Epigenetics in Pediatric Acute Lymphoblastic Leukemia

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Evidence suggests that leukemogenesis in acute lymphoblastic leukemia (ALL) is widely influenced by epigenetic modifications. These changes include: DNA hypermethylation, histone modification and miRNA alteration. DNA hypermethylation in promoter regions, which leads to silencing of tumor suppressor genes, is a common epigenetic alteration in ALL. Histone modifications are mainly caused by an increased expression of histone deacetylases. A dysregulation of miRNA results in changes in the expression of their target genes. Several hundred genes were identified as suppressed by epigenetic mechanisms in ALL. What is promising is that epigenetic alterations in ALL may be used as potential biomarkers for classification of subtypes, predicting relapse and disease progression and assessing minimal residual disease. Furthermore, since epigenetic lesions are potentially reversible, an activation of epigenetically silenced genes with the use of hypomethylating agents or histone deacetylase inhibitors may be utilized as a therapeutic strategy for ALL.

acute lymphoblastic leukemia children and adolescents epigenetics

1. Introduction

Acute lymphoblastic leukemia (ALL) predominantly affects children (80% of cases). In recent times, the 5-year survival rates of pediatric ALL for children (age 0 to 14 years) and adolescents (age 15 to 19 years) have significantly augmented: from 73% and 55% in the years 1980–1990 to 93% and 74% in the years 2010–2017, respectively [1].

Since the St Jude Total Therapy Study 16 on pediatric ALL patients revealed that the intensity of conventional chemotherapy has reached its limit, there is a need to combine or replace traditional chemotherapy with immunotherapy and molecular targeted therapy [2][3]. The study of epigenetic modifications opens the door for further increasing the survival rates and quality of life of patients with childhood ALL.

Epigenetics is a term used to describe a gene regulation mechanism that takes place without changes in the DNA sequence. Epigenetic dysregulation, alongside genetic lesions, has been well-recognized as a significant factor contributing to the development and progression of many cancers [4][5]. However, as opposed to genetic changes, epigenetic alterations are potentially reversible.

2. Modifications of Histones in Pediatric ALL

Epigenetic modifications also apply to histones. Histones are highly conserved proteins that are involved in the packaging of genomic DNA. Together with DNA, histones build a nucleosome—a complex of DNA wrapped on histones [6]. They perform various functions: histones participate in cellular processes, such as: transcription regulation, control of cellular cycle, chromosome stability and repair of DNA damage [7]. Overall, histones can be classified as core histones: H2A, H2B, H3 and H4 and linker histones: H1 and H5 [8]. The core histones are associated with ALL development mainly through aberrations in their post-translational modifications and disturbances of the enzymes regulating these modifications. These modifications are the acetylation and methylation of histones [9][10].

2.1. Acetylation of Histones

Histone acetylation and deacetylation are processes that are engaged in the regulation of gene expression. According to the study by Janczar K et al., a loss of global histone H4 acetylation is common in pediatric BCP-ALL. Moreover, preserved histone H4 acetylation is associated with a favorable outcome of the disease: longer relapse-free survival, event-free survival and overall survival [11]. Histone acetylation and deacetylation are also involved in the regulation of Protocadherin 17 protein coding gene (PCDH17). PCDH17 is a tumor suppressor gene in ALL. Repression of histone deacetylation causes upregulation of PCDH17 expression. This suggests that inhibition of histones deacetylation may be a potential pharmaceutical target for ALL with the disfunction of PCDH17 expression treatments [12]. Histone acetylation and deacetylation are catalyzed by enzymes: histone acetyltransferase (HAT) and histone deacetylase (HDAC). Acetylation is linked with an increase of transcriptional activation, while deacetylation is associated with transcriptional deactivation [13]. CREB Binding Protein (CREBBP) is one of HAT. The mutation causing the inactivation of CREBBP occurs in ALL [14]. In the study by Gao C et al., low CREBBP expression is associated with adverse clinical risk factors: high WBC count, T-cell immunophenotype, carrying BCR-ABL and lack of ETV6-RUNX. Additionally, low CREBBP was correlated with a poor prednisone response. Moreover, the CREBBP expression level can be used to predict patient outcomes—the lower expression level was associated with a worse prognosis [15]. Research carried out on ALL cell lines showed that downregulation of CREBBP is associated with resistance to chemotherapy by daunorubicin. Low expression of CREBBP causes inhibition of leukemia cell proliferation, this lead to a decrease in the effectiveness of daunorubicin [16]. Low CREBBP expression is also related to the risk of relapse—CREBBP mutation was present in the clones that survived therapy [17].

