and metabolic disorders. This study explores the complex interactions between host and microbiota, highlighting current research trends and future prospects for microbiome-based therapeutic and preventive strategies in veterinary science (Afzal et al., 2024).

Notwithstanding considerable progress, obstacles persist in converting epigenetic knowledge into lasting clinical advantages. The epigenetic variability both within and among patients challenges the development of biomarkers and the targeting of therapies. Furthermore, the reversible and context-dependent characteristics of epigenetic alterations might lead to dynamic resistance mechanisms, even against epigenetic therapeutics. The toxicities and off-target effects provide challenges, highlighting the necessity for more selective inhibitors and reliable biomarkers of response. Future research will necessitate the thorough integration of multi-omics data, functional validation of critical epigenetic drivers and the formulation of strategies to selectively target leukemic stem cells. The progress in spatial epigenomics and systems biology methodologies offers potential solutions to these deficiencies and facilitates the clinical use of epigenetic treatments. This review will analyze the complex function of epigenetics in leukemia biology, assess the clinical ramifications of epigenetic dysregulation, and evaluate current and novel treatment methods designed to address drug resistance and enhance patient outcomes.

## Epigenetic Landscape in Leukemia:

Epigenetic modifications are a defining feature of leukemogenesis, influencing transcriptional pathways that regulate cell proliferation, differentiation and survival. Leukemia is originated and driven by recurrent genetic mutations; however, increasing data suggests that epigenetic dysregulation is equally vital in creating malignant phenotypes, sustaining leukemic stem cells and promoting therapeutic resistance (Baylin & Jones, 2016). The primary

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epigenetic mechanisms associated with leukemia encompass abnormal DNA methylation, histone changes, chromatin remodeling and the dysregulation of non-coding RNAs. The layers of regulation interact dynamically resulting in a complex and adaptable landscape that presents both biological flexibility and therapeutic difficulties.

**DNA methylation:**

One of the most well-known epigenetic changes is DNA methylation, which is the covalent attachment of a methyl group to the 5-carbon of cytosine residues in CpG dinucleotides. In normal hematopoiesis, DNA methylation regulates lineage-specific gene expression and maintains stable repression of transposable elements (Khalid et al., 2024). Aberrant DNA methylation patterns are prevalent in leukemia and facilitate oncogenesis via gene suppression and the activation of aberrant pathways (Figueroa et al., 2010). A key characteristic of leukemic cells is the simultaneous presence of localized promoter hypermethylation and global hypomethylation. Hypermethylation often affects tumor suppressor genes such as CDKN2B (p15), TP73, and DAPK. This leads to silenced transcription and disrupted apoptosis (Esteller, 2008). In contrast, genome-wide hypomethylation makes genomic stability less reliable and activates proto-oncogenes and repetitive sequences. This promotes clonal evolution and reduces the effectiveness of treatments (Wouters & Delwel, 2016).

Recurrent mutations in DNA methylation regulators strengthen the link between methylation changes and leukemia. Mutations in DNMT3A, a de novo DNA methyltransferase, occur in about 20-30% of acute myeloid leukemia (AML) cases and are associated with a poor prognosis (Ley et al., 2010). The loss-of-function mutations in TET2 is an enzyme that aids in active DNA demethylation through hydroxymethylation, hinder blood cells from differentiating. This pushes stem cells towards self-renewal, increasing their chances of developing into myeloid cancers (Ko et al., 2010). Similarly, neomorphic mutations in IDH1/2 create the oncometabolite 2-hydroxyglutarate. This substance inhibits TET enzymes, resulting in a hypermethylation phenotype and blocking differentiation (Figueroa et al., 2010). These findings highlight DNA methylation as both a trigger and a marker of leukemogenesis.

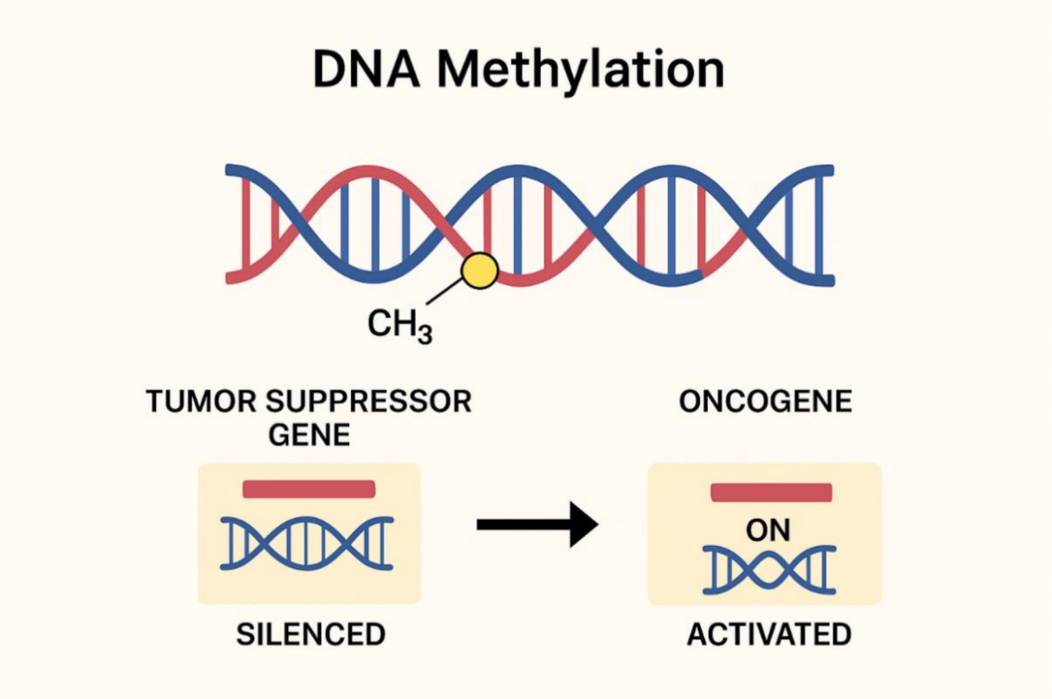

Figure 1: DNA Methylation.

