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REVIEW ARTICLE

EPIGENETIC ALTERATIONS IN MYELOID MALIGNANCIES: LINKING CHROMATIN REMODELING TO DISEASE PROGRESSION

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Abstract

Myeloid cancers, such as acute myeloid leukemia (AML), myelodysplastic syndromes (MDS), and myeloproliferative neoplasms (MPNs), develop from the clonal alteration of hematopoietic stem and progenitor cells. Apart from genetic mutations, epigenetic dysregulation has become a key factor in disease onset, advancement, and resistance to treatment. Anomalies in DNA methylation, histone changes, and chromatin rearrangement interfere with normal blood cell differentiation, promote clonal growth, and create diverse malignant cell populations. Alterations in essential epigenetic regulators like DNMT3A, TET2, IDH1/2, ASXL1, and EZH2-collaborate with oncogenic alterations to facilitate leukemogenesis and resistance to treatment. These epigenetic changes act as prognostic indicators and offer targetable weaknesses, such as DNA methyltransferase inhibitors, histone deacetylase inhibitors, and therapies aimed at mutant IDH or EZH2. This review compiles existing information on the epigenetic features of myeloid tumors, emphasizing its importance in disease advancement and treatment strategies.

Keywords: Chromatin remodeling, disease progression, epigenetic alterations, leukemogenesis, myeloid malignancies.

INTRODUCTION

Myeloid malignancies include a varied set of blood disorders that stem from the clonal alteration of hematopoietic stem and progenitor cells. These encompass acute myeloid leukemia (AML), myelodysplastic syndromes (MDS), and myelo-proliferative neoplasms (MPNs), all distinguished by differing clinical manifestations, genetic profiles, and treatment results[1-3]. Traditionally, categorizing diseases depended significantly on morphological evaluation and cytogenetic analysis. Nevertheless, progress in genomic and epigenomic profiling has shown that myeloid malignancies are influenced not only by genetic mutations but also by significant epigenetic dysregulation, which affects cellular identity, differentiation capacity, and disease progression[4,5]. Epigenetics pertains to inheritable modifications in gene expression that take place without changes in the DNA sequence. These modifications encompass DNA methylation, changes in histones, chromatin restructuring, and regulation by non-coding RNAs. In typical hematopoiesis, these processes guarantee correct lineage commitment, self-renewal, and differentiation of progenitor and stem cells. Interference with these regulatory networks may hinder differentiation, enhance the survival of abnormal clones, and foster conditions conducive to leukemic transformation[6].

Alterations in epigenetic regulators like DNMT3A, TET2, IDH1/2, ASXL1, and EZH2 are commonly found in myeloid cancers and typically occur before obtaining further oncogenic changes. These initial epigenetic changes aid in pre-leukemic clonal growth, creating a pool of cells ready for cancerous development. Moreover, epigenetic dysregulation collaborates with genetic abnormalities and environmental signals to enhance genomic instability, intratumoral variability, and resistance to therapy[7].

Crucially, the reversible characteristics of numerous epigenetic alterations offer a distinct chance for therapeutic intervention. Agents like DNA methyltransferase inhibitors, histone deacetylase inhibitors, and mutated IDH or EZH2 inhibitors can influence the epigenetic environment, reinstate normal differentiation processes, and improve chemo-sensitivity[8]. This review compiles existing insights on the epigenetic

framework of myeloid cancers, emphasizing chromatin alteration, its role in disease advancement, and its effects on clinical treatment. Through the integration of findings from molecular and translational research, we seek to establish a detailed framework for comprehending how epigenetic disturbances lead to leukemogenesis and guide precision medicine strategies.

The aim of this narrative review is to synthesize current evidence on epigenetic alterations in myeloid malignancies, emphasizing the role of chromatin remodeling in disease progression, therapeutic resistance, and clinical heterogeneity.

METHODS

This narrative review employed a structured, non-systematic approach to synthesize experimental, clinical, and epidemiological evidence on epigenetic alterations in myeloid malignancies. Literature searches were conducted across PubMed, Scopus, Web of Science, and Google Scholar using combinations of the following terms: myeloid malignancies, epigenetics, chromatin remodeling, DNA methylation, histone modification, SWI/SNF, NuRD, EZH2, DNMT3A, TET2, and IDH1/2. Reference lists of relevant articles were manually screened for additional sources.