2.2. HDAC Inhibitors in ALL Treatment

Dysregulation of histone acetylation and deacetylation can be used as a therapeutic target. Inhibition of histone deacetylase seems to be applicable in the treatment of ALL. A mechanism of HDAC Inhibitors (HDACi) is correlated with restoring acetylation homeostasis in cells and reactivating the expression of tumor suppressors, which lead to an induction of cell-cycle arrest, apoptosis, differentiation and inhibition of angiogenesis and metastasis [18]. Givinostat is one of the HDACi which showed potential therapeutic value in ALL treatment. The study by Li Y et al. suggests that givinostat is effective in ALL with Philadelphia chromosome (Ph+) treatment. Givinostat induces apoptosis and inhibits cellular proliferation of Ph + Pre-B ALL cell lines [19]. Givinostat is also

useful in the treatment of cytokine receptor-like factor 2 (CRLF2)-rearranged BCP-ALL. This mutation is associated with a poor outcome. In a study from 2017, givinostat exerts cytotoxicity against leukemic cells in the form of growth inhibition and an induction of apoptosis in ALL cells [20]. The research by Yang L et al. showed that a class I and IIb HDAC highly selective inhibitor purinostat mesylate exhibited an antitumor effect on Ph+ B-ALL. The use of purinostat mesylate results in attenuated progression and significantly prolonged survival time in a mouse model [21]. The other HDAC inhibitor panobinostat seems to be effective in the treatment of Mixed Lineage Leukaemia (MLL)-rearranged ALL. In the mouse model panobinostat has strong anti-leukaemic effects, extending survival and reducing the overall disease burden [22]. Another study suggests that panobinostat has better efficiency in combination with the curaxin CBL0137 in MLL-rearranged ALL treatment. These twice anti-cancer drugs destabilize nucleosomes and increase histone acetylation levels. Due to these two processes, CBL0137 and panobinostat decondensed chromatin, respectively, which leads to downstream anti-cancer processes. This combination causes a limit of progression and extends the survival time in the mouse model [23]. Romidepsin also showed efficiency in MLL-rearranged ALL. Research carried out on a mouse model showed that the use of romidepsin significantly enhanced the effect of cytarabine: romidepsin probably affects the cytidine-metabolizing pathway by reducing the expression of cytidine deaminase, an enzyme involved in deactivation of cytarabine, and increases the DNA damage–response to cytarabine [24][25].

2.3. Methylation of Histones

Acetylation of histones is not the only histone modification that is involved in ALL development, but also histones methylation is engaged. According to the study by Mei M et al., symmetric dimethylation of H4R3 (H4R3sme2) was upregulated and was due to high expression of protein arginine methyltransferase 5 (PRMT5) in BCP-ALL pediatric patients. Upregulation of H4R3sme2 and PRMT5 occurs in patients with pediatric ALL and is associated with dysregulation of B-cell lineage differentiation. Therefore, an inhibition of PRMT5 expression and its methylation activity may be a potential therapeutic target [26]. Other histones' methyltransferase plays an important role in the development of ALL. DOT1L is a methyltransferase involved in histone H3 lysine methylation (H3K79me) [27]. This methylation is an important driver of MLL-rearranged ALL, because it is associated with increased transcription of MLL-rearranged ALL genes [28]. For this reason, inhibition of DOT1L can be a therapeutic option in MLL-rearranged ALL treatment, but more research is needed to evaluate the usefulness of DOT1L enzymatic activity inhibitors, DOT1L degraders, protein–protein interaction inhibitors, and combinatorial interventions in MLL-rearranged ALL treatment [29].