### Histone Modifications:

The nucleosomes are formed by histones. These proteins can be acetylated, methylated, phosphorylated, ubiquitinated and sumoylated after formation. These alterations affect chromatin accessibility and transcription. In leukemia, histone-modifying enzyme alterations alter oncogene expression and decrease tumor suppressors (Shih et al., 2012). Histone acetyltransferases (HATs) relax chromatin structure, boosting transcription. In contrast, histone deacetylases (HDACs) remove acetyl groups, closing chromatin. Leukemia development is connected to HDAC overexpression, which silences differentiation-related genes. HDAC inhibitors (HDACis) may restore transcriptional activity, thus researchers have investigated them (Garcia-Manero, 2015).

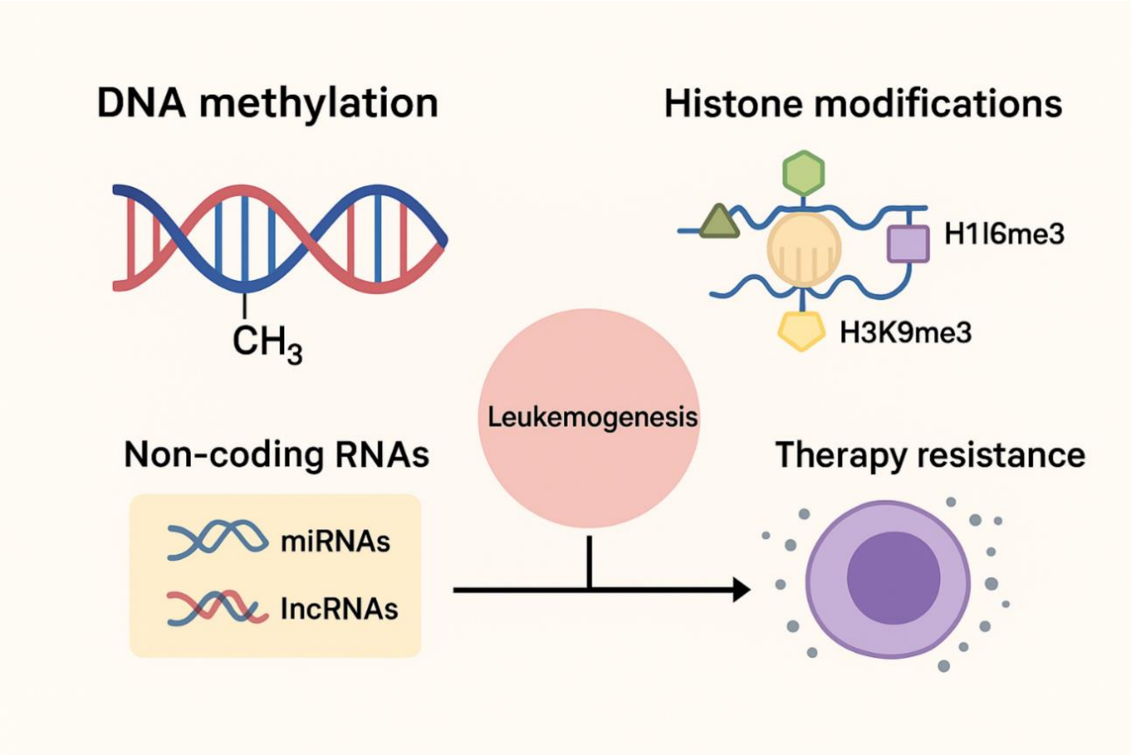

**Figure 2: Epigenetic Mechanisms Driving Leukemogenesis and Therapy Resistance.**

Histone methylation serves as another significant regulator. This alteration can either activate or inhibit transcription, contingent upon the residue and the level of methylation, which differs from acetylation. Methyltransferases such as EZH2, a key component of Polycomb Repressive Complex 2 (PRC2), excessively trimethylate histone H3 lysine 27 (H3K27me3), leading to the suppression of tumor suppressor genes and the promotion of leukemia (Cao et al., 2014). ASXL1 mutations inhibit PRC2 recruitment, leading to epigenetic instability and unfavorable outcomes in acute myeloid leukemia and myelodysplastic syndromes (Shih et al., 2012). The MLL/KMT2A fusion proteins, prevalent in juvenile and therapy-related leukemias, facilitate leukemogenesis through the inappropriate recruitment of histone methyltransferases such as DOT1L, which maintains the activity of HOXA gene clusters and stemness programs (Krivtsov & Armstrong, 2007). Histone phosphorylation and ubiquitination influence DNA damage repair, chromatin remodeling, and gene expression in leukemia; however, the mechanisms underlying these processes remain inadequately understood. Histone modifications collaboratively establish a dynamic and meticulously regulated code. In leukemia, this code is frequently disrupted to maintain cancerous transcriptional states (Shahid et al., 2023).

### Chromatin Remodeling:

Apart from covalent modifications to DNA and histones, chromatin remodeling complexes that are ATP-dependent actively change the chromatin scaffolding. The SWI/SNF, ISWI, CHD, and INO80 complexes reposition nucleosomes to regulate the accessibility of transcription factors. Mutations in the components of these complexes are recognized as common abnormalities in leukemia, underscoring their importance in maintaining normal hematopoiesis (Kadoch & Crabtree, 2015). Mutations in ARID1A and SMARCA4, components of the SWI/SNF complex, disrupt enhancer regulation and impair cellular differentiation, resulting in leukemic transformation. Alterations in CHD4, a component of the NuRD complex, influence DNA repair and transcriptional repression pathways, thereby reducing the efficacy of therapy (Mathur, 2018). Chromatin remodelers often interact with transcription factors and signaling pathways, leading to context-dependent impacts on leukemic development. Due to their significant impact on chromatin accessibility, they play a crucial role in transcriptional plasticity and therapeutic evasion. Chromatin remodeling plays a crucial role in the survival of leukemic stem cells. Aberrant nucleosome placement at the promoters of self-renewal genes promotes the durability of leukemic stem cells (LSCs), while the inhibition of differentiation pathways ensures the continuous spread of the disease (Kreso & Dick, 2014). The ability to reverse chromatin remodeling has made these complexes appealing targets for drugs, and researchers are now looking into synthetic lethality methods.

