DNA Methylation in Leukemia, Myelodysplastic Syndrome, and Lymphoma

Subjects: Oncology

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DNA methylation represents a crucial mechanism of epigenetic regulation in hematologic malignancies. The methylation process is controlled by specific DNA methyl transferases and other regulators, which are often affected by genetic alterations. Global hypomethylation and hypermethylation of tumor suppressor genes are associated with hematologic cancer development and progression. Several epi-drugs have been successfully implicated in the treatment of hematologic malignancies, including the hypomethylating agents (HMAs) decitabine and azacytidine. However, combinations with other treatment modalities and the discovery of new molecules are still the subject of research to increase sensitivity to anti-cancer therapies and improve patient outcomes.

hematologic malignancies epigenetic regulation DNA methylation

1. Introduction

Hematologic malignancies form a heterogeneous group of acute and chronic diseases, clonally expanding into the blood, bone marrow, and lymph nodes. Due to their highly aggressive manner, blood cancers are characterized by rapid progress, affecting both pediatric and adult patients. Improved treatment response and outcomes have been documented in pediatric patients, who achieve remission in the overwhelming majority. Genetic and epigenetic changes lead to the clonal proliferation of stem and progenitor cells. Alterations in downstream signaling pathways contribute to the disruption of the self-renewal ability of hematopoietic cells and their differentiation into other lineages.

Although epigenetic mechanisms have been largely evaluated in embryonic development, differentiation, and organogenesis [1][2], mounting evidence supports their critical role in cancer development and treatment. In a very recent concept, aberrant epigenetic programming is one of the hallmarks of malignant progression [3]. The process of DNA methylation is the most studied epigenetic mechanism in both normal and cancer cells, and its correct regulation is crucial for the transcription of different regulating genes, maintaining genome integrity, and proper immune responses [4]. Genetic changes in DNA methylation enzymes and regulators together with abnormal DNA methylation are associated with cancer-promoting changes [5]. In addition to gene silencing by promoter hypermethylation at CpG islands, DNA genome hypomethylation is a typical sign of human cancers [4].

DNA methylation plays a critical role in hematopoiesis and hematopoietic stem cell differentiation and proliferation [6]. Epigenetic modulation by DNA methylation is involved in several stages, including blood cell lineaging and the formation of the final cell types [7]. According to the findings, aberrant DNA methylation patterns during

hematopoiesis linked to the dysfunction of DNA methylation-related enzymes often lead to blood cancer development [8]. With heterogeneity and different clinical severity of individual subtypes, it is more than inevitable that investigations into new diagnostic and therapeutic possibilities are performed.

2. DNA Methylation of Target Genes in Leukemias, Myelodysplastic Syndromes, and Lymphomas

Genetic changes in regulators of the DNA methylation process can cause alterations in genome-methylation levels in the form of a loss of global methylation. On the other hand, almost intact global methylation was found in several hematologic malignancies. Genome-wide methylation studies in acute myeloid leukemia (AML), chronic myeloid leukemia (CML), chronic lymphocytic leukemia (CLL), acute lymphoblastic leukemia (ALL), and lymphomas described different regions with aberrantly methylated genes, which could help to elucidate the malignant transformation process and find potential targets for diagnosis, prognosis, or therapy of hematological cancers [9][10][11][12][13][14].

2.1. Aberrant Methylation in MDS and AML

Myelodysplastic syndrome (MDS) and AML belong to the group of hematologic malignancies characterized by clonal hematopoiesis. Both diagnoses share similar clinical and pathologic features, but they differ in the percentage of blasts in peripheral blood and bone marrow. DNA methylation of different target genes has been described in patients with MDS and acute/chronic leukemia (**Figure 1**).

