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Review Article

ROLE OF EPIGENETIC MODIFICATIONS IN THE PATHOGENESIS OF LEUKAEMIA: A NARRATIVE REVIEW

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ABSTRACT
Epigenetics refers to heritable changes in gene expression that occur without altering the underlying DNA sequence. Mechanisms such as DNA methylation, histone modifications, and non-coding RNAs regulate key cellular processes, including development, differentiation, and responses to environmental stimuli. Dysregulation of these mechanisms has been strongly linked to the pathogenesis of leukaemia, a diverse group of blood cancers characterised by uncontrolled proliferation of abnormal white blood cells. Aberrant DNA methylation, including hypermethylation of tumour suppressor genes and global hypomethylation, is frequently observed in both acute and chronic leukaemias. Alterations in histone modifications disrupt chromatin structure, influencing transcriptional regulation of genes essential for cell cycle control and apoptosis. In addition, non-coding RNAs such as microRNAs and long non-coding RNAs contribute to leukemogenesis by modulating oncogenic and tumour suppressor pathways. These epigenetic abnormalities are now recognised as active drivers of disease onset and progression, with distinct patterns across leukaemia subtypes, including acute myeloid leukaemia, acute lymphoblastic leukaemia, chronic myeloid leukaemia, and chronic lymphocytic leukaemia. Importantly, epigenetic insights are guiding the development of diagnostic biomarkers and novel therapies, such as DNA methyltransferase and histone deacetylase inhibitors. This narrative review highlights the role of epigenetic modifications in leukaemia pathogenesis.

Keywords: Epigenetics, Methylation, Histones, MicroRNAs, Leukemogenesis, Therapy

INTRODUCTION

Epigenetics is the study of heritable changes in gene expression that occur without alterations to the underlying DNA sequence. These changes are regulated through mechanisms such as DNA methylation, histone modifications, and non-coding RNAs, which act collectively to determine how genes are activated or silenced within cells (Kumsta, 2019). By shaping transcriptional programs, epigenetic modifications play essential roles in development, cell differentiation, and responses to environmental cues (Prasha *et al*., 2020). Over the past two decades, epigenetics has become increasingly recognised as a central player in human health and disease, particularly in complex disorders such as cancer, where both genetic and epigenetic factors drive disease onset and progression (Ntontsi *et al*., 2021).

Among cancers, leukaemia provides a clear example of how epigenetic dysregulation contributes to pathogenesis (Ntziachristos *et al*., 2016). Leukaemia is a diverse group of haematological malignancies characterised by the uncontrolled proliferation of abnormal white blood cells in the bone marrow and peripheral blood (Choi *et al*., 2024). While early research focused mainly on genetic mutations as the basis of leukaemogenesis, it is now evident that epigenetic alterations are equally important in shaping the disease course (Goldman *et al*., 2019). Abnormal DNA methylation patterns, including hypermethylation of tumour suppressor genes and global hypomethylation of the genome, have been consistently reported in both acute and chronic leukaemias (Blecua *et al*., 2020). Likewise, disruptions in histone modification landscapes alter chromatin accessibility and gene transcription, influencing key pathways involved in cell cycle control and apoptosis (Kim *et al*., 2019). In addition, non-coding RNAs, such as microRNAs and long non-coding RNAs, are increasingly recognised as regulators of hematopoietic development and mediators of therapy resistance (Bhat *et al*., 2020). In this review, we aim to synthesise current evidence on the role of epigenetic modifications in the pathogenesis of leukaemia by highlighting the molecular mechanisms involved and their clinical implications.

