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The Impact of Epigenetics on Leukemia and Current Target Therapy.

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ABSTRACT

Epigenetics is the study of how gene expression is regulated by factors other than the DNA sequence itself. Unlike genetic changes, epigenetic changes are reversible and do not change the DNA sequence but change how the body reads the sequence if more methylation is involved. Leukaemia is a type of blood cancer that affects the production and maturation of white blood cells caused by genetic mutations, chromosomal abnormalities, and epigenetic changes that disrupt the normal regulation of haematopoiesis. DNA methylation, histone modifications, and non-coding RNAs are the main epigenetic mechanism that influences the development and function of different cell types, as well as their response to environmental stimuli. These mechanisms affect the way leukaemic cells communicate with the surrounding components of the tumour, and the immune microenvironment, and play key roles in leukaemia progression. It is becoming more and more obvious that abnormal post-translational modifications, in addition to genetic mutations, have resulted in DNA changes, linked to leukaemogenesis. This review aims to evaluate the epigenetic mechanism and targeted therapy using organic food elements such as Curcumin (Turmeric), Genistein (Soybean), Tea Polyphenols (Green Tea), Resveratrol (Grapes), and Sulforaphane (Cruciferous Vegetables) to obliterate leukaemia.

Keywords: Epigenetic; Leukaemia; Target Therapy, Gene Silencing and Gene Activation

INTRODUCTION

The term “leukaemia” refers to a group of malignant conditions characterized by elevated leucocyte counts in the bone marrow or blood, based on the rate at which cells proliferate and the type of cell they originated from, leukaemias can be categorized as either acute or chronic. Acute Myeloid Leukaemia (AML), Chronic Myeloid Leukaemia (CML), Acute Lymphoblastic Leukaemia (ALL), and Chronic Lymphocytic Leukaemia (CLL) [1].

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Acute Lymphoblastic Leukaemia (ALL) is most common in early childhood and rare in adults, whereas Acute Myeloid Leukaemia (AML) is less common than ALL in children but becoming more common in older adults, while they can present at any age, different forms have very different age distributions [1]. With a median diagnosis age of over 70 years, CLL is the most common form of leukaemia in the Western world and is almost exclusively found in people over 40. CML is extremely rare in young children. and with a median diagnosis age of over 70 years. Males are more likely than females to have ALL, and the disease is more prevalent in some ethnic groups than others, with Hispanic people having the highest prevalence [1]. Mature white blood cells are the source of some less common variations, including mature B-cell and T-cell leukaemia, and NK cell-related leukaemia. Nonspecific symptoms may include fever, exhaustion, loss of weight, pain in the bones, bruises, or bleeding [2].

Global Cancer Trends Observatory GLOBOCAN reported 474,519 cases globally, with 67,784 cases in North America. It was reported to be 3.40/100,000 in the West African region [3]. and 2.3% in Nigeria in Africa. The mortality rate is roughly 3.2 of all cancer cases and the age-standardized rates are about 11 per 100,000.[4],[5]. It is still unclear what causes leukaemia specifically. Leukaemia can arise from several causes, the most common of which are genetic mutations, epigenetic lesions, ionic radiation, chemical and other occupational exposures, smoking, prescription medications, and certain viral agents [6].

These risk factors differ among populations of different ages, genders, and geographic locations. These differences may be caused by variations in the prevalence of various environmental and genetic risk factors for leukaemia [7],[8],[9],[10]. Genetic risk factors have been identified, and these include Klinefelter and Down syndromes, ataxia telangiectasia, Bloom syndrome, and telomeropathies like Fanconi anaemia, dyskeratosis congenita, and Schwachman-Diamond syndrome; germline mutations in RUNX1, CEBPA, to mention a few. Risk factors that are not genetic include Acute leukaemia has also been linked to viral infections related to the Epstein Barr virus, the human T-cell lymphotropic virus, radiation therapy, ionizing radiation exposure, exposure to benzene in the environment, history of smoking, history of chemotherapy with alkylating agents, and topoisomerase II agents [10]. The term “epigenetics” refers to the dynamic molecular alterations that are deposited on chromatin in the nucleus of a cell. These alterations have the functional consequence of controlling various DNA-related processes, including RNA transcription and splicing, DNA repair, and chromatin organization. Heritable aspects of a cellular phenotype that were unaffected by variations in DNA sequence were first described as epigenetics. As a result of countless research and enlightened viewpoints, chromatin-based reactions that control DNA-template processes are now defined by epigenetics [11].

Since the advent of epigenetic techniques, research has shown how the epigenome affects leukaemia and examined the function of epigenetic regulation in haemopoiesis. Therefore, the purpose of this review is to elucidate the use of organic food elements for epigenetic therapeutic targets as hypomethylating agents, histone deacetylase inhibitors, inhibitors of histone methyltransferases and demethylases which are used to obliterate leukaemia [11].