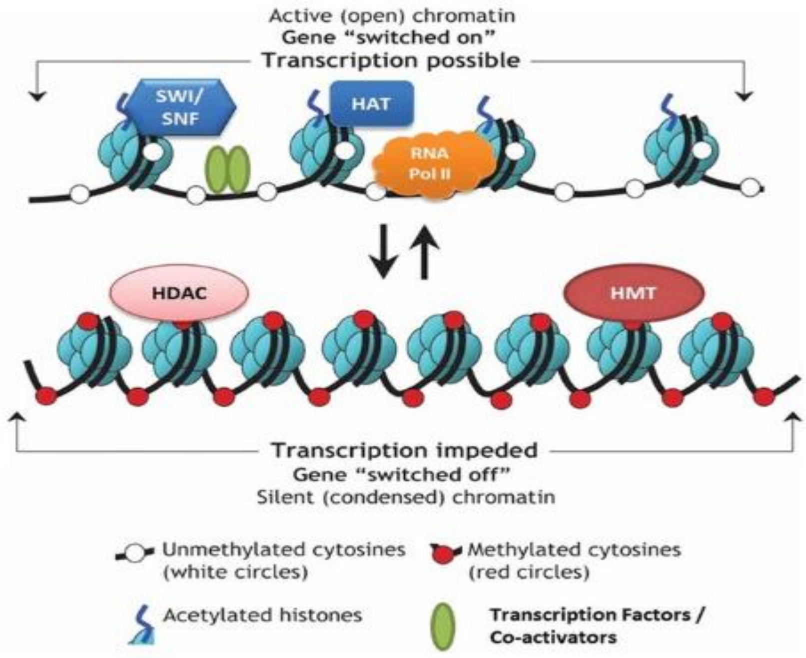

**Figure 3: Epigenetic regulation of gene expression via chromatin remodeling (Kronfol et al., 2017).**

### Non-coding RNAs:

Non-coding RNAs (ncRNAs) including as microRNAs (miRNAs), long non-coding RNAs (lncRNAs), and circular RNAs, constitute a significant component of epigenetic control. These molecules control gene expression through several processes, including post-transcriptional repression, chromatin remodeling, and the regulation of protein complexes. In leukemia, abnormal non-coding RNAs coordinate cancer-related transcriptional networks and help establish resistance to treatment (Garzon et al., 2009). MicroRNAs (miRNAs) adjust gene expression by binding to the 3' untranslated regions (UTRs) of target mRNAs. This binding either leads to their breakdown or stops them from being translated. In acute myeloid leukemia (AML), the reduced levels of tumor suppressor miRNAs, such as miR-29b that result in the overproduction of DNA methyltransferases, which worsens hypermethylation traits (Garzon et al., 2009). On the other hand, excess oncogenic miRNAs like miR-125b prevent stem cells from developing. Leukemia develops faster (Bousquet et al., 2012). The long non-coding RNAs (lncRNAs) regulate transcription and chromatin structure. LncRNA HOTAIRM1 modulates myeloid cell differentiation, while HOTAIR recruits PRC2 to target locations to inhibit tumor suppressor gene transcription (Prensner & Chinnaiyan, 2011). Leukemia persists when these lncRNAs are disrupted in altering epigenetics. Also, ncRNAs are associated to therapeutic resistance. Li et al. (2017) found that miRNAs can activate drug efflux transporters and lncRNAs can change apoptosis and DNA repair pathways to assist cells survive therapy.

### Epigenetic Mechanisms in Leukemia Progression

The development of leukemia involves several stages, marked by the accumulation of genetic mutations and alterations in gene regulation. These alterations disturb the fragile balance present in hematopoietic cells among self-renewal, differentiation, growth and apoptosis processes. The gene regulation alterations introduce an additional dimension influencing cellular interpretation of DNA. Although established driver mutations such as FLT3, NPM1, and BCR-ABL1 significantly impact this process, they are not the sole contributors. Dawson and Kouzarides (2012) indicate that this control is essential for sustaining the viability of leukemic stem cells (LSCs) and promoting diversity within the leukemia cell population when present. The epigenetic mechanisms cannot modify the DNA sequence. The mechanisms encompass DNA methylation, histone modifications, chromatin alterations and regulation of non-coding RNA. Conversely, they influenced gene expression in potentially heritable manners. This enables leukemic cells to endure and respond to diverse stressors. This section examines the role of various pathways in the development of leukemia.

### Disruption of Normal Hematopoietic Differentiation:

The process of hematopoiesis is highly structured and normally begins with HSCs (multipotent hematopoietic stem cells) and ends with fully matured blood cells. Epigenetic programs control gene expression specific to a lineage, ensuring proper cell differentiation. In leukemia, abnormal epigenetic regulation interrupts this process causing differentiation to halt which is a key feature of leukemogenesis (Passegué et al., 2003).

DNA hypermethylation of essential differentiation-related genes, such as CDKN2B and CEBPA, leads to reduced transcription and maintains progenitor-like states (Esteller, 2008). Additionally, the abnormal recruitment of histone methyltransferases by oncogenic fusion proteins like MLL-rearranged KMT2A fusions, keeps the expression of HOXA9 and MEIS1 elev ated.. These transcription factors are essential for stemness but harmful when continuously active (Krivtsov & Armstrong, 2007). This epigenetic block to differentiation causes an accumulation of immature blasts that grow uncontrollably forming the harmful basis of acute leukemia.

### Maintenance of Leukemic Stem Cell Renewal:

Leukemic stem cells are a group of self-renewing cells that help start, grow, and return leukemia. Their persistence is why treatments often fail and the disease reoccurs (Kreso & Dick, 2014). Epigenetic programs are crucial for the maintenance of LSCs as they impose stem cell-like transcriptional states and prevent differentiation. The hypermethylation of apoptosis-inducing genes and hypomethylation of stemness-related enhancers distinguish LSCs from HSCs (Ng et al., 2016). The presence of H3K27me3 at differentiation genes inhibits transcription and H3K4me3 enrichment at stemness loci guarantees self-renewal, two histone modifications that bolster this characteristic (Rathert et al., 2015). The small non-coding RNAs play an important role in regulating LSCs. Overexpression of miR-125b enhances self-renewal and proliferation in AML models (Bousquet et al., 2012). The accessibility of chromatin is increased by LncRNAs like HOTAIR, which promotes cancer programming (Prensner & Chinnaiyan, 2011). Epigenetic regulation promotes LSC adaptability.