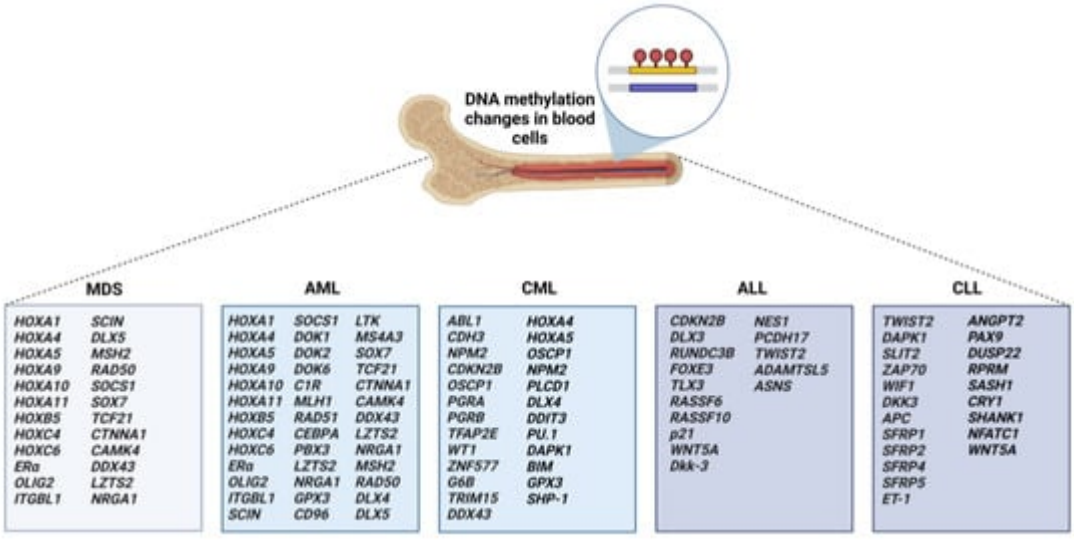

Figure 1. Methylation-affected genes associated with leukemias and myelodysplastic syndromes. DNA methylation plays a key role in the initiation and progression of hematological malignancies. DNMTs catalyze transferring of the methyl group (a red circle) to the 5-carbon position of cytosine within CpG dinucleotides in DNA sequence (each strand of double-stranded DNA is marked by different colors, yellow and blue), leading to the formation of 5-methyl-cytosine. Abnormal methylation patterns in bone marrow cells may predict responsiveness to the treatment. A panel of aberrantly methylated genes shown to have diagnostic and prognostic value. Targeting the

hypermethylated promoters of tumor suppressor genes might represent a perspective trend for hypomethylating drug therapy alone or in combination. Abbreviation: DNMTs, DNA methyltransferases.

The *HOX* gene family represents the most studied genes, which are regulated by DNA methylation in AML. In an extensive study, Gao et al. identified 29 genes whose expression correlated with differently methylated CpG sites. Within the HOX family, high methylation was found in *HOXA7*, *HOXA9*, *HOXA10*, and *HOXB3* genes [9]. Similar results were found in mesenchymal stromal cells from bone marrow in MDS and AML patients, where preferentially aberrant methylated genes were *HOXA1*, *HOXA4*, *HOXA5*, *HOXA9*, *HOXA10*, *HOXA11*, *HOXB5*, *HOXC4*, and *HOXC6* [15].

Promoters of many tumor suppressor genes (TSGs) are most commonly inhibited by methylation. Cyclin-dependent kinase inhibitors *p15* and *p16*, important in the regulation of proliferation, are frequently methylated in AML patients. Their higher methylation was associated with lower (overall survival) OS, recurrence-free survival (RFS), and frequency of CR [16][17][18]. In AML and MDS patients, the relationship between gene methylation status and shorter OS was reported for *ERα*, *OLIG2*, *ITGBL1*, *SCIN*, *DLX5*, *MSH2*, *RAD50*, and *SOCS1* genes [19][20][21][22][23][24].

The DOK protein family, characterized as phosphotyrosine adapters with several functions in cell biology, is commonly expressed in myeloid cells. In a study comprising AML patients, He et al. observed that hypermethylation-mediated decreased expression of *DOK1* and *DOK2* genes was associated with lower OS [25]. Similarly, the higher methylation status of another member *DOK6* gene was found in AML patients, but with the opposite effect on OS [26]. Longer OS was associated with higher promoter methylation in other genes, including *C1R* and DNA repair genes *MLH1* and *RAD51* [23][27].