Eligible publications included original research, review articles, and mechanistic studies that addressed epigenetic regulation, chromatin remodeling, and clinical implications in AML, MDS, and MPNs. Non-English articles and studies unrelated to epigenetic mechanisms in myeloid disorders were excluded. Data extraction focused on study population, epigenetic mechanism, chromatin remodeling complex involvement, functional consequences on hematopoiesis, and therapeutic relevance. Findings were narratively synthesized to highlight mechanistic pathways, interactions with genetic lesions, and implications for disease progression and treatment.

Epigenetic dysregulation in myeloid malignancies

Epigenetic irregularities are being increasingly acknowledged as a key factor in the development and advancement of myeloid cancers. In contrast to genetic mutations that change the DNA sequence, epigenetic changes affect gene expression via DNA methylation, histone alterations, chromatin remodeling, and non-coding RNA regulation, while leaving the fundamental genomic code unchanged. In typical hematopoiesis, these processes are closely coordinated to regulate stem cell self-renewal, lineage commitment, and differentiation. Interruption of this regulatory network can distort hematopoietic differentiation, promote the survival of abnormal clones, and create a conducive environment for leukemic transformation[10]. Mutations in important epigenetic regulators are a characteristic feature of myeloid cancers. DNMT3A, a DNA methyltransferase, is often mutated in AML and MDS, hindering de novo methylation and permitting the clonal expansion of pre-leukemic hematopoietic cells. Likewise, TET2, responsible for DNA demethylation, is frequently disrupted, leading to abnormal methylation patterns that hinder normal differentiation and elevate the risk of malignant trans-formation. Mutations in IDH1 and IDH2 generate the oncometabolite 2-hydroxyglutarate, which hampers TET2 activity and disrupts DNA methylation balance, connecting metabolic changes to epigenetic misregulation[11].

Chromatin remodeling complexes and enzymes that modify histones are also often impacted. Mutations in ASXL1, frequently seen in MDS and secondary AML, disrupt nucleosome remodeling and transcriptional control, leading to the repression of differentiation genes. Dysregulation of EZH2, a histone methyltransferase, causes abnormal trimethylation of H3K27, inhibiting tumor suppressor genes and promoting leukemic growth. Changes in KMT2A (MLL) and other enzymes that modify histones additionally disturb the equilibrium between activation and repression of transcriptional processes essential for hematopoietic stability[12]. These epigenetic alterations frequently work alongside genetic mutations in oncogenes and tumor suppressors, like FLT3, NPM1, and TP53, establishing an environment favorable for clonal evolution and the advancement of the disease.

Epigenetic changes can occur early in the progression of the disease, aiding the expansion of pre-leukemic clones, or they might be developed later, leading to resistance to treatment and subsequent relapse. The resulting epigenetic diversity leads to differing clinical phenotypes and makes treatment responses more challenging[13]. Significantly, the reversible nature of epigenetic modifications presents distinct therapeutic possibilities. Agents that focus on DNA methylation, histone changes, and chromatin remodeling can promote differentiation, inhibit proliferation, and improve chemosensitivity in myeloid cancers. As we gain deeper insights into the epigenetic landscape, incorporating epigenetic profiling into clinical practice is essential for risk assessment, treatment choices, and developing precision medicine approaches[14].

DNA methylation and myeloid transformation

DNA methylation is a critical epigenetic process that controls gene expression in hematopoietic cells. It mainly entails the incorporation of a methyl group at the 5’ position of cytosine residues in CpG dinucleotides, a change driven by DNA methyl-transferases (DNMTs). In typical hematopoiesis, this mechanism guarantees accurate lineage determination, preserves genomic integrity, and inhibits unsuitable gene expression. The disruption of DNA methylation balance, however, is a characteristic trait of myeloid cancers and plays a key role in the transformation to leukemia[15].

Altered hyper-methylation of promoter CpG islands can mute tumor suppressor genes and differentiation regulators, effectively trapping hematopoietic progenitors in an undifferentiated state and encouraging clonal expansion. In contrast, global hypo-methylation can trigger oncogenes or repetitive sequences, leading to genomic instability and disease advancement. Mutations in DNMT3A, often found in AML and MDS, hinder de novo methylation and establish a favorable epigenetic setting for clonal prevalence. These mutations frequently arise early in the

progression of the disease, identifying pre-leukemic clones that may endure for years prior to obtaining further transformative alterations[16]. Alterations in TET2, responsible for DNA demethylation, additionnally disturb the equilibrium of methylation by hindering the transformation of 5-methylcytosine into 5-hydroxymethylcytosine. Likewise, mutations in IDH1 and IDH2 produce the oncometabolite 2-hydroxyglutarate (2-HG), leading to TET2 activity inhibition and the induction of hypermethylation at regulatory sites. Collectively, these changes disrupt typical differentiation processes, promote the self-renewal of cancerous clones, and aid in the development of leukemia[17]. Abnormalities in DNA methylation are linked to clonal diversity and the advancement of the disease. Different subclones in the same patient may possess varying methylation signatures, leading to diverse gene expression patterns, differing responses to treatment, and unique clinical outcomes. Longitudinal research shows that methylation patterns change over time, especially under selective pressures like chemotherapy, promoting the development of resistant subclones and relapse[18].