### Reprogramming of Transcriptional Networks:

Leukemia is characterized by epigenetic instability, which alters the transcription mechanisms that determine cell destiny. Leukemic cells alter the activation of promoters and enhancers through unique epigenetic landscapes, according to genome-wide research. According to Whyte et al. (2013), this causes abnormal gene expression and infidelity in the lineage. Oncogene activation via super-enhancers, which are big clusters of enhancers containing transcription factors, is a common mechanism in leukemia. An example would be the aberrant super-enhancer activity that promotes cell growth and survival that is typically linked to MYC and BCL2 (Lovén et al., 2013).

Chromatin remodeling complexes also affect the accessibility of enhancers. This allows transcription programs to change in response to environmental signals (Kadoch & Crabtree, 2015).

Epigenetic regulators work alongside genetic changes. For example, changes in transcription factors like RUNX1 and CEBPA alter chromatin occupancy while changes in epigenetic modifiers simultaneously worsen transcriptional dysregulation. This collaboration creates an environment that fosters leukemic transformation. It emphasizes the interplay between genetics and epigenetics in the progression of leukemia (Shih et al., 2012).

### Contribution to Clonal Evolution and Disease Heterogeneity:

Leukemia is marked by clonal diversity which relates to the genetic and epigenetic profiles of different subclones. Epigenetic flexibility allows for non-genetic variation helping clonal populations to quickly adapt to selective pressures without new mutations (Ding et al., 2012). The differences in DNA methylation among subclones lead to distinct transcriptional outputs. Meanwhile, variations in histone modifications affect lineage potential. The observed differences foster competition among clonal populations, enabling the emergence of epigenetically favored subclones during progression or relapse (Corces-Zimmerman et al., 2014). The single-cell epigenomic research has demonstrated significant variability in enhancer landscapes across tumors indicating that clonal growth is influenced in part by stochastic epigenetic alterations (Buenrostro et al., 2018). The treatment acts as a selection pressure, modifying the epigenetic landscape and facilitating the development of resistant clones. The hypomethylating agents have the capacity to reactivate the tumor suppressor genes and modify histones. This may contribute to cancer recurrence (Garcia-Manero, 2015). The epigenetic reprogramming increases the disease heterogeneity and accelerates the progression through clonal selection into the body.

### Epigenetics and Therapy Resistance

The resistance to therapy presents a considerable obstacle in the treatment of leukemia. This results in reduced remission rates and poorer patient outcomes. The adaptability of leukemic cells frequently renders chemotherapy, targeted therapies, and immunotherapies ineffective. Epigenetic modifications, in conjunction with genetic mutations, contribute to the treatment resistance of leukemic cells, modify their gene expression, and facilitate the development of drug tolerance (Lu et al., 2020). Cancer cells persist in the presence of chemotherapy and immune therapies due to their ability to rapidly alter and revert their epigenome (van der Helm et al., 2021). This section examines the role of epigenetics in conferring resistance to chemotherapy, targeted therapy, and immunotherapy.

### Epigenetic Chemotherapy Resistance Mechanisms:

The chemotherapy is the main treatment for acute lymphoblastic leukemia (ALL) and acute myeloid leukemia (AML); however, resistance to agents like cytarabine, daunorubicin, and anthracyclines frequently arises from epigenetic modifications (Khalid et al., 2024). These modifications inhibit apoptotic regulators, impair DNA repair mechanisms, and sustain leukemic progenitor cells. Hypermethylation of tumor suppressor genes, such as p15INK4b and BIM, along with alterations in histone modifications specifically increased H3K27me3 and decreased H3K9 acetylation hinders apoptosis and DNA repair mechanisms, thereby enhancing cell survival in the context of chemotherapy stress (Yang et al., 2019; Nguyen et al., 2020). Epigenetic remodeling maintains leukemic stem cell dormancy and promotes resistant subclones, evidenced by enhancer reprogramming and histone acetylation variability in cytokine-resistant AML cells (Ding et al., 2021; Stomper et al., 2021). These findings underscore the dual role of chemotherapy in eradicating sensitive cells while facilitating the emergence of resistant clones via epigenetic reprogramming.

### Epigenetic Reprogramming in Targeted Therapy Resistance:

There have been numerous advancements in treatment, with tyrosine kinase inhibitors (TKIs) such as imatinib being particularly useful for AML and BCR-ABL-positive chronic myeloid leukemia (CML). In spite of their effectiveness, resistance continues to pose a significant clinical challenge. Epigenetic changes and medication target point mutations contribute to adaptive resistance. The AML patients with FLT3 drug resistance have extensive DNA methylation alterations that activate bypass signaling pathways, including the MAPK and PI3K/AKT cascades (Stomper et al., 2021). Chronic TKI exposure in CML remodels chromatin to restore survival signaling without kinase activity (Abdel-Wahab & Levine, 2021). The enhanced reprogramming by histone acetylation allows leukemia cells to maintain growth-promoting transcription factors like MYC, enabling drug tolerance (Bell et al., 2022). These findings have prompted epigenetic-drug combos to delay or prevent resistance. TKIs can impair enhancer activity and reduce adaptive transcriptional responses when combined with HDACis or BET inhibitors (Wu et al., 2021).

### Epigenetic Immunotherapy Resistance Modulation:

The monoclonal antibodies, bispecific T-cell engagers, and CAR T-cell therapy have revolutionized leukemia treatment. Patients often relapse following initial responses due to resistance. Epigenetic processes strongly influence antigen presentation, immunological checkpoint regulation and immune evasion. DNA hypermethylation of antigen-processing machinery genes reduces immune effector cell detection of leukemia antigen (Shen et al., 2020). Histone alterations also affect immunological checkpoint molecule transcription, such as PD-L1, which exhausts T cells (Ghoneim et al., 2021). The long non-coding RNAs and dysregulated microRNAs reduce interferon signaling and cytotoxic immune responses (Xie et al., 2022). Epigenetic immune escape is shown by CAR T-cell treatment resistance. Relapsed B-cell ALL leukemic cells often epigenetically silence CD19, the therapeutic target antigen, rendering CAR T-cells useless (Sotillo et al., 2022). Drug reversal of these epigenetic alterations is being studied to restore antigen expression and sensitize leukemic cells to immunotherapy.