DNA methylation, chromatin structure changes, and noncoding RNA are the main epigenetic mechanisms [2]. One important epigenetic regulation mechanism in haematologic malignancies is DNA methylation. Certain DNA methyl transferases and other regulators, which are frequently impacted by genetic changes, regulate the methylation process. Tumour suppressor gene global hypo- and hypermethylation are linked to the onset and spread of haematologic cancer [12].

MECHANISM OF EPIGENETIC

Epigenetic mechanisms involve alterations such as DNA methylation, histone modification, and non-coding RNA regulation. These changes impact gene expression without altering the DNA sequence itself,

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influencing cellular function and disease outcomes [13].

Histone modifications, noncoding RNA, and DNA methylation are the main epigenetic mechanisms [14]. The ability of epigenetic modifications to be passed down through generations (via meiotic inheritance) and between mother and daughter cells (through mitotic inheritance) is a crucial characteristic. Epigenetics is one theory that explains why cells and organisms with the same DNA can have phenotypic differences. Researchers have found correlations between lifestyle and disease risk [15]. These correlations may be explained by intriguing developments in the field of epigenetics, as diet and environmental exposures can modify the extent and level of epigenetic regulation. Furthermore, it has been shown that epigenetic control of gene expression plays a critical role in the aetiology of many diseases, most notably cancers [16].

DNA methylation:

When it was discovered that DNA is the hereditary material found in mammals, DNA methylation was initially identified in pneumococcal types [14]. DNA methylation is the addition of a methyl group to the cytosine's carbon-5 position, resulting in 5-methylcytosine (5mC) [16]. The DNA methyltransferase (DNMT) enzymes typically methylate DNA at the cytosine-guanine dinucleotide (CpG) sites. Several different enzymes are involved in DNA methylation, and they fall into three categories according to the type of modification they catalyse, these are Writers, Readers, and Erasers [17].

DNA methylation is precisely regulated by the balance between writers, readers, and erasers; dysregulation of this balance leads to several diseases, including cancer. [17].

Writers: When methyl groups are added to cytosine bases, DNA methyltransferases (DNMTs) specifically target the cytosines that come before guanines, resulting in CpG dinucleotides. The enzymes are as follows: DNMT1 maintains preexisting methylation patterns during DNA replication, while DNMT3A and DNMT3B create new methylation during cellular differentiation and development. [17].

Readers: Methyl-CpG-binding domain (MBD) proteins function as readers by identifying and attaching to methylated CpG sites. To control chromatin structure and gene expression, MBD proteins enlist the aid of additional factors. Depending on the situation, they can either repress or activate transcription [18].

Erasers: The main demethylases are called ten-eleven translocation (TET) enzymes. Like the Jumonji C (JMJC) domain-containing proteins, they can directly remove methyl groups from cytosines and oxidize 5-methylcytosine (5-mC) to 5-hydroxymethylcytosine (5-hmC) and other derivatives. They also start active DNA demethylation [19].

DNA methylation in the overall cancer cells:

Numerous illnesses, such as cancers, inflammatory diseases, and precancerous conditions, interfere with normal epigenetic processes. In general, these diseases are characterised by global hypo- or hypermethylation of the genome along with localised hyper- or hypomethylation of CpG islands in the DNA. Dysregulation of pathways is caused by aberrant expression combined with a loss of DNA methylation of repeat and transposable elements. The inhibition of tumour-suppressor genes and functional genes is associated with the hypermethylation of unmethylated promoter CpG islands. On the other hand, CpG-poor regions in CpG island shores or enhancers typically undergo methylation in cancer cells, and the hypomethylation of methylated promoter CpG islands is linked to the activation of oncogenes [20].

The change of DNA methylation in Leukemia:

Numerous investigations have revealed that leukaemic stem cells (LSCs) ability to proliferate and function

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is significantly influenced by DNA methylation patterns in regulatory regions. The methylation level of methyltransferase genes themselves and mutations of methyltransferase or demethylase genes are the two main ways that the change in DNA methylation in haematologic malignancies is often observed [21].

Histone Modifications.

These primarily consist of phosphorylation, methylation, and acetylation. Histone modifications in normal haematopoiesis: the chromatin configuration changes from the condensed repressive status to the open active status due to posttranslational modifications of amino acids, particularly lysine, at the N-terminal tail of the histone-core. Histone modifications include acetylation, methylation, phosphorylation, ubiquitylation, sumoylation, and ADP ribosylation, to name just sixteen. Acetylation, methylation, and phosphorylation are the three histone modifications most crucial for haematopoiesis and haematologic malignancy oncogenesis [22].