MATERIALS AND METHODS

The study adopted a narrative review methodology. This design was chosen to discuss existing literature on the role of epigenetic modifications in the pathogenesis of leukaemia, and the need to bring the evidence together to provide information for researchers. This review relied on information available on electronic databases, including PubMed, Google Scholar, Scopus, and Web of Science, using a non-systematic search strategy. The review made use of published information, and the study authors were only contacted when the full text of the studies was not directly available online. The search strategy used a combination of subject headings, keywords and Boolean operators. The keywords included *epigenetics, DNA methylation, histone modifications, non-coding RNA, leukaemia,* and *leukemogenesis*. Additional relevant articles were identified by manually screening the reference lists of selected publications. Articles were included based on their scientific relevance, clarity, and contribution to understanding epigenetic mechanisms in leukaemia. No strict inclusion or exclusion criteria were applied, and data were synthesised qualitatively, with findings organised in a thematic and structured manner.

LEUKAEMIA

Leukaemia is a malignant disorder that arises in the blood-forming organs, primarily the bone marrow and lymphatic system. It is defined by the uncontrolled proliferation of abnormal white blood cells, which normally play a central role in immune defence (Hemalatha *et al*., 2025). The excessive production of these defective cells suppresses the growth of normal blood components, resulting in immune dysfunction, anaemia, and bleeding tendencies. Clinically, leukaemia may manifest in acute or chronic forms and is further classified according to the specific lineage of white blood cells involved. Common clinical features include

persistent fatigue, recurrent infections, easy bruising, lymphadenopathy, and unexplained weight loss (Sankar and Villa, 2021). Therapeutic strategies typically include chemotherapy, radiation, molecularly targeted agents, and stem cell transplantation, with treatment tailored to the disease subtype and progression. Despite notable advances in therapy that have improved patient outcomes, leukaemia continues to be a major global health burden, often associated with high morbidity and mortality (Bair *et al*., 2020). In 2018, it ranked as the fifteenth most frequently diagnosed cancer worldwide, with an estimated 437,033 new cases and 309,006 deaths, placing it as the eleventh leading cause of cancer-related mortality (Tebbi, 2021). While the incidence is higher in developed regions, death rates remain disproportionately elevated in developing countries (Sharma and Jani, 2022).

Risk Factors of Leukaemia

The root causes of the different types of leukaemias remain largely unknown; however, several risk factors have been identified that increase susceptibility to the disease and its progression to fatal stages. Prior chemotherapy is one such factor, as exposure to cytotoxic agents can induce secondary malignancies. Inherited syndromes also play a role, with certain genetic predispositions increasing vulnerability to leukaemogenesis. Environmental and lifestyle factors, such as ionising radiation, smoking, alcohol consumption, and occupational exposure to harmful chemicals, have been implicated in elevating risk. Infectious agents, notably the Human T-cell leukaemia virus type I (HTLV-I), are associated with specific subtypes of the disease (Bispo *et al*., 2020). In addition, individuals with pre-existing haematological disorders such as myelodysplastic syndrome are at heightened risk of developing leukaemia. Finally, family history and advancing age have consistently been recognised as significant contributors, underscoring both genetic and age-related vulnerabilities in disease pathogenesis (Lin *et al*., 2020).

Acute Lymphoblastic Leukaemia

Acute lymphoblastic leukaemia (ALL) represents the most prevalent childhood cancer, accounting for nearly one-quarter to one-third of all paediatric malignancies. In the United States, the disease occurs at an estimated rate of 4.6 cases per 100,000 children aged 0–14 years, with the highest incidence observed between ages 2 and 5. Interestingly, during infancy, the occurrence is marginally higher in females compared to males (Malard and Mohty, 2020). A variety of environmental exposures have been implicated in its development, including parental preconception factors, in utero and postnatal exposure to ionising radiation, as well as contact with non-ionising radiation, pesticides, hydrocarbons, and other chemicals. Lifestyle-related influences, such as parental smoking, alcohol intake, and illicit drug use, have also been examined for their contribution to risk. Beyond environmental influences, genetic predisposition plays a fundamental role in ALL pathogenesis. Evidence from studies of identical twins demonstrates a strong concordance, showing the role of inherited or early genetic alterations (Lin *et al*., 2020). Notably, some cases are believed to originate in utero, driven by leukemogenic chromosomal translocations or fusion gene events. Furthermore, siblings of affected children exhibit an elevated, though relatively small, risk of developing the disease (Smith and Spector, 2024).