### Epigenetic Change and Survival:

Epigenetic plasticity leukemic cells' ability to dynamically and reversibly change their epigenome in response to therapy unites resistance across all treatment modalities. This adaptability allows drug-tolerant persister (DTP) states with reversible quiescence, metabolic rewiring, and stem-like transcriptional programs (Mishra et al., 2021). Even within genetically homogeneous populations, single-cell multi-omics studies show that subpopulations have varied chromatin accessibility patterns that affect medication responses (Petti et al., 2022). This flexibility permits certain leukemia cells to survive initial treatment and re-expand to cause recurrence. The therapy targeting epigenetic plasticity is emerging. Preclinical studies demonstrate that BET, HDAC, and DNMT inhibitors reduce drug tolerance and restore susceptibility to chemotherapy, TKIs and immunotherapies (Wu et al., 2021). These techniques may help achieve sustained remissions by overcoming medication resistance's adaptive survival mechanisms.

**Table 1: Epigenetic mechanisms contributing to therapy resistance in leukemia.**

| Therapy Type | Epigenetic Mechanism | Impact on Resistance | Key References |
|---|---|---|---|
| **Chemotherapy** | DNA hypermethylation of apoptosis genes; histone modifications repressing DNA repair | Reduced apoptosis, persistence of LSCs, drug tolerance | Yang et al., 2019; Nguyen et al., 2020 |

| | | | |
|---|---|---|---|
| **Targeted Therapy** | DNA methylation changes activating bypass pathways; enhancer reprogramming via histone acetylation | Sustained signaling despite TKI inhibition | Stomper et al., 2021; Bell et al., 2022 |
| **Immunotherapy** | Hypermethylation silencing antigen-presentation genes; histone-driven PD-L1 upregulation; ncRNA dysregulation | Immune evasion, antigen loss, T-cell exhaustion | Shen et al., 2020; Ghoneim et al., 2021; Sotillo et al., 2022 |
| **Cross-modal (Plasticity)** | Dynamic epigenetic reprogramming (chromatin accessibility, enhancer activity) | Entry into drug-tolerant persister states, relapse | Mishra et al., 2021; Petti et al., 2022 |

## Epigenetic Biomarkers in Leukemia

Epigenetic dysregulation is increasingly acknowledged as a contributor to leukemogenesis. It is a significant source of biomarkers for the diagnosis, prognosis and therapeutic monitoring of leukemia. Recent developments in high-throughput sequencing, single-cell profiling, and multi-omics methodologies have expedited the identification of epigenetic biomarkers relevant to risk stratification, monitoring of minimal residual disease (MRD), and forecasting therapeutic responses (Ntziachristos et al., 2019). This section emphasizes the clinical importance of epigenetic biomarkers in the management of leukemia.

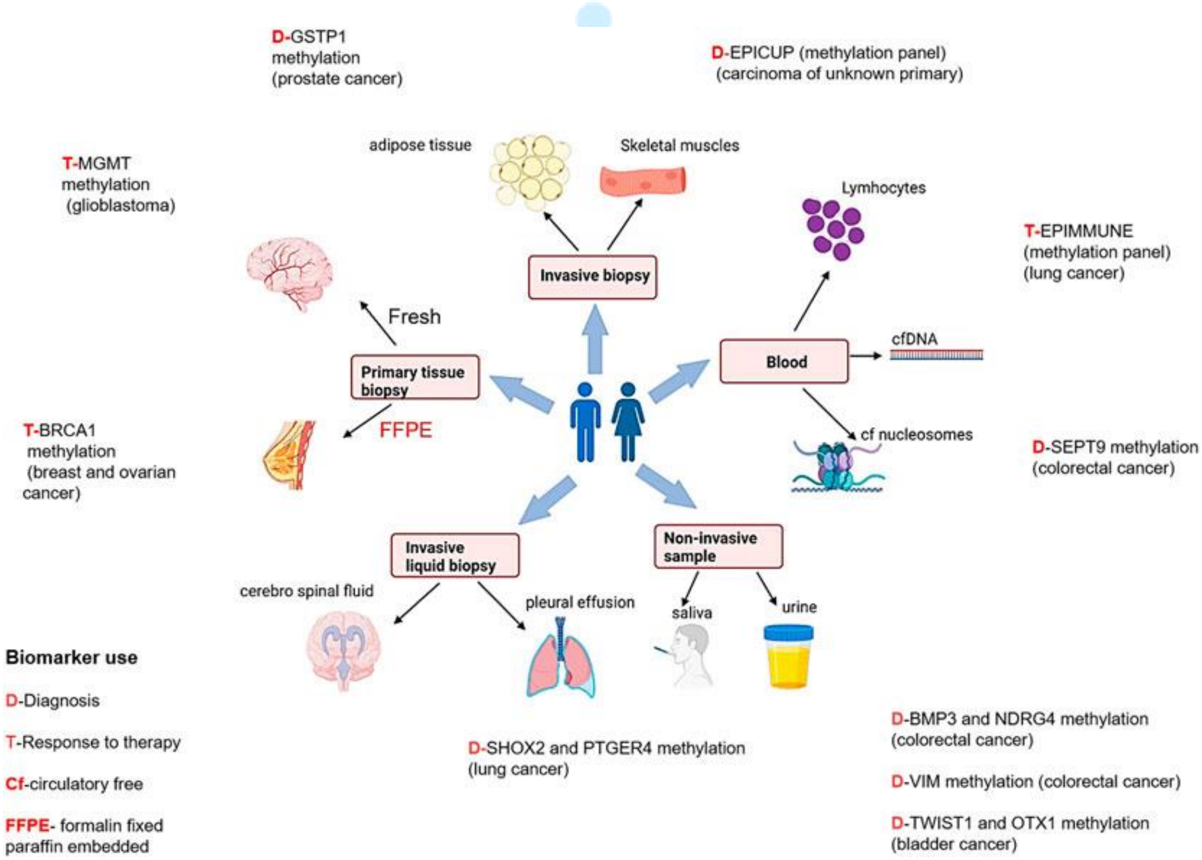

**Figure 4: Epigenetic biomarkers and different sample types for diagnosis, prognosis, and treatment therapies in different cancers (Tulsyan et al., 2022).**