The change of histone acetylation pattern in Leukemia.

Chromatin immunoprecipitation sequence (ChIP-seq), which reveals histone acetylation at promoters and enhancers of actively transcribed genes, shows that acetylation lowers the positive charge of lysins, which in turn weakens the interaction between histones and negatively charged DNA, resulting in an open active euchromatin status [23]. Condensed repressive heterochromatin status results from histone deacetylase (HDAC) erasing the acetyl group from lysine in the N-terminus. This amplifies the positive charge of lysine and strengthens the interaction between histones and the negatively charged DNA [24]. HDAC and histone lysine acetyltransferase (HAT) modestly oppose each other to maintain the balance of haematopoiesis. Normal erythropoiesis is regulated by acetylation levels of H3 and H4, which are increased by recruiting HAT to the β-globin locus by erythroid-stimulating transcription factors like GATA-1. This upregulates globin during erythropoiesis. Malignancies arise when epigenetic dysregulation leads to aberrant expression of wild-type or chromosomal-fused transcription factors, disrupting the balance of haematopoiesis [25].

Histone modification Writers:

Histone acetylation is catalyzed directly by histone acetyltransferases. There are two categories for HATs. The five families of type A HATs—p300/CBP, MYST, GNAT, general transcription factor/orphan HAT, and Steroid Receptor Coactivator/Nuclear Receptor Coactivator (SRC/NCoA)—are mostly nuclear. HAT1 and other Type B HATs are primarily cytoplasmic. The most important HATs in the oncogenesis of haematologic malignancies are the p300/CBP family and the MYST family, which together make of the numerous HAT families [26]. Histone methylation is directly catalysed by histone methyltransferases. Lysine methyltransferases (KMTs) and protein arginine methyltransferases (PRMTs) are the two primary categories of histone methyltransferases. The KMT2, KMT6, NSD, and KMT1 families make up the majority of KMTs. Catalysing the methylation of H3K4 are members of the KMT2 family, namely KMT2A (also called MLL1), KMT2B (also called MLL2), KMT2C (also called MLL3), KMT2D (also called MLL4), KMT2F (also called SETD1A), and KMT2G (also called SETD1B). During haematopoiesis, MLL is necessary for lineage differentiation and proliferation. MLL can inhibit genes by enlisting HDACs and Polycom group (PcG) proteins in addition to activating genes by methylating H3K4 and attracting HAT.389-Numerous haematologic malignancies have been reported to harbour recurrent mutations and fusion proteins related to MLL. On the one hand, KMT2A mutations have been linked to high-grade B-cell lymphoma (14%), T-ALL (5.6%), and AML (2.5%) [27].

Histone modification Readers:

Histone acetylation is detected by acetyl-lysine binding proteins, which then mediate the subsequent reactions. The bromodomain (BRD), a highly conserved binding domain, is one of the readers of histone

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lysine acetylation. The BRD2, BRD3, BRD4, and BRD members of the bromodomain and extra terminal (BET) family are among the most studied and sought-after readers. Few research, nevertheless, has demonstrated how BET family genetic changes contribute to the oncogenesis of haematologic malignancies. Further research is necessary as there is insufficient evidence to support the idea that histone acetylation readers contribute to haematologic malignancies [28].

The PHD finger was discovered to read H3K4me2/3 and inhibit its removal at various lineage differentiation transcription factors in Nucleoporin 98-PHD (NUP98-PHD) (Plant Homeodomain Finger, PHF or JARID1A) fusion AML. This resulted in persistent activation of Hox, Pbx1, and Gata3 transcription factors and leukaemogenesis. Leukaemogenesis was demonstrated to be hindered by mutations in PHD fingers that blocked H3K4me2/3 reading, demonstrating the critical role that methyl reading plays in leukaemogenesis [29].

Histone modification Erasers:

Already acetylated are removed by histone deacetylases. There are four classes of HDACs: class I, class II, and class IV are zinc-dependent classic HDACs, and class III is a NAD+-dependent non-classic HDAC. Based on sequence homology to yeast deacetylases, the three classes of classic HDACs can be separated. Class I histone deacetylases (HDACs) comprise HDAC1, HDAC2, HDAC3, and HDAC8. They are primarily found in the nucleus and are homologous to reduced potassium dependency-3 (Rpd3) [30]. These HDACs regulate transcription and proliferation by forming multiprotein complexes. Histone deacetylase-1 (Hda1) is homologous to class II HDACs. HDACs of class IIa, such as HDAC4, HDAC5, HDAC7, and HDAC9, are translocated between the cytoplasm and the nucleus. Compared to nucleus-localising class IIb HDACs, such as HDAC6 and HDAC10, which have two catalytic domains, class IIa HDACs only have one catalytic domain and are less capable of deacetylation. Class IV HDACs are found in the nucleus and have a homologous sequence with both Rpd3 and Hda1. HDAC11 is the only HDAC in class IV, and it is the smallest of the different HDACs. SIRT1–7 make up the non-classic class III HDACs [24]. Histone methylation is eliminated by histone demethylases. Two groups comprise the lysine demethylases (KDMs) that have been studied the most. The first group, which can only demethylate mono-or dimethyl-lysine, needs an amine oxidation reaction that uses flavin adenine dinucleotide (FAD) as a cofactor. The second category, known as Jumonji demethylase, is capable of methylating mono-, di-, and trimethyl-lysine and depends on oxidation and radical attack, such as α-ketoglutarate [22].