Sestakova et al. performed an extensive validation study for 27 genes from 14 studies to verify the predictive role of aberrant DNA methylation in AML. The results showed that hypermethylation of *CEBPA*, *PBX3*, *LZTS2*, and *NRGA1* serves as a predictor for longer survival [28]. In addition, higher methylation of *GPX3* and *DLX4* correlated with a favorable treatment impact, which is in contrast to previously reported studies documenting their correlation with lower OS [29][30].

In some cases, mutations in important transcription factors can lead to alterations in epigenetic modifications. Genetic changes in Runt-related transcription factor 1 (RUNX1), a key player in hematopoiesis, led to aberrant methylation in target genes. The study on the *RUNX1*-mutated AML cohort identified 51 differential methylated genes. As shown, the changes in expression profiles were found in ten of them. Hypermethylation of *CD96*, *LTK*, and *MS4A3* correlated with poor prognosis, which could be related to their effects on cell cycle regulation and differentiation [31]. Higher methylation of *SOX7*, *TCF21*, *CTNNA1*, and *CAMK4,* as well as hypomethylation of *DDX43*, *LZTS2*, or *NRGA1,* was observed in MDS/AML patients. Due to the lack of prognostic potential in numerous studies, complex evaluation requires further investigation [32][33][34][35][36][37].

2.2. Aberrant Methylation in CML

CML is characterized by the presence of translocation-creating oncoprotein BCR-ABL1, and the development of this disease consists of three phases, namely, the chronic phase (CP), accelerated phase (AP), and blast crisis phase (BP) [38]. The high content of aberrantly methylated CpG compared to healthy donors was found through a methylome analysis of CML patients. Moreover, the number of abnormally methylated CpG increased from CP to the BP phase. Most of the CpG sites with increased methylation (88%) were located in GpG islands or in the very close region, which overlapped with 348 genes in the peripheral blood of BP patients [10].

Jelinek et al. observed that among 10 selected genes analyzed by pyrosequencing, *ABL1*, *CDH3*, and *NPM2* presented the highest methylation in all phases of CML. Furthermore, increased methylation of *CDKN2B* (*p15*), *OSCP1*, *PGRA*, *PGRB*, and *TFAP2E* genes was described during CML progression [39]. Another extensive study defined 33 highly methylation-affected regions with hypermethylation of *ABL1*, *WT1*, *ZNF577*, and hypomethylation of *G6B* and *TRIM15* [40]. *DDX43* represents a frequently overexpressed gene in hematological malignancies. Epigenetic regulation of *DDX43* by promoter methylation and a negative correlation between hypomethylation and higher expression of *DDX43* was observed in CML patients. Moreover, the frequency of *DDX43* hypomethylation increased in CP, AP, and BP by 23.4%, 25.0%, and 33.3%, respectively [41].

Promoter hypermethylation is mostly associated with TSGs involved in crucial cell functions, including the regulation of differentiation, proliferation, apoptosis, cell cycle, and growth. Similar to AML, *HOXA4* and *HOXA5* were hypermethylated in CML patients, and the presence of promoter methylation correlated with resistance to imatinib, belonging to a group of TKIs. Patients with *HOXA4* and *HOXA5* methylation levels higher than 63% showed 3.78- and 3.95-times-higher risk for imatinib resistance, respectively [42]. Imatinib resistance was also recorded in the case of higher methylation of *OSCP1* and *NPM2* genes [39]. Aberrant methylation of TSGs, including *PLCD1*, *DLX4*, *DDIT3*, *PU.1*, *DAPK1*, *BIM*, and *GPX3,* could represent potential prognostic or therapeutic targets in CML [43][44][45][46][47][48][49]. Accordingly, the downregulation of *SHP-1* and relevant protein expression was associated with the presence of promoter methylation in advanced CML patients. SHP-1, a protein tyrosine phosphatase, is expressed mainly in HSC and plays a critical role in the regulation of JAK/STAT and MYC, AKT, and MAPK pathways. Alterations in *SHP-1* methylation status could lead to the deregulation of included pathways and blastic transformation in CML patients [50].