### Diagnostic and prognostic significance:

The aberrant DNA methylation patterns represent highly reliable diagnostic biomarkers in leukemia. A unique methylation patterns can differentiate leukemia subtypes and separate malignant hematopoietic cells from normal ones (Mumtaz et al., 2024). The promoter hypermethylation of the

CDKN2B (p15INK4b) and WT1 genes is commonly observed in acute myeloid leukemia (AML) and acute lymphoblastic leukemia (ALL), functioning as an early diagnostic marker (Figueroa et al., 2016). The global hypomethylation is associated with genomic instability and poor survival outcomes, while specific hypermethylation patterns correlate with therapy resistance and an increased risk of relapse (Glass et al., 2017). Histone modification profiles, including the enrichment of H3K27me3 have been associated with negative clinical outcomes and heightened stemness characteristics in AML (Nguyen et al., 2020).

### Epigenetic signatures for risk stratification:

Epigenetic signatures have been incorporated into risk classification systems, enhancing the precision of cytogenetic and mutational analyses. Zhang et al. (2019) indicate that methylation-based classifiers can enhance predictive value by categorizing AML patients into prognostic groups, independent of genetic mutations. Research indicates that DNA methylation at the DNMT3A, TET2, and IDH1/2 target loci correlates with an increased risk of relapse and a poor prognosis, even among patients classified as having intermediate genetic risk (Papaemmanuil et al., 2016). The microRNA signatures and other non-coding RNAs work as potential indicators. Research by Garzon et al. (2016) indicates that poor outcomes in acute myeloid leukemia (AML) correlate with the downregulation of miR-181a while high-risk of acute lymphoblastic leukemia (ALL) is linked to the overexpression of miR-155. In acute myeloid leukemia (AML), a poorer prognosis is associated with the elevated levels of the long non-coding RNA HOTAIRM1 (Bhan et al., 2017). This illustrates the role of lncRNAs in enhancing the risk classification.

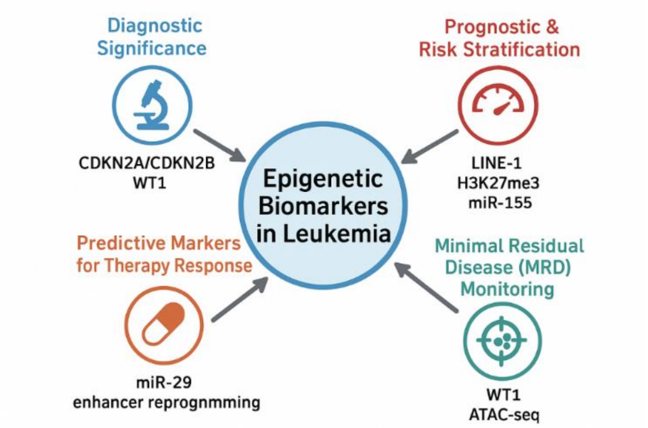

**Figure 5: Epigenetic Biomarkers in Leukemia.**

### Monitoring minimal residual disease (MRD):

The accurate identification of minimal residual disease (MRD) is essential for enhancing treatment approaches and forecasting relapse in leukemia. Conventional flow cytometry and PCR-based assays are constrained by their dependence on identifiable genetic abnormalities, which diminishes sensitivity. Epigenetic biomarkers, especially DNA methylation, offer a significant complementary method. In acute myeloid leukemia (AML), hypermethylation of the WT1 and CDKN2A promoters is associated with an increased risk of relapse, suggesting the presence of residual disease (Liu et al., 2018). Methylation-based panels have shown efficacy in detecting leukemic cells at levels below those identified by conventional assays (Schroeder et al., 2020). Additionally, emerging biomarkers, including DNA methylation signatures and chromatin accessibility patterns identified through ATAC-seq, facilitate the identification of residual leukemic clones exhibiting epigenetic characteristics that differ from normal hematopoiesis (Petti et al., 2022).

### Predictive markers for therapy response:

The epigenetic biomarkers predict therapeutic efficacy and guide therapy selection. The response to hypomethylating agents (HMAs) like azacitidine and decitabine is anticipated based on the methylation status of the genes associated with DNA repair and apoptosis (Itzykson et al., 2017). Glass et al. (2017)

indicate that the sensitivity to HMAs correlates with hypermethylation of CDKN2B whereas the resistance is associated with the reactivation of stemness-related transcriptional processes (Maryam et al., 2024). The histone modification profiles including H3K27 acetylation at enhancer regions, predict responses to BET inhibitors in acute myeloid leukemia (Bell et al., 2022). Moreover, the expression levels of non-coding RNAs, including members of the miR-29 family, have been demonstrated to predict responses to DNMT inhibitors indicating their regulatory function in DNA methylation pathways (Han et al., 2020). The predictive biomarkers are essential for the advancement of precision epigenetic therapies, facilitating personalized treatment approaches that enhance response rates and minimize toxicity (Akram et al., 2022).