Histone phosphorylation and hematologic malignancies

Haematologic malignancies show less evidence of histone phosphorylation than acetylation and methylation. Typically occurring on threonine, tyrosine, and serine residues, histone phosphorylation is involved in several important cellular processes, such as transcription, apoptosis, DNA repair, and replication. Hetero-phosphorylating enzymes (kinases) also promote signal transduction. It is commonly found that MPN, ALL, and AML are associated with mutations in Janus Kinase 2 (JAK2). Phosphorylation of H3Y41 by JAK2 was observed to cause disruptions in the binding of the chromatin repressor Heterochromatin proteins 1α (HP1α) and to activate the Lmo2 oncogene to facilitate leukaemogenesis [31].

Noncoding RNAs (MicroRNAs and Long Noncoding RNAs) Epigenetic Regulatory Function

RNA transcripts that don’t encode proteins are referred to as non-coding RNAs (ncRNAs) [32]. While approximately 75% of the human genome is transcribed, only 2% of that is translated into messenger RNAs (mRNAs), which code for proteins [33]. Catalytic, structural, and regulatory RNAs are translated from a significant portion of the human genome [34]. Research has shown that some ncRNA transcripts are also capable of encoding short peptides that are no longer than 100 amino acids. NcRNAs play a range of roles in cellular processes, control the expression of genes and the function of proteins, and have a functional role

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in healthy development, physiological processes, and the aetiology of disease. RNA length can be used to distinguish between a wide variety of non-coding RNAs. Long noncoding RNAs (LncRNAs) and microRNAs (miRNAs) are currently the ncRNAs that have been studied the most. All the characteristics of cancer initiation and progression, including haematologic malignancies, have been linked to the dysregulation of miRNAs and lncRNAs [34].

MicroRNAs

MiRNAs are small, single-stranded noncoding RNAs (ncRNAs) that are typically 22 nucleotides (nt) in length. Studies on the development of *Caenorhabditis elegans* (C. elegans) first identified miRNAs in 1993 [35]. MiRNAs primarily control the expression of posttranscriptional genes by binding to the 3' untranslated region (3' UTR) of the target messenger RNA (mRNA) in a sequence-complementary manner. This binding causes the associated mRNA to be degraded or protein expression to be suppressed [35]. Additionally, miRNAs can interact with other targets, including ncRNAs, intronic and intergenic transcripts, loci of the protein-coding region of mRNAs [36]. 5' UTRs of mRNAs, and other targets [37].

When frequent deletions and down-regulation of the miR15 and miR16 genes were found in CLL, the role of miRNAs in cancer was first identified in 2002. As negative regulators of the BCL2 oncogene and the receptor kinase-like orphan receptor 1 (ROR1) gene, miR-15/16 have been found. As a result, miRNA dysregulation has been discovered in nearly every type of cancer that has been studied, including solid tumours and haematologic malignancies. Two primary roles for miRNAs in cancer are as oncogenes or tumour suppressors [38].

THE RELATION BETWEEN EPIGENETIC AND LEUKAEMIAS

DNA methylation writers and leukaemia

There have been various reports regarding the role of DNMT1 in the progression of haematological malignancies. Conditional DNMT1 knockout prevented leukaemia from developing, while DNMT1 haploinsufficiency hindered leukaemic stem cells (LSC) ability to self-renew while maintaining normal haematopoiesis and delayed the development of leukaemogenesis. Research on AML revealed that miR-148a negatively regulated the expression of DNMT1 in AML cell lines and that the expression level of DNMT1 in AML patients was lower than in healthy controls [39].

Moreover, some clinical traits in leukaemia were linked to DNMT3A mutations. Research revealed that the DNMT3A mutation was linked to the intermediate-risk cytogenetic group in de novo AML as well as age; also, the mutation was associated with the M4/M5 immuno-phenotype; FLT3 mutation; NPM1 mutation; IDH1/2 mutation; and CEBPA mutation in AML [39]. A higher age, high WBC, high percentage of bone marrow (BM) blast cells, and extra-medullary disease were also linked to DNMT3A mutation in T-ALL patients [40].