Therapeutically, DNA methylation represents a tractable target. DNA methyltransferase inhibitors (DNMTi), including azacitidine and decitabine**,** can reverse aberrant hypermethylation, restore expression of silenced tumor suppressor genes, and induce differentiation of malignant cells. These agents are particularly effective in MDS and AML, including in older patients who may not tolerate intensive chemotherapy. Combination strategies that integrate DNMTi with histone deacetylase inhibitors, targeted therapy, or immunotherapy are under active investigation to enhance efficacy and overcome resistance[19].

Histone modifications and chromatin remodeling in myeloid malignancies

Modifications to histones and alterations in chromatin structure play crucial roles in regulating gene expression, influencing how accessible DNA is to transcriptional factors and consequently affecting cell fate choices. During typical hematopoiesis, dynamic modifications of histones, including methylation, acetylation, phosphorylation, and ubiquitination, orchestrate the processes of differentiation, self-renewal, and proliferation in stem and progenitor cells. Perturbation of these epigenetic pathways is a characteristic of myeloid cancers, leading to hindered differentiation, clonal growth, and leukemic advancement[20].

Alterations in histone modifying enzymes are frequently seen in myeloid neoplasms. For example, gain-of-function mutations in EZH2 increase H3K27 trimethylation, suppress tumor suppressor genes and differentiation-critical genes, thus fostering clonal dominance and leukemic transformation. In the same way, changes in KMT2A (MLL) interfere with H3K4 methylation, resulting in the inappropriate activation of oncogenic transcriptional pathways. Mutations in ASXL1, which is part of the Polycomb Repressive Complex, disrupt chromatin remodeling and transcriptional repression, promoting self-renewal and inadequate differentiation in MDS and secondary AML[21]. Complexes that remodel chromatin, like SWI/SNF and cohesin, are essential for the positioning of nucleosomes and the formation of higher-order chromatin structures. Impairment of these complexes changes gene accessibility, enables faulty transcription, and could lead to genomic instability. These modifications frequently interact with DNA methylation abnormalities and genetic mutations, forming a conducive environment for clonal evolution and resistance to therapy[22].

Table 1: Key epigenetic regulators and their alterations in myeloid malignancies.

Gene / Regulator	Type of Alteration	Functional Consequence	Clinical Relevance
DNMT3A	Loss-of-function mutation	Impaired de novo DNA methylation; clonal expansion	Early pre-leukemic lesions; poor prognosis in AML
TET2	Loss-of-function mutation	Impaired DNA demethylation; blocked differentiation	Associated with MDS, AML, and clonal hematopoiesis; therapy resistance
IDH1 / IDH2	Gain-of-function mutation	2-hydroxyglutarate accumulation; inhibits TET2; hypermethylation	Drives leukemic transformation; targetable with IDH inhibitors
ASXL1	Loss-of-function mutation	Defective chromatin remodeling; transcriptional dysregulation	Common in MDS and secondary AML; adverse prognosis
EZH2	Gain-of-function mutation	H3K27 trimethylation; silencing of differentiation genes	Promotes proliferation and therapy resistance; targetable with EZH2 inhibitors
KMT2A (MLL)	Translocation / mutation	H3K4 methylation dysregulation; aberrant transcription	Associated with aggressive AML; poor clinical outcomes
CREBBP / EP300	Loss-of-function / mutation	Impaired histone acetylation; transcriptional repression	Contributes to blocked differentiation and poor response to therapy
Cohesin Complex (SMC1A, STAG2, RAD21)	Mutation	Altered chromatin architecture; genomic instability	Contributes to clonal evolution and therapy resistance
SWI/SNF Complex	Loss-of-function / mutation	Nucleosome remodeling defects; altered gene accessibility	Promotes clonal expansion and differentiation block
HDACs	Overexpression / dysregulation	Histone hypoacetylation; transcriptional repression	Targetable with HDAC inhibitors; modulates therapy response

Histone acetylation serves as an important process in controlling chromatin dynamics. Altered function of histone acetyl-transferases (HATs) or histone deacetylases (HDACs) disturbs the equilibrium of acetylation marks, resulting in transcriptional inhibition of genes that promote differentiation. This leads to the buildup of immature, proliferating myeloid blasts and facilitates leukemic advancement. Dysregulation of HDAC also interacts with additional signaling pathways, such as PI3K/AKT and NF-κB, which further strengthens malignant characteristics[23].