**Table 2:Representative Epigenetic Biomarkers and Their Clinical Applications in Leukemia.**

| Biomarker Type | Representative Examples | Clinical Relevance | Leukemia Subtype | References |
|---|---|---|---|---|
| **DNA Methylation** | *CDKN2B (p15INK4b)*, *WT1*, *CDKN2A* | Diagnostic markers; MRD detection; predictor of HMA sensitivity | AML, ALL | Figueroa 2016; Liu 2018; Schroeder 2020 |
| **Global Hypomethylation** | LINE-1 elements, repetitive DNA regions | Associated with genomic instability and poor prognosis | AML | Glass 2017 |
| **Histone Modifications** | H3K27me3, H3K79me2 | Prognostic indicators of stemness and aggressive disease; predictor of response to BET inhibitors | AML | Nguyen 2020; Bell 2022 |
| **MicroRNAs (miRNAs)** | miR-155 (↑), miR-181a (↓), miR-29 family | Risk stratification; predictor of therapy response (DNMT inhibitors) | AML, ALL | Garzon 2016; Han 2020 |
| **Long Non-Coding RNAs (lncRNAs)** | *HOTAIRM1*, *MALAT1* | Prognostic markers; associated with relapse and inferior outcomes | AML | Bhan 2017; Garzon 2016 |
| **Chromatin Accessibility** | ATAC-seq–defined profiles | MRD detection; identifies leukemic clones distinct from normal hematopoiesis | AML | Petti 2022 |

## Therapeutic Targeting of Epigenetic Alterations in Leukemia:

The identification of epigenetic dysregulation as a key feature of leukemia progression and treatment resistance has led to the creation of targeted therapies designed to correct abnormal chromatin configurations (Naeem et al., 2024). The epigenetic alterations differ from genetic mutations in that they are reversible, which renders them appealing as therapeutic targets (Dawson, 2021). The epigenetic drugs, commonly known as "epidrugs," include inhibitors of DNA methyltransferases (DNMTs), histone deacetylases (HDACs), bromodomain and extra terminal (BET) proteins as well as histone methyltransferases like DOT1L and EZH2. Furthermore, strategies targeting non-coding RNAs (ncRNAs) and chromatin remodelers are increasingly being recognized. These strategies, whether implemented independently or alongside chemotherapy, targeted agents or immunotherapies have the potential to address resistance and enhance patient outcomes (Fong et al., 2022).

### DNA Methyltransferase Inhibitors (DNMTis):

DNMT inhibitors were among the initial epigenetic agents to be utilized in clinical field. Azacitidine and decitabine, cytidine analogs that integrate into DNA and inhibit DNMTs have demonstrated effectiveness in acute myeloid leukemia (AML) and myelodysplastic syndromes (MDS), prolonging overall survival and achieving sustained remissions (DiNardo et al., 2020). Their mechanism of action involves hypomethylation of tumor suppressor genes including CDKN2B and TP53 pathway regulators which restores normal transcriptional activity (Faisal et al., 2024).

**Histone Deacetylase inhibitors (HDACis):**

The aberrant histone deacetylation inhibits transcription of the tumor suppressor genes and enhances leukemic survival. HDAC inhibitors, including vorinostat, panobinostat, and belinostat that have shown both preclinical and clinical efficacy in acute myeloid leukemia (AML) and acute lymphoblastic leukemia (ALL) (Peirs et al., 2020). HDAC inhibitors induce histone hyperacetylation, leading to a relaxed chromatin structure and the transcriptional activation of silenced genes. They impair the DNA damage response and increase the sensitivity of leukemic cells to chemotherapy (Zhou et al., 2021). Clinical outcomes with HDAC inhibitors as monotherapy have been modest; however, combination therapies demonstrate potential. HDAC inhibitors combined with DNMT inhibitors or chemotherapy agents (such as cytarabine and anthracyclines) improve anti-leukemic efficacy by targeting transcriptional and apoptotic pathways (Peirs et al., 2020). Recent findings indicate that selective HDAC inhibitors, particularly HDAC6 inhibitors, may offer enhanced therapeutic windows while minimizing toxicity.

**Bromodomain and Extra-Terminal Domain (BET) Inhibitors:**

BET proteins, especially BRD4, modulate the transcription of essential oncogenes including MYC and BCL2. BET inhibitors (BETis) impede the interactions between bromodomains and acetylated histones, thereby inhibiting oncogenic transcriptional programs. Preclinical studies indicate significant anti-leukemic efficacy of BET inhibitors in acute myeloid leukemia (AML), acute lymphoblastic leukemia (ALL) and mixed-lineage leukemias with MLL rearrangements (Dawson, 2021). The resistance to BET inhibitors has been noted, frequently facilitated by compensatory enhancer reprogramming. Combination therapies have been explored to address this issue including the use of BET inhibitors in conjunction with FLT3 inhibitors, venetoclax, or HDAC inhibitors (Fong et al., 2022). Multiple BET inhibitors including OTX015 and CPI-0610, are presently undergoing early-phase clinical trials, demonstrating acceptable safety profiles and initial efficacy indicators.

**Targeting histone methyltransferases and demethylases:**

Histone methylation, specifically H3K79 and H3K27 modifications, is essential in the process of leukemogenesis.

- DOT1L inhibitors, such as pinometostat impede the abnormal methylation of H3K79 caused by MLL-fusion proteins, thereby interfering with the transcriptional activation of leukemogenic programs (Nguyen et al., 2020). Single-agent activity has been limited; however, combination strategies involving chemotherapy or venetoclax are currently under investigation.
- EZH2 inhibitors, such as tazemetostat specifically target the methyltransferase that mediates H3K27 trimethylation, a repressive epigenetic mark prevalent in leukemia stem cells. The inhibition of EZH2 reactivates differentiation pathways and demonstrates clinical potential in specific subsets of AML and T-cell leukemias (Kim et al., 2021).

Inhibitors of histone demethylases especially those aimed at LSD1 (KDM1A), are currently being developed. The inhibition of LSD1 promotes differentiation and enhances the sensitivity of AML cells to ATRA (all-trans retinoic acid), presenting a new strategy for differentiation therapy beyond APL (acute promyelocytic leukemia) (Kerenyi et al., 2019).

**Targeting non-coding RNAs (ncRNAs):**

The altered expression of microRNAs (miRNAs) and long non-coding RNAs (lncRNAs) plays a significant role in the progression of leukemia and the development of drug resistance. Therapeutic modulation strategies encompass miRNA mimics, antagomirs (inhibitors of miRNA) and antisense oligonucleotides targeting lncRNA. For instance: The miR-29 family mimics enhance sensitivity to DNMT inhibitors in acute myeloid leukemia (Han et al., 2020). The strategies targeting anti-miR-155 mitigate chemoresistance and enhance survival in preclinical models of acute myeloid leukemia (Bhatia et al., 2021). The targeting oncogenic lncRNAs, including MALAT1 and HOTAIRM1, inhibits leukemic growth and enhances cellular sensitivity to chemotherapy (Zhang et al., 2021). The RNA-based therapeutics while in preliminary development that demonstrate significant translational potential for precision therapy in leukemia.