Haematologic malignancies are primarily affected by DNMT3B. Studies have shown that mixed lineage leukaemia-AF9 (MLL-AF9) progresses more quickly when DNMT3B is lost [41]. Additional research revealed that in T-ALL and BL, elevated DNMT3B expression was linked to aberrant DNA methylation and MYC-driven tumour development [42].

DNA methylation readers and leukaemia

MBD2 and MeCP2 were found to be expressed more frequently in CML. Research on B-CLL revealed that MBD2 and MeCP2 were deregulated in the epigenetic repertoire [43]

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As MM. suggests, MeCP2 may epigenetically control the expression of SOCS5 in T-ALL and the SPAN-XB core promoter sequence in other haematological disorders. Epigenetically, the pro-apoptotic gene BIM in ALCL could be silenced by the MeCP2/SIN3A deacetylating complex [44].

DNA methylation Erasers and leukaemia

Oncogenesis has been linked to the disruption of regular DNA de-methylation. In haematologic malignancies, there have been reports of both genetic mutations and aberrant TET family protein expression. TET1 has been identified as an oncogene in MLL-rearranged leukaemia by earlier research [45]. TET1 expression was downregulated in AML, while TET2 and TET3 expression was upregulated. TET1 expression was higher in patients with refractory AML than in those responding to treatment. Furthermore, overexpression of TET1, TET2, and TET3 has been linked to a poor prognosis in AML [46]. TET2 expression was linked to a longer survival time in CLL, while TET1 and TET3 expression declined with the disease [47].

Furthermore, haematological malignancies may also exhibit TET mutations. TET2 was the most frequently mutated gene in patients with acute adult T-cell leukaemia (ATL) caused by the human T-cell lymphotropic virus type I (HTLV-I), TET2 mutations occurred in 32%. Patients with T-ALL and AML also showed TET2 mutations. TET1 aided in the of T-ALL in the experimental investigation and was counteracted by PARP inhibition [48].

Multiple clinical characteristics have been linked to TET2 mutations. TET2 was linked to high age, low PLT count, high WBC count, and normal karyotype [49].

In lower-grade MDS and CMML, arginase 1 overexpression was linked to DNMT3A and TET2 mutations. Apart from the genetic modification of TET2, patients with haematological malignancies exhibited distinct TET2 protein expression compared to healthy individuals. For instance, it was shown that TET2 expression was elevated in B-CLL but decreased in AML and childhood ALL and this difference was associated with a lower survival rate [50].

Histone modification and leukaemias

Blood-forming stem cells, the endothelial to haematopoietic transition, which begins at the early arterial endothelial cell, haemogenic endothelial cell, pre-HSC, and long-term HSC stages, has been shown to give rise to SCs. According to reports from investigations using low-input ChIP-seq and Hi-C assays, early arterial endothelial cells and haemogenic endothelial cells already have the stimulative histone modifications H3K27-ac and H3K4me1, which control enhancer activation, at the initiation stage. The steady expression of HSC genes is caused by the gradual increase of the stimulative H3K27-ac and the decrease of the repressive H3K27me3 during HSC differentiation [51]. Histone modification is also a major factor in lineage differentiation. By modifying the histone modifications of the promoters of pro-haematopoietic factors and myelopoiesis-promoting factors, BAP1, a critical lineage-mediating protein, controls the balance between lymphopoiesis and myelopoiesis. H2AK119-ub1 and H3K27me3 are enhanced on the promoter of the pro-haematopoietic factor Scf upon BAP1 deficiency, resulting in its downregulation. Furthermore, the promoter of the myelopoiesis-promoting factor Csf3 is strengthened by H3K4-me3 and H3K27-ac, which causes its upregulation and directs differentiation toward the myeloid lineage, resulting in CMML-like disease [51].

Haematopoiesis and oncogenesis depend on the dynamic balance between the writers, readers, and erasers of histone modifications. Acute myelomonocytic leukaemia (AMML) and chronic myelomonocytic leukaemia (CMML) have been linked to the specific stimulation of granulocyte/macrophage progenitors

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(GMPs) by the MLL-CBP chromosomal translocation [52].

Histone modification writers and leukaemia

MLL fusion proteins resulting from chromosome 11q23 translocation and more than 60 counterparts have been found in leukaemia, including the t(9;11) translocation, the t(4;11) translocation found in de novo AML and ALL, and the t(11;16) translocation found in therapy-related AMML and CMML [31]. DNA binding domains were found to be preserved in MLL fusion proteins, and HOX genes were overexpressed and promoted leukaemogenesis [53]. Additionally, partial tandem duplication (PTD) of MLL was also found in AML patients with normal karyotypes; this occurred following DNA methylation-related mutations (TET2, DNMT3A, IDH1/2) but before kinase mutations (FLT3, RAS). MLL-PTD was found to be significantly associated with worse prognoses in AML patients.