Acute Myeloid Leukaemia (AML)

Acute myeloid leukaemia (AML) shows a bimodal pattern of incidence, with cases most commonly appearing in early childhood and again in later adulthood. The typical age at diagnosis is around 66 years, although the condition can arise across all age groups. Nonetheless, it remains uncommon in individuals younger than 40 years. The aetiology of AML is unclear. A significant amount of information and knowledge concerning leukemogenic agents, especially chemotherapy regimens used for the treatment of a variety of malignant disorders, has accumulated (Shallis *et al*., 2019). Associations of certain molecular pathogenesis such as t (8;21) translocation and inversion of chromosome 16 in AML, have been reported (Raj *et al*., 2022). In addition to genetic mutations, epigenetic mechanisms also play an important role in the development of AML, with promoter hypermethylation of genes such as p15/INK4b leading to their silencing and progression of the disease. Research also suggests that specific genetic abnormalities may increase susceptibility to AML, particularly in children (Goldman *et al*., 2019). Furthermore, individuals with inherited conditions like Down syndrome have a significantly higher risk of developing malignant disorders, including AML. For example, children with Trisomy 21 have a 10- to 20-fold increased potential of developing acute leukaemia, mostly AML (Laurent *et al*., 2020).

Chronic Lymphocytic Leukaemia

Chronic lymphocytic leukaemia (CLL) is the most frequently diagnosed leukaemia in adults across Western countries, representing nearly a quarter of all leukaemia cases and occurring in about 4.1 per 100,000 individuals in the United States (Hallek, 2019). The disease primarily arises from B lymphocytes (B-CLL) and is strongly linked to the overexpression of the anti-apoptotic protein Bcl-2, seen in the majority of cases (Ko *et al*., 2021). A smaller subset of patients develops leukaemia from T lymphocytes (T-CLL), in which p53 mutations have been documented; this subtype generally responds poorly to treatment (Bosch and Dalla-Favera, 2019). The World Health Organisation now classifies T-CLL under T-cell prolymphocytic leukaemia (PLL). Unlike most forms of leukaemia, CLL is not associated with exposure to ionising radiation, drugs, or chemicals. However, family studies indicate a hereditary component, with 5–10% of cases occurring among relatives of affected individuals (Hussein *et al*., 2021). Clinically, patients often present with symptoms such as fatigue, weight loss, and night sweats, along with lymphadenopathy, splenomegaly, and hepatomegaly. On a molecular level, alterations in B-cell maturation, particularly somatic hypermutation of the immunoglobulin heavy chain variable region (IgVh) within lymphoid follicles, play a critical role in disease progression (Ko *et al*., 2021).

Chronic Myeloid Leukaemia

Chronic myeloid leukaemia (CML) is an uncommon haematological malignancy, accounting for approximately 14% of all leukaemia cases and about one-fifth of adult leukaemias globally. Its annual incidence is estimated at 1.6 per 100,000 adults, with a male-to-female ratio of roughly 1.4:1 in the United States (Kantarjian *et al*., 2019). The likelihood of developing CML rises markedly with advancing age, with the median age at diagnosis reported between 65 and 67 years. In contrast, the disease is exceptionally rare in paediatric populations. Current evidence indicates that CML is neither inherited nor preventable, as no hereditary, familial, geographic, ethnic, or socioeconomic links have been identified.

Furthermore, unlike many other cancers, there is no strong evidence implicating chemical exposure or genetic predisposition in the development of CML. Ionising radiation in high doses is the only known risk factor (Rühm *et al*., 2022). CML can also be due to a reciprocal chromosomal translocation, which involves the ABL1 proto-oncogene on chromosome 9 and the BCR gene (i.e., the breakpoint cluster region) on chromosome 22 to form the Philadelphia chromosome (Kantarjian *et al*., 2019).