2.3. Aberrant Methylation in ALL

ALL represents hematological cancer of immature T or B cells. T-ALL and B-ALL represent approximately 15–20% and 85% of all cases, respectively [51]. A genome-wide methylation analysis, based on nine genes with the identified CpG methylator phenotype, was capable of predicting a poor outcome subgroup of adult T-ALL. Patients with low methylation levels reported shorter OS and a higher risk of death in univariate and multivariate analyses. According to the results, the lowest methylation levels in patients were significantly associated with gender, younger age, and a higher count of white blood cells [52]. Similar to AML, *CDKN2B* (*p15*) presented decreased expression in most T-ALL cases, originating from deletion and promoter hypermethylation. *CDKN2B* hypermethylation frequently occurred together with mutations in *DNMT3A* and *NRAS* genes. In addition to the association with an older age of onset, the results showed a relatively early presence of T-cell precursors of ALL,

causing the quick arrest of T-cell differentiation [53]. *DLX3*, belonging to the *DLX* gene family with a wide range of functions during hematopoiesis, could be active in the resistance to apoptosis. In pediatric B-cell ALL, Campo Dell Orto et al. observed aberrant methylation of *DLX3* with reduced gene expression in patients with MLL-AF4 fusion, while no methylation was found in the subgroup with the TEL-AML1 fusion protein. The results suggested a potential role of *DLX3* methylation in B-cell acute leukemias [54]. Some epigenetic promoter alterations can be lineage-specific. Higher methylation and methylation-mediated downregulation of *RUNDC3B* expression are typical for lymphoid but not myeloid malignancies [55]. RUNDC3B participates in the MAPK cascade in the role of Rap2-MAPK signaling mediator. Silencing by promoter methylation could disrupt the MAPK signaling pathway and promote leukemogenesis of lymphoid cells [55].

Several specific methylation profiles were found to be diagnostic, prognostic, or therapeutic markers for ALL. Chatterton et al. monitored the methylation of *FOXE3* and *TLX3* genes, showing their ability to discriminate between cancerous and healthy bone marrow samples with high specificity and sensitivity, which indicates their potential as diagnostic markers. Furthermore, *TLX3* methylation correlated with minimal residual disease (MRD) in pediatric ALL patients [56]. In B-ALL and T-ALL-, *RASSF6* and *RASSF10* genes were frequently methylated and associated with the MRD in peripheral blood samples of adult ALL patients. In addition, the hypermethylation of *RASSF6* is significantly associated with shorter OS in precursor B-ALL patients [57][58]. In a series of further studies, Roman-Gomez et al. described the role of promoter hypermethylation in a prognostic manner while observing the association of higher methylation of *p21*, *WNT5A*, *Dkk-3*, and *NES1* genes with shorter disease-free survival (DFS) and OS [59][60][61][62]. Higher methylation of the *PCDH17* gene was frequently observed in both B-ALL and T-ALL with a relationship with lower OS and increased risk for relapse and death [63][64].

Importantly, the specific gene methylation profiles can represent a predictive therapeutic marker because aberrant methylation can be responsible for chemotherapeutic resistance. *TWIST2* hypermethylation and its inactivation were observed in more than 50% of ALL patients and 91% of samples from relapsed patients. In vitro experiments showed that the re-expression of TWIST2 increased apoptosis and sensitivity to chemotherapeutics [65]. A comparison of chemo-resistant and sensitive B-ALL pediatric patients detected higher levels of methylation in *ADAMTSL5* (93% vs. 38%) and *CDH11* (79% vs. 40%) in chemo-resistant vs. chemo-sensitive patients, respectively [66]. On the other hand, hypomethylation of the *ASNS* gene in T-ALL childhood patients was associated with poor outcomes and resistance to asparaginase, which is a high-dose drug involved in T-ALL therapy [67].