In patients with AML and MDS related to radiation, NSD3 was also observed to fuse to NUP98, which was caused by the translocation. PRMT plays a role in the epigenetic control of leukaemogenesis by catalysing the mono- and demethylation of histone arginine. It was discovered that PRMT4 was essential for developing MLL AF9-driven AML. By methylating CBP [54]. PRMT4 may potentially adversely affect the coactivation of CBP and PRMT5 activated the Wnt/ β-catenin pathway in CML, which promoted the self-renewal and viability of LSCs [55]. The loss of PRMT7 downregulated glycine decarboxylase and accelerated glycine metabolism to produce toxic methylglyoxal in LSCs without affecting normal haematopoiesis. It was demonstrated that PRMT7 regulates glycine metabolism to preserve LSCs in CML. Based on primary CD34+ cells from CML patients and CML mouse models, PRMT7 inhibition inhibited leukaemogenesis [55].

Histone modification readers and leukaemia

LSD1 has been shown to regulate erythroid differentiation, promote erythroleukaemia by inhibiting GFI1 super-enhancers, and mediate the action of the transcription factors TAL1, GATA-1, and C/EBPa in haematopoiesis. In mouse models, it has been shown that LSD1 inhibition eliminates AML and reactivates PU.1-dependent enhancers [56].

The KDM5 family includes KDM5A, KDM5B, KDM5C, and KDM5D. The KDM5 family demethylates H3K4. In AML patients, KDM5A translocation with NUP98 was often found to be pathogenic, and KMD5A downregulation inhibited proliferation and caused AML cells to undergo apoptosis [57].

In haematopoiesis and haematologic malignancies, KDM6A, also known as UTX, has a variety of functions. Haematopoietic stem progenitor cells (HSPCs) in their youth must be shielded from ageing by UTX. Reactive oxygen species accumulation decreased DNA damage repair, and ageing in HSPCs was linked to UTX deficiency. UTX mutations were discovered in 8% of patients with CMML to haematologic malignancies [58].

Tumour suppressor UTX has been shown to suppress myeloid leukaemogenesis and maintain drug sensitivity in MDS, AML, APL, and even T-ALL.433–437 Studies did, however, also find that UTX functioned as a pro-oncogenic cofactor that was essential to the development of leukaemia in TAL1-positive T-ALL and that UTX inhibition markedly reduced the development of TAL1-positive leukaemia [59].

Histone modification erasers and leukaemia

Leukaemic stem cells (LSCs) were more sensitive to imatinib when SIRT1 was inhibited, but SIRT1 increased DNA repair and made HSCs more susceptible to stepwise mutation development in CML. There is comparatively little evidence that the SIRT family influences haematologic malignancies. It will take

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more research to fully understand their relationships [60].

Targeted Therapy Based on Epigenetic Regulation

The development of medications to control gene expression over epigenetic marks is made possible by our growing understanding of epigenetic regulators, which control gene expression. Several epigenetic regulators involved in histone remodelling are inhibited and altered by epigenetic medications [24]. Chemotherapy-resistant patients frequently have closed chromatin structures that can be opened by medications that target epigenetic regulators. Based on how they modify their DNA, epigenetic regulators fall into three categories: writers, readers, and erasers on DNA or amino acid residues on histone tails, epigenetic writers affix epigenetic marks. Heme acetyltransferases (HATs), histone methyltransferases (HMTs), and protein arginine methyltransferases (PRMTs) are a few examples [61]. Medications that target these include bromodomains, HDAC inhibitors, and DNA hypomethylating agents. Proteins known as epigenetic readers have Tudor, chromo, and bromodomains, which enable them to bind to epigenetic marks on chromatin. Histone deacetylases, lysine demethylases, and phosphatases are examples of epigenetic erasers that catalyse the removal of epigenetic marks [62].

Targeting DNA methylation DNA hypomethylating agents (HMAs).

Numerous non-nucleoside analogues have been identified as DNA HMAs; these compounds are typically small-molecule inhibitors that target catalytic sites directly instead of interacting with DNA. A DNMT1-selective inhibitor, GSK3685032, could block transcriptional activation, DNA methylation, and the inhibition of cancer cell proliferation in vitro [63]. The most potent polyphenol in green tea was epigallocatechin gallate (EGCG), which inhibited APL, AML, and CML cells from proliferating by DNMT expression inhibition. (Vitkeviciene, 2018) A significant component of Nigella sativa seeds, thymoquinone (TQ) can cause DNMT1 dysfunction and potentially improve demethylation in AML [64].