MECHANISMS OF EPIGENETIC DYSREGULATION IN LEUKAEMIA

DNA Methylation Alterations

Leukaemia often exhibits aberrant DNA methylation patterns, encompassing both hypermethylation of promoter regions in tumour suppressor genes and hypomethylation of oncogenes. Promoter hypermethylation typically results in the transcriptional silencing of tumour suppressor genes, such as p15INK4B and p16INK4A, which play critical roles in cell cycle regulation (Giacopelli *et al*., 2021). Conversely, hypomethylation of oncogenes, like MYC and RAS family members, can lead to their overexpression and contribute to Leukaemogenesis (Nagaraja and Nagarajan, 2021). These alterations in DNA methylation status are often attributed to dysregulated DNA methyltransferases (DNMTs) or ten-eleven translocation (TET) enzymes, which are involved in DNA methylation and demethylation processes, respectively (Gerecke *et al*., 2022).

Histone Modifications

Epigenetic abnormalities in leukaemia are not limited to DNA methylation but also extend to disruptions in histone modifications, which are crucial for regulating chromatin organisation and gene transcription. Leukaemic cells frequently exhibit abnormal patterns of histone acetylation and methylation. Acetylation of histones, mediated by histone acetyltransferases (HATs), is generally linked to the activation of gene expression as it loosens chromatin and promotes accessibility for transcription factors (Liu *et al*., 2020). In contrast, histone methylation has a more complex role, functioning either to enhance or suppress gene activity depending on the specific amino acid residue modified and the extent of methylation present. Dysregulated histone-modifying enzymes, such as histone deacetylases (HDACs), histone methyltransferases (HMTs), and histone demethylases (HDMs), contribute to these alterations, leading to perturbed gene expression profiles associated with Leukaemia pathogenesis (Jambhekar *et al*., 2019).

Non-coding RNA Dysregulation

Abnormal regulation of non-coding RNAs, including microRNAs (miRNAs) and long non-coding RNAs (lncRNAs), plays a significant role in the onset and advancement of leukaemia (Bhat *et al*., 2020). MiRNAs, which primarily act as post-transcriptional modulators of gene expression, can function either as oncogenes or tumour suppressors depending on the specific genes they target. Dysregulated levels of particular miRNAs, such as miR-155 and the miR-17-92 cluster, have been implicated in leukaemogenesis through their influence on genes controlling cell proliferation, apoptosis, and differentiation (Anelli *et al*., 2021). Likewise, lncRNAs can regulate gene activity through multiple mechanisms, including chromatin remodeling, transcriptional modulation, and RNA processing. Altered expression of lncRNAs, including HOTAIR and MALAT1, has been linked to leukaemia initiation, disease progression, and resistance to therapy (Statello *et al*., 2021).

EPIGENETIC MODIFICATION IN LEUKAEMIA

Acute Lymphoblastic Leukaemia

DNA methylation patterns are often altered in ALL, with hypermethylation of tumour suppressor genes like CDKN2A, leading to their silencing and contributing to uncontrolled cell growth (Alshammari *et al*., 2022). Histone modifications, such as reduced levels of acetylation, particularly on histone H3 and H4, are associated with gene repression in ALL. This can lead to the silencing of tumour suppressor genes and other critical regulatory genes (Zaib *et al*., 2022). Additionally, non-coding RNAs, including specific microRNAs like miR-155 and miR-708, are dysregulated, further influencing the expression of genes involved in cell cycle regulation and apoptosis. The chromatin structure is frequently remodeled due to mutations in chromatin remodeling genes, leading to aberrant gene activation or repression. Understanding these epigenetic changes in ALL offers potential avenues for therapies that can reverse these modifications and restore normal cellular function (Pierouli *et al*., 2022).