2.4. Aberrant Methylation in CLL

CLL belongs to the most common leukemias in the adult population, characterized by the clonal expansion of malignant B cells [68]. Similar to some other hematological malignancies, global hypomethylation is a characteristic sign of CLL. However, aberrantly methylated regions were characterized for this diagnosis in previous years [69]. In a genome-wide methylation study, Pei et al. identified approximately 1764 known genes with different methylation at 5’ regulatory regions. Among them, the results showed the presence of aberrant methylation in all four *HOX* gene clusters [11]. Previously, several studies found higher promoter methylation of genes, including *TWIST2*,

DAPK1, *SLIT2*, or *ZAP70* [70][71][72][73]. Increased expression of *ZAP70* predicts poor outcomes for CLL patients, and CpG sites important for the regulation of transcription were identified in the 5' regulatory region. According to these findings, a decreased methylation level in this specific CpG dinucleotide is a predictive biomarker for poor prognosis [73]. The WNT signaling pathway is generally involved in carcinogenesis and leukemogenesis. The constantly activated WNT pathway associated with the detection of hypermethylation of the seven WNT antagonist genes *WIF1*, *DKK3*, *APC*, *SFRP1*, *SFRP2*, *SFRP4*, and *SFRP5* was observed in the peripheral blood of CLL patients. However, no association between methylation and clinical parameters was confirmed [74][75].

The hormone peptide Endothelin-1 (ET-1) plays a role in various cell functions, including proliferation. Microenvironment stimuli activated downstream receptors, leading to increased *ET-1* expression in CLL. The unmethylated *ET-1* gene was observed in healthy donors, while CLL patient samples exhibited 32% unmethylated and 68% methylated profiles. As shown, high methylation of the first *ET-1* intron decreased its expression, suggesting the importance of epigenetic regulation [76]. The same authors detected that low methylation levels of neoangiogenic factor *ANGPT2* correlated with increased expression and are associated with shorter OS and poor prognosis in CLL patients [77]. The prognostic potential of aberrant methylation in CLL was also observed in other genes, including *PAX9*, *DUSP22*, *RPRM*, *SASH1*, and *CRY1* [78][79][80]. In the low-risk CLL subgroup, the hypermethylated *CRY1* promoter inactivated its expression and was associated with better outcomes [80]. For CLL diagnosis, the most differentially methylated gene *SHANK1* positively correlated with the absolute lymphocyte count. Increased *SHANK1* methylation was found in samples during the pre-CLL diagnosis period, suggesting that epigenetic modification of *SHANK1* occurred early in CLL carcinogenesis [81]. In comparison with *SHANK1*, the *NFATC1* gene belongs to the most hypomethylated genes identified in CLL. A decreased methylation level is strongly associated with *NFATC1* upregulation, resulting in the deregulation of target gene expression. Inactivation of NFAT regulator calcineurin by ibrutinib increased apoptosis in leukemic cells. Thus, *NFACT1* might represent a potential therapeutic target in CLL diagnosis [82].

Two subgroups of CLL patients are classified according to the presence of somatic mutations in immunoglobulin *(Ig)* genes. The Ig heavy chain variable region (IGHV) with high mutational prevalence (IGHV-M) correlated with a more favorable prognosis compared to IGHV unmutated (IGHV-UM) CLL patients [83]. In the IGHV-UM subgroup, *VHL* and *ABI3*, acting as TSGs, were preferentially methylated and correlated with decreasing expression [84]. In contrast, the expression of *WNT5A* distinguished patients with worse outcomes in the IGHV-M subgroup. Reduced *WNT5A* expression through hypermethylation preferentially in three CpG dinucleotides within the regulatory region correlated with good prognoses [85].

2.5. Aberrant Methylation in Malignant Lymphomas

Malignant lymphomas (MLs) represent a heterogeneous group of hematologic malignancies in primary or secondary lymphatic organs arising from various types of B and T lymphocytes or NK cells. Generally, MLs cover classical Hodgkin lymphomas (HL) and diverse groups of non-Hodgkin lymphomas (NHL) [86]. Pathogenesis of HL is presumably associated with family anamnesis or infection with Epstein–Barr virus (EBV). According to the previous findings in HL, DNA methylation led to the silencing of *RASSF1A*, *p16INK4a*, *p18INK4c, p15INK4b*, *SYK*,

BOB.1/OBF.1, and *CD79B* [87][88][89]. Recently, differences in DNA methylation signatures were detected in a study with monozygotic triplets with HL. Two of the triplets with HL shared DNA methylation changes in naive B-cells and marginal zone-like B-cells compared to a healthy non-HL-triplet. Hypermethylation of one region within chromosome 18 in naive B-cells was found exclusively in HL triplets [90].