Targeting Histone Deacetylase (HDAC):

In addition to inducing cell differentiation, apoptosis, autophagy, and cell cycle arrest, histone deacetylase inhibitors also modulate immune responses and prevent angiogenesis in a variety of haematologic malignancies and solid tumours [52]. It has been postulated that malignant cells exhibit greater selectivity and specificity over normal cells due to their increased susceptibility to epigenetic therapy [52]. Numerous HDAC inhibitors have been created and shown to be successful in the treatment of haematologic cancers. Several clinical trials have shown the use of valproic acid in conjunction with chemotherapy to treat CLL, AML, MDS, and lymphoma. The drug has been approved for the treatment of seizures. It was discovered that AR-42 in AML selectively induces LSC apoptosis without impacting normal HSCs, suppresses the NF-κB pathway, and down-regulates oncogenic Kit via HSP90 disruption [65]. In B-cell lymphoma, bendamustine and BCL_2 inhibitors worked in concert, while in HL and MM, entinostat induced apoptosis on its own. Numerous clinical trials are examining its effectiveness in treating lymphoma, MDS, AML, and CMML. When bendamustine and azacytidine were administered together, the ORR and OS in AML and MDS patients were lower than when azacytidine was administered alone. This suggests that the two agents are antagonistic to one another and are more toxic in this situation [66]

Targeting other histone modification agents

Despite being the most studied and used epigenetic regimen, agents that target other histone modification agents are also being developed. These include HDAC inhibitors. CBP/P300 inhibitors are the primary class of agents that target writers concerning histone acetylation. An NHL, MM, AML, and MDS patient is being treated with CCS1477, a CBP inhibitor, in a phase I/IIa trial (NCT04068597). BET inhibitors are among the

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agents that are aimed at readers [67].

Targeted Therapy Based On Organic Food Elements

Natural dietary supplements, such as fruits, vegetables, and spices, have demonstrated remarkable promise in the prevention and treatment of numerous illnesses, including cancer. Many of the bioactive compounds found in plants, many of which have been used as traditional medicines for ages, make up dietary agents. In addition to being a great source of vitamins, minerals, and fiber, dietary agents also include bioactive ingredients like phenolics, alkaloids, and polyphenols that may have uses beyond simple nourishment. The dietary phytochemicals comprising tea polyphenols, genistein, curcumin, resveratrol, sulforaphane, isothiocyanates, silymarin, diallyl sulfide, lycopene, rosmarinic acid, apigenin, and gingerol are the bioactive components that have been demonstrated to have the most effectiveness against cancer, these bioactive components have demonstrated significant promise in cancer prevention by altering genetic and epigenetic targets [68].

Targeted Therapy using Curcumin (Turmeric)

In recent years, researchers have explored the therapeutic potential of **curcumin**, the active compound found in **turmeric**, as an epigenetic modulator [69].

Induction of cellular apoptosis and cell cycle arrest in different cancer cells are the primary mechanisms by which curcumin-mediated chemoprevention is enhanced. Studies have shown that curcumin also prevents histone modifications such as HDAC inhibition in carcinogenesis and DNMT activities [68].

Targeted Therapy using Genistein (Soybean)

The flavonoid component genistein is an isoflavone that can be found in a variety of plants, such as soybeans, kudzu, psoralea, lupin, and fava beans. It has been discovered that genistein and other isoflavones have anti-angiogenic and anti-cancer effects on a variety of malignancies. Moderate doses of genistein have been shown in multiple trials to have inhibitory effects on brain, breast, colon, prostate, and cervical malignancies [68]. It has been determined that genistein has antiproliferative and anticancer effects through several pathways, including inhibition of angiogenesis, activation of cellular apoptosis, avoidance of DNA mutation, and decreased proliferation of cancer cells. The possibility that genistein regulates gene transcription or suppressing activity by influencing epigenetic processes including DNA methylation and/or chromatin alterations has drawn a lot of interest recently. Genistein has been shown in multiple studies to exhibit both histone modification and DNA methyltransferase inhibitory action in cancer cells [68].

Targeted Therapy using Tea polyphenols.

In more than 30 nations, the tea plant Camellia sinesis is grown. The average daily consumption of tea is approximately 120 milliliters, making it the most popular beverage drank globally, only surpassed by water [70]. Tea contains polyphenolic chemicals, which may lower the risk of cancer and coronary heart disease, among other ailments. These findings are supported by laboratory research and epidemiologic evidence. Catechins, which include (−)-epicatechin (EC), (−)-epicatechin-3-gallate (ECG), (−)-epigallocatechin (EGC), and (−)-epigallocatechin 3-gallate (EGCG), are the most prevalent chemical molecule found in green tea beverages. Of them, EGCG makes up about half of the polyphenol content overall and is the active component of green tea [71]. One of green tea's main and most beneficial ingredients is EGCG. Consequently, EGCG has been used in most in vitro and in vivo investigations on the effects of green tea. In a concentration-dependent way, tea polyphenols (catechin, epicatechin, and EGCG) and bioflavonoids (quercetin, fisetin, and myricetin) have been found to block DNMT and DNMT1-mediated DNA

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methylation [68].