**Table 3: Major Classes of Epigenetic Drugs in Leukemia and Their Clinical Applications.**

| Drug Class | Examples | Primary Targets | Clinical Applications | Limitations |
|---|---|---|---|---|
| **DNMT inhibitors** | Azacitidine, Decitabine, Guadecitabine | DNMT1, DNMT3A/B | AML, MDS | Limited monotherapy efficacy, resistance |
| **HDAC inhibitors** | Vorinostat, Panobinostat, Belinostat | HDAC1-11 | AML (trials), MDS | Toxicity, modest activity as single agents |
| **BET inhibitors** | OTX015, CPI-0610, Birabresib | BRD4, BRD2, BRD3 | AML, ALL (clinical trials) | Resistance, transient responses |
| **IDH inhibitors** | Ivosidenib, Enasidenib | Mutant IDH1/2 | IDH-mutated AML | Limited to mutation carriers |
| **EZH2 inhibitors** | Tazemetostat | EZH2 (PRC2) | Lymphoid leukemias, AML (early trials) | Early-stage development |
| **DOT1L inhibitors** | Pinometostat | DOT1L (H3K79 methylation) | MLL-rearranged AML | Limited clinical efficacy so far |
| **RNA-based therapies** | miRNA mimics, anti-miRs | miRNAs, lncRNAs | Preclinical leukemia models | Delivery, off-target effects |

**Technological Advances Driving Epigenetic Insights:**

The recent technological advancements have enhanced the comprehension of epigenetic regulation in leukemia, transitioning from bulk-level assays to high-resolution, single-cell, and spatially resolved methodologies. Next-generation sequencing (NGS) techniques, such as whole-genome bisulfite sequencing (WGBS), reduced-representation bisulfite sequencing (RRBS), and chromatin immunoprecipitation sequencing (ChIP-seq), facilitate thorough mapping of DNA methylation, histone modifications, and chromatin accessibility. Single-cell epigenomic platforms, including scATAC-seq and scNMT-seq, reveal intratumoral heterogeneity and therapy-resistant subclones that contribute to clonal evolution (Grosselin et al., 2019; Clark et al., 2018). Integrative multi-omics frameworks such as MOFA and iClusterPlus synthesize genomic, epigenomic, transcriptomic, and proteomic data to elucidate leukemia-specific regulatory networks, prognostic signatures, and therapeutic vulnerabilities (Zhu et al., 2020; Argelaguet et al., 2020). Spatial multi-omics tools, including spatial ATAC-seq, Slide-seq, and multiplexed imaging, elucidate the mechanisms by which leukemic stem cells utilize bone marrow niches to sustain epigenetic plasticity and resist therapeutic interventions (Baryawno et al., 2019; Marx, 2021). Artificial intelligence and network biology methodologies improve biomarker discovery, delineate enhancer–promoter interactions, and facilitate drug repurposing, thereby optimizing the development of epigenetic-based therapeutics (Chen et al., 2021; Li et al., 2022). These innovations integrate mechanistic epigenetic insights with precision oncology, facilitating patient stratification, optimizing therapy selection, and advancing personalized care in leukemia.

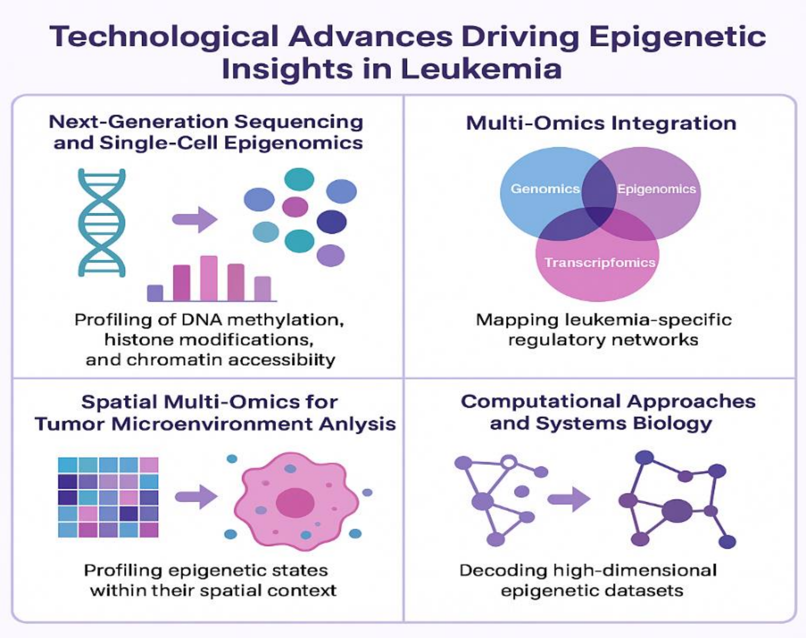

**Figure 6: Integration of NGS, Single-cell, Multi-omics and spatial technologies to reveal leukemia epigenetics**.

## Conclusion

Epigenetic dysregulation has become a key factor in leukemogenesis, therapy resistance and disease relapse, alongside genetic alterations. Recent findings emphasize the interaction of DNA methylation, histone modifications, chromatin remodeling and non-coding RNAs in maintaining leukemic stem cells, reprogramming transcriptional networks and facilitating clonal adaptability in response to therapeutic stress. Epigenetic therapeutics, including DNA methyltransferase inhibitors, histone deacetylase inhibitors, BET inhibitors and IDH-targeted agents, exhibit significant clinical potential, especially when used in conjunction with chemotherapy, targeted therapy, or immunotherapy. The limited efficacy of single-agent epigenetic therapies, along with challenges from tumor heterogeneity, dynamic clonal evolution and microenvironmental influences, highlights the necessity for biomarker-guided treatment strategies. The translational gaps persist, as numerous preclinical findings have not yet resulted in sustained clinical benefits. Future developments in single-cell epigenomics, spatial multi-omics, and computational integration are poised to enhance patient stratification and uncover new therapeutic targets. The utilizing these technologies in precision oncology frameworks allows for the transformation of epigenetic insights into personalized strategies that enhance outcomes, reduce relapse and redefine leukemia care.

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