Bethge et al. identified 233 downregulated genes in a cohort of B-cell NHL patients. From the analyzed gene panel, *DSP*, *FZD8*, *KCNH2*, and *PPP1R14A* exhibited promoter methylation in 28%, 67%, 22%, and 78%, respectively. In addition, the highest methylation level after treatment with demethylating agents was detected in *LRP12* and *CDH1* genes, presenting 94% and 92%, respectively [91][92]. Another study evaluated eight genes associated with lymphoma pathogenesis and found decreased *SIRT1* and increased *KLF4*, *DAPK1*, and *SPG20* gene methylation levels. In vitro analysis revealed that DNMT1 did not affect hypermethylation maintenance of *KLF4*, *DAPK1*, and *SPG20* genes [93][94].

Most DNA methylation studies have been performed in NHL, specifically in diffuse large B-cell lymphoma (DLBCL) (**Figure 2**). The results from the genome-wide methylation study reported approximately 200 differentially methylated genes in DLBCL patients with the aberrant methylation of *p16/CDKN2A*, *p21/CDKN1A*, and *p27/CDKN1B* [95]. However, only 37% of DLBCL patients had *p16* methylation higher than 5%. According to the results, patients younger than 65 years manifested better progression-free survival (PFS) when the *p16* methylation level reached more than 25% [96]. Aberrant methylation of another from CDK inhibitors, *p57/KIP2,* suggested that epigenetic modification of *p57* could be established as a biomarker for MRD in DLBCL [97]. Shawky et al. analyzed the panel of 20 TSGs for promoter hypermethylation and correlation with clinical characteristics and patient outcomes in the DLBCL group. The methylation of several studied genes associated with survival and chemoresistance, specifically *RUNX3*, *DAPK1*, and *MT16*, represent prognostic factors for DFS. Moreover, hypermethylation of *RUNX3* and *CDH1* was shown to be an independent prognostic factor for OS [98].