Targeted Therapy using Resveratrol.

Dietary polyphenols such as resveratrol can be found in peanuts, berries, grapes, and other plants. By altering the signal transduction pathways that regulate cell division and development, apoptosis, inflammation, angiogenesis, and metastasis, resveratrol has been shown to have potent anti-cancer effects. The capacity of resveratrol to impede the growth of numerous human tumour cell types, including those found in the skin, breast, prostate, lung, and colon, has provided evidence for its anti-cancer properties. It has been demonstrated that compared to other dietary bioactive ingredients like EGCG, resveratrol has less DNMT inhibitory action. In MCF-7 human breast cancer cells, resveratrol inhibits the epigenetic silencing of BRCA-1 caused by the aromatic hydrocarbon receptor (AHR) [72].

Targeted Therapy using Sulforaphane (Cruciferous Vegetables)

Widely consumed cruciferous vegetables like broccoli, broccoli sprouts, cabbage, and kale naturally contain sulforaphane (SFN), an isothiocyanate that has been demonstrated to lower the risk of developing a few common malignancies [73]. In MCF-7 and MDAMB-231 breast cancer cells as well as CaCo-2 colon cancer cells, it was discovered that SFN inhibited DNMTs [74]. also showed that SFN treatment had minimal effects on normal control cells and that it inhibited human telomerase reverse transcriptase (hTERT), the catalytic regulatory subunit of telomerase, in both MCF-7 and MDA-MB-231 human breast cancer cells. The amount of DNA methyltransferases (DNMTs), particularly DNMT1 and DNMT3a, was likewise reduced in breast cancer cells treated with SFN. More intriguingly, the downregulation of DNMTs led to site-specific CpG demethylation, which mostly happened in the first exon of the hTERT gene. This made it easier for CTCF to bind to the hTERT gene, which is linked to hTERT repression and cell death in breast cancer cells [74].

Possible challenges associated with targeted therapy using organic foods.

Most of the research examining the anticancer properties of natural substances or cofactor metabolism has been carried out in animal models or in vitro with exact controls on food consumption or dietary exposures. However, given the complexity of diets, the precision of methods used to measure them, and the multifactorial nature of human nutrition (affected, among other things, by genetic background, physical activity, and microbiota), evaluating the impacts of food on humans may be more challenging. It is difficult to comprehend from a scientific perspective how food consumption results in the build-up of substances in the cell nucleus at a level that can hinder the epigenetic machinery. Furthermore, bioactive compounds may have the ability to bind several targets, and cofactors may influence many activities with varying results. (For instance, RNA, histone, and DNA methylation may be impacted by SAM availability). It is well known that eating a healthy diet can help prevent cancer and that this has an epigenetic effect. However, to define specific and personalized diets that influence epigenetics for cancer prevention and to support cancer treatment, a deeper understanding of nutrition and the molecular action of nutritional biomolecules will be required [75].

CONCLUSION

The ontogenesis of haematologic malignancies and haematopoiesis are fundamentally influenced by epigenetic regulation. In leukaemia, abnormal DNA methylation profiles are often seen, including genome-wide hypomethylation and aberrant hypermethylation or hypomethylation of CpG islands. YAML is characterized by the pathogenic upregulation or mutation of DNA methylation writers (DNMT1, DNMT3A, and DNMT3B). MBD-containing proteins, methyl-CpG binding zinc fingers, and SRA domain-containing proteins are the primary readers of DNA methylation and are frequently found to be upregulated in CML

and AML. The TET family is a major group of DNA methylation erasers; mutations, translocations, and upregulation of this family are relatively common in AML. HMAs are effective in treating AML and CMML, and they have been developed to target aberrant DNA methylation profiles. Moreover, leukaemia is related to histone methylation and acetylation.

Curcumin, the golden spice, and other organic food elements hold promise as an epigenetic ally in our fight against leukaemia. Let us explore its full potential and unlock new avenues for effective and personalised therapies as epigenetics cause on-and-off gene activities whereas organic food elements reverse the effect by complementing the on-and-off of the gene function due to epigenetics. The intersection of epigenetics and nutrition offers hope in the fight against leukaemia. Let us explore these organic food elements as allies in our quest for effective and personalized therapies.

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