Acute Myeloid Leukaemia (AML)

Acute Myeloid Leukaemia (AML) involves the rapid growth of abnormal myeloid cells, with epigenetic dysregulation being a significant factor in its development (Shallis *et al*., 2019). DNA hypermethylation of promoters in genes such as CDKN2B and CEBPA silences these critical regulators of cell differentiation and proliferation. Aberrant histone modifications are also prevalent, with altered acetylation and methylation patterns impacting the expression of genes essential for myeloid differentiation. Global reductions in histone acetylation levels, leading to more condensed chromatin and reduced gene expression, are commonly observed in AML (Yang *et al*., 2019). The involvement of non-coding RNAs, particularly microRNAs like miR-29b and miR-181a, modulates gene expression post-transcriptionally, contributing to leukemic transformation. Chromatin remodeling defects, including mutations in genes like DNMT3A and TET2, disrupt normal chromatin dynamics and gene expression profiles. These epigenetic abnormalities highlight potential therapeutic targets, such as DNMT inhibitors and histone deacetylase inhibitors, aiming to correct the epigenetic landscape in AML (Yang *et al*., 2019).

Chronic Myeloid Leukaemia (CML)

Chronic Myeloid Leukaemia (CML) is driven by the BCR-ABL fusion gene, with epigenetic modifications contributing to disease progression (Kantarjian *et al*., 2019). DNA methylation changes, including hypermethylation of the p15INK4B and p16INK4A genes, result in the repression of tumour suppressor functions, facilitating leukaemic cell proliferation (Bhootra *et al*., 2023). Histone modifications are also dysregulated, with altered acetylation and methylation patterns affecting the expression of genes involved in cell differentiation and proliferation. The BCR-ABL fusion protein can alter histone modifications indirectly by affecting signaling pathways (like the JAK/STAT and RAS/MAPK pathways) that regulate histone-modifying enzymes, leading to changes in histone acetylation and methylation patterns (Amarante-Mendes *et al*., 2022). Non-coding RNAs, such as miR-203 and miR-29, are involved in regulating key pathways associated with CML pathogenesis, including the suppression of BCR-ABL expression. Chromatin remodeling defects, including mutations in ASXL1 and other chromatin modifiers, further increase the disruption of normal

gene expression and chromatin architecture. Epigenetic therapies, including histone deacetylase inhibitors and DNA methyltransferase inhibitors, are being explored to restore normal epigenetic regulation and improve therapeutic responses in CML (Bansal *et al*., 2024).

Chronic Lymphocytic Leukaemia (CLL)

Chronic lymphocytic leukaemia (CLL) is marked by the build-up of functionally defective lymphocytes, with epigenetic alterations playing a pivotal role in disease development. Irregular DNA methylation, including hypermethylation of promoters in genes such as DAPK1 and TCL1, results in the suppression of critical genes that regulate apoptosis and cell cycle progression (Chatzidavid *et al*., 2024). In addition, modifications to histone proteins, including changes in acetylation and methylation patterns, further disturb gene expression and the organisation of chromatin. Dysregulation of histone H3 lysine 4 trimethylation (H3K4me3), a mark typically linked to active transcription, contributes to abnormal gene activation or repression in CLL, highlighting the importance of epigenetic mechanisms in shaping the molecular landscape of this disease. Also, increased activity of histone deacetylases (HDACs) leads to reduced acetylation of histone proteins, promoting chromatin compaction and gene silencing (Hartmann *et al*., 2020). Non-coding RNAs, particularly miRNAs like miR-15a and miR-16-1, are dysregulated, affecting the expression of genes involved in B-cell receptor signaling and apoptosis. Chromatin remodeling is also impaired due to mutations in genes such as ATM and TP53, leading to aberrant chromatin accessibility and transcriptional regulation. Targeting these epigenetic alterations with therapies such as HDAC inhibitors and DNA methylation inhibitors holds promise for improving outcomes in CLL (Zhang and Li, 2022).

Conclusion

Epigenetic modifications play an important role in the pathogenesis and progression of various forms of Leukaemias. These modifications, such as DNA methylation, histone modification, and non-coding RNA dysregulation, impact gene expression and cellular behaviour without altering the underlying DNA sequence. It is necessary to understand these epigenetic mechanisms to gain valuable insights into Leukaemias and discover potential targets for innovative therapies aimed at correcting these dysregulated epigenetic states, ultimately improving treatment outcomes for leukaemia patients.

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