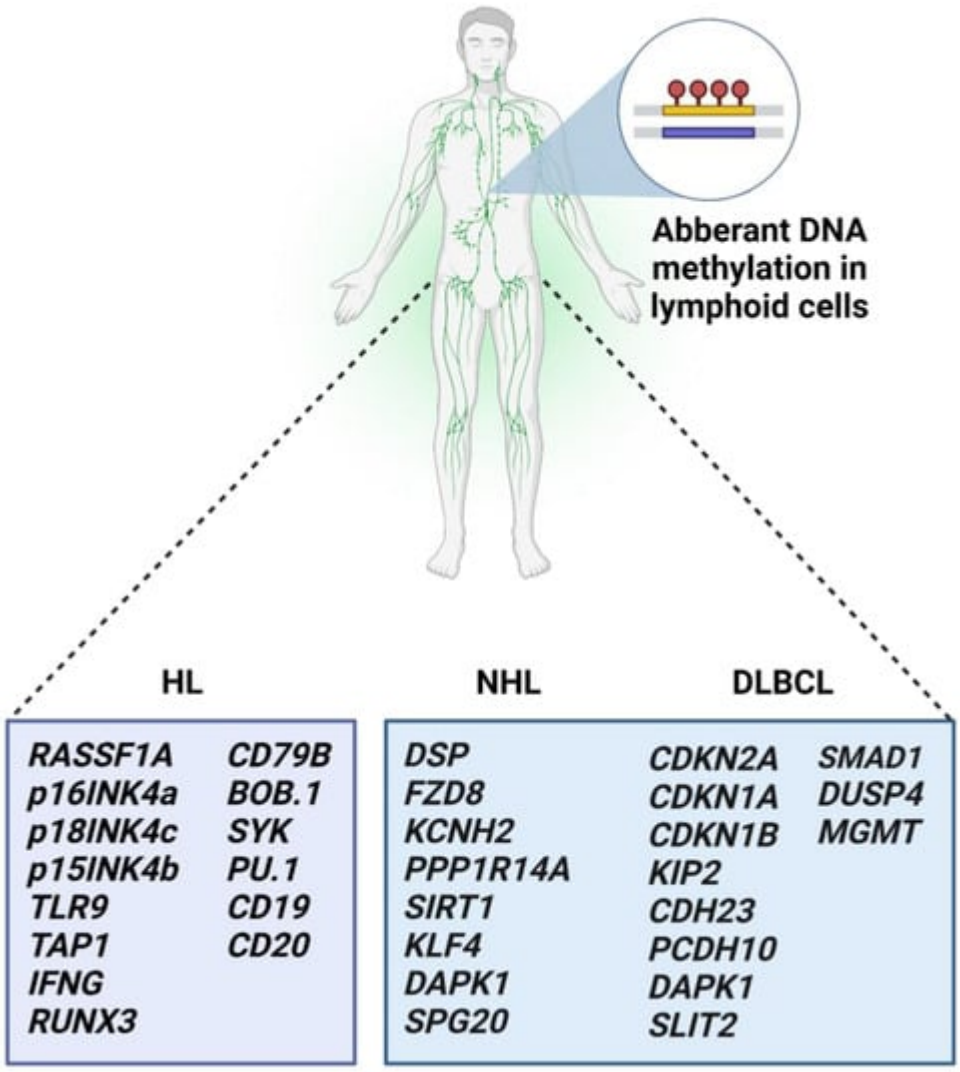

Figure 2. Methylation-affected genes associated with lymphomas. Aberrant DNA methylation (a red circle) regulates gene expression in Hodgkin, Non-Hodgkin, and Diffuse large B-cell lymphomas. Abnormally methylated genes might be used as potential biomarkers for therapeutic decisions and as predictive markers for patient outcomes.

Promoter methylation analysis of genes coding cadherins and protocadherins uncovered the association of *CDH23* and *PCDH10* hypermethylation and downregulated expression with worse outcomes in DLBCL patients. As noted, methylation of these genes could serve as a risk marker or a potential therapeutic target [99][100]. Several methylation studies investigated the *DAPK1* gene showing higher methylation significantly associated with lower OS, disease-specific survival, and 5- year survival in the DLBCL patient cohort [101][102]. In addition, a prognostic and predictive potential of increased *DAPK1* methylation in plasma samples was revealed in DLBCL. Patients with decreased methylation levels survived longer than patients with unchanged or regained *DAPK1* methylation [103]. Specific promoter methylation with prognostic significance for DLBCL patients was discovered in several other genes, including *SLIT2*, *DUSP4*, and *MGMT* [104][105][106]. Importantly, Clozel et al. documented the link between aberrant DNA methylation and resistance to chemotherapeutics. Methylation analysis in chemoresistant DLBCL patients found nine hypermethylated genes. Among them, *SMAD1* was a critical player. In a clinical trial on DLBCL

patients, treatment with azacitidine followed by chemoimmunotherapy showed demethylation of *SMAD1* and increased chemosensitivity [107].

In conclusion, DNA methylation is one of the main epigenetic mechanisms, besides known genetic alterations, that play a role in cancer initiation and progression. In the future, DNA methylation-based stratification of hematologic patients might lead to more personalized treatment with better outcomes. The reversibility of changes in DNA methylation landscapes enables broad clinical implications. However, adverse events associated with indiscriminate global hypomethylation with DNA methylation inhibitors are a matter of concern, and further investigations are highly warranted. According to the findings, DNA methylation processes in hematologic malignancies are usually associated with other mechanisms of epigenetic regulations, including histone modifications and miRNA regulation. Thus, evaluating the role of epigenetic modifications in a more complex matter would be beneficial for blood cancer patients.

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