Clinically, histone modification and chromatin remodeling abnormalities offer actionable therapeutic targets. HDAC inhibitors (e.g., vorinostat, panobin-ostat) and emerging EZH2 inhibitors (e.g., tazemetostat) have demonstrated efficacy in modulating chromatin states, restoring differentiation programs, and enhancing sensitivity to conventional chemotherapies. Targeting chromatin remodelers in combination with DNA methylation inhibitors or pathway-specific therapies represents a promising strategy to overcome clonal heterogeneity and treatment resistance (Table 1)[24].

Epigenetic contributions to disease heterogeneity

Epigenetic dysregulation significantly influences intratumoral heterogeneity in myeloid malignancies, leading to diverse clinical phenotypes, varied therapeutic responses, and disease advancement. In contrast to genetic mutations that change the DNA sequence, epigenetic changes are fluid and reversible, enabling hematopoietic clones to quickly adapt to internal and external pressures, such as treatment and microenvironmental signals[25]. Different subclones in the same patient frequently exhibit varied epigenetic profiles, comprising variations in DNA methylation, histone modifications, and chromatin accessibility. As an illustration, pre-leukemic clones containing DNM T3A or TET2 mutations might exist alongside subclones that display further changes in ASXL1, IDH1/2, or EZH2, resulting in a mosaic of functional and transcriptional states. This epigenetic variation allows subclones to show different rates of proliferation, differentiation abilities, and sensitivity to drugs, making treatment outcomes more complex[26].

Epigenetic variability is tightly connected to clonal development. Under selective pressures like chemotherapy, specific subclones with advantageous epigenetic setups such as inhibited apoptotic pathways or improved stemness programs can endure and proliferate, resulting in relapse. Likewise, dynamic chromatin remodeling can promote the development of therapy-resistant clones by modifying the accessibility of genes related to cell survival, DNA repair, and differentiation[27]. Single-cell and longitudinal epigenomic research have revealed the temporal development of epigenetic diversity in myeloid cancers. At the time of diagnosis, subclones exhibit unique patterns of DNA methylation and histone modifications, which may vary over time due to therapy or disease advancement. These results highlight the significance of epigenetic oversight for the early identification of high-risk subclones and for informing adaptive treatment approaches[28].

Therapeutically, targeting epigenetic heterogeneity offers promising avenues. DNA methyltransferase inhibitors (azacitidine, decitabine)**,** histone deacetylase inhibitors**,** and mutant IDH or EZH2 inhibitors can selectively modify aberrant epigenetic states, restoring differentiation and sensitizing resistant subclones to therapy. Combination approaches that integrate epigenetic modulators with conventional chemotherapy or targeted agents may help overcome subclonal diversity and improve patient outcomes[29].

Therapeutic implications of epigenetic alterations

The elucidation of epigenetic dysregulation in myeloid malignancies has opened new avenues for targeted therapy, transforming clinical management and offering hope for improved patient outcomes. Unlike genetic mutations, epigenetic modifications are reversible, making them particularly attractive therapeutic targets.

Table 2: Therapeutic targets and epigenetic interventions in myeloid malignancies.

Target / Pathway	Therapeutic Agent	Mechanism of Action	Clinical Application
DNA Methylation (DNMTs)	Azacitidine, Decitabine	Inhibit DNA methyltransferase; restore tumor suppressor gene expression	Standard of care for MDS; used in AML (especially older/unfit patients)
Histone Deacetylation (HDACs)	Vorinostat, Panobinostat	Increase histone acetylation; enhance chromatin accessibility	Combination therapy with DNMTi or chemotherapy; promotes differentiation
IDH1 / IDH2 Mutations	Ivosidenib (IDH1), Enasidenib (IDH2)	Restore TET2 function; induce differentiation	Targeted therapy in IDH-mutant AML
EZH2 Dysregulation	Tazemetostat	Inhibit H3K27 trimethylation; reactivate differentiation genes	Investigational in MDS/AML with EZH2 alterations
BET Bromodomain Proteins	OTX015, CPI-0610	Inhibit transcriptional coactivators; downregulate oncogenic programs	Under clinical evaluation in AML
Combination Epigenetic Therapy	DNMTi + HDACi / IDH / EZH2 inhibitors	Target multiple epigenetic mechanisms; overcome resistance	Enhances chemosensitivity; prevents clonal escape
Chromatin Remodelers (SWI/SNF, Cohesin)	Experimental agents	Restore nucleosome positioning and gene accessibility	Preclinical and early-phase trials targeting differentiation and proliferation
Immuno-Epigenetic Modulation	DNMTi + immune checkpoint inhibitors	Epigenetic priming enhances immune response against leukemia	Investigational in AML/MDS

Interventions aimed at restoring normal DNA methylation, histone modifications, or chromatin structure have shown efficacy in modulating disease course and overcoming therapy resistance (Table 2)[30].

DNA Methyltransferase Inhibitors (DNMTi)

Agents such as azacitidine and decitabine inhibit DNA methyltransferase activity, reversing aberrant promoter hypermethylation and reactivating tumor suppressor genes. These drugs induce differentiation of malignant myeloid cells and reduce clonal proliferation. DNMT inhibitors are now standard-of-care for MDS and are widely used in AML, particularly in older or unfit patients, often in combination with targeted therapies[31].

Histone Deacetylase Inhibitors (HDACi)

HDAC inhibitors, including vorinostat and panobinostat, modulate histone acetylation, thereby enhancing chromatin accessibility and promoting transcription of differentiation and apoptotic genes. HDACi therapy can synergize with DNMTi or conventional chemotherapy to overcome resistance and improve clinical responses[32].

Mutant IDH Inhibitors

Mutations in IDH1 and IDH2 disrupt normal DNA and histone demethylation through accumulation of the oncometabolite 2-hydroxyglutarate. Targeted inhibitors ivosidenib (IDH1) and enasidenib (IDH2)- restore TET2 function, induce differentiation, and have demonstrated durable responses in IDH-mutant AML[33].

EZH2 and other chromatin-modifying enzyme inhibitors

Gain-of-function mutations in EZH2 or dysregulation of other histone-modifying enzymes contribute to transcriptional repression of differentiation genes. EZH2 inhibitors (e.g., tazemetostat) have shown efficacy in preclinical models and early clinical trials, particularly in MDS and AML subtypes with epigenetic lesions[34].

Combination and precision therapies

The epigenetic heterogeneity of myeloid malignancies, combination therapies targeting multiple epigenetic regulators alongside conventional chemotherapy, immunotherapy, or targeted molecular agents may maximize efficacy and prevent clonal escape. Precision medicine approaches, guided by genomic and epigenomic profiling, allow for tailored interventions, identification of high-risk subclones, and dynamic adaptation of therapy to prevent relapse[35].

Emerging approaches

Novel strategies, including BET bromodomain inhibitors**,** histone methyltransferase inhibitors**,** and epigenetic modulators combined with immunotherapy, are under investigation. These approaches aim to remodel the epigenetic landscape comprehensively, overcome resistance mechanisms, and enhance the immune-mediated eradication of malignant clones[36].

CONCLUSIONS

Epigenetic disruption is a key factor in myeloid cancers, facilitating clonal growth, hindered differentiation, and progression of the disease. Alterations in DNA methylation, histone changes, and chromatin restructuring interfere with typical hematopoietic processes, facilitate leukemogenesis, and play a role in intratumoral diversity and resistance to therapy. Alterations in important epigenetic regulators like DNMT3A, TET2, IDH1/2, ASXL1, and EZH2 typically happen early in the progression of the disease, forming pre-leukemic clones that pave the way for later genetic and epigenetic changes. The reversible characteristics of epigenetic changes provide distinct treatment possibilities. Agents that focus on DNA methylation, histone deacetylation, and altered epigenetic enzymes have shown effectiveness in promoting differentiation, decreasing clonal expansion, and improving chemosensitivity. Incorporating epigenetic profiling into clinical practice allows for precision medicine tactics, assists in risk stratification, and guides adaptive treatment methods designed to address resistance.

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AUTHOR'S CONTRIBUTION

Obeagu EI: conceived the idea, writing the manuscript, literature survey. **Musimwa I:** formal analysis, data processing. Final manuscript was checked and approved by both authors.

DATA AVAILABILITY

The empirical data used to support the study's conclusions are available upon request from the corresponding author.

CONFLICTS OF INTEREST

The authors declare no conflict of interest

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