3. MiRNA in Pediatric ALL

In ALL, expression of some specific microRNAs (miRNA) can be increased or decreased. For this reason, they can be classified as oncomiRs or tumor suppressors: the upregulation of expression suggests that miRNA is oncomiR, whereas downregulation classifies miRNA as tumor suppressor. A distortion of the level of expression of some specific miRNAs can be used in the diagnosis, classification and treatment of ALL [30]. MiRNAs are short non-coding fragments of RNA consisting of 21–22 nucleotides. In normal conditions, by participating in the post-transcriptional regulation of genes, they regulate basic biological processes in the cell, such as growth, proliferation

and apoptosis [31]. MiRNA is also involved in the regulation of function and maturation of lymphocytes, regulations of tyrosine kinase and Ras signaling pathways [32].

3.1. Epigenetic Regulation of miRNA Expression in ALL

The expression of miRNA can be regulated through hypermethylation and hypomethylation of miRNAs gene promoters. The study from 2009 showed that expression of miR-124a can be regulated by hypermethylation of miR-124a gene promoters: hypermethylation of the promoter is associated with downregulation of miR-124a in ALL cells [33]. Additionally, research by Mi S et al. carried out on 18 bone marrow samples with MLL-rearranged ALL showed that the expression of miR-128 depends on hypomethylation of the CGIs in the promoter region: the expression level of the miRNA has a negative correlation with the degree of methylation of the CGIs [34]. Another study from 2011 suggests that miR 34b expression in MLL-rearranged ALL is downregulated by methylation of CGIs in its gene promoter [35]. In BCP, ALL with TCF3-PBX1 genetic subtype promoters of miR1273G, miR1304 and miR663 were hypermethylated, whereas promoters of miR4442, miR155 and miR3909 where hypomethylated [36]. A study by Faber J et al. suggests that in Ph+ ALL downexpression of miR-203 is induced by promoter CpG hypermethylation [37].

3.2. Use of miRNA in Diagnosis and Treatment of ALL

According to a study by Shafik RE et al., miRNA-128 is one of the miRNAs that may be used in the diagnosis of ALL. This analyzed the miRNA-128 levels in bone marrow cells from 56 newly diagnosed patients with childhood ALL. Overall, 83.9% (n = 47) of patients showed overexpression of miRNA-128. Compared to the control group, the level of miRNA-128 in ALL patients was higher [38]. Moreover, the study from 2021 showed that a higher level of miRNA-128-2-5p and miR-378 detected in the blood is associated with ALL relapse, and they can be used as biomarkers for early detection of ALL relapse [39]. The level of miR-181a is also increased in ALL [40]. According to the study by Lyu X et al., miR-181a-5p promotes ALL cell proliferation—suppression of Wnt Inhibitory Factor 1 (WIF1) gene by miR-181a-5p lead to the Wnt pathway activation, resulting in carcinogenesis through dysregulation of cell proliferation and differentiation. For this reason, inhibition of miR-181a-5p can be used as a therapeutic strategy for the treatment of ALL [41]. Moreover, in research by Egyed B et al. carried out on various ALL genetic subgroups as normal karyotype, hyperdiploid, high hyperdiploid, KMT2A-rearranged, P2RY8-CRLF2 translocated, CDKN2A deleted and ETV6 deleted, the level of miR-181a or miR-181a in combination with Vascular endothelial growth factor A (VEGF-A) detected in the cerebrospinal fluid can be useful in the future as a marker of central nervous system (CNS) involvement in pediatric ALL [42][43]. A study by El-Khazragy N et al. found that a high level of miR-181a and miR-155 in bone marrow cells was correlated with a higher risk of recurrence and poor response to treatment. This also showed that the levels of both miRNAs were downregulated after chemotherapy, which suggest that they can be used as markers of successful therapy [44]. MiR-155 can also promote ALL cell proliferation and inhibit apoptosis, its high level is associated with poor prognosis. Because of that, miR-155 had potential value as a biomarker for predicting prognosis [45]. The study from 2021 suggest that an increased level of circulating MiR-146a in the plasma seems to be a non-invasive predictive biomarker for B-ALL and T-ALL. Monitoring the expression of miR-146a can be used to assess the response to treatment: a reduction of miR-146a

expression after chemotherapy seems to be associated with a good response to treatment [46]. Moreover, Anti-miR-146a, Anti-miR-155, and Anti-miR-181a have antileukemic effects. The study by Durmaz B et al. suggests that they affect viability, proliferation, cell cycle and apoptosis of leukemia cell lines and may be useful in therapies for pediatric ALL [47]. A study by Boldrin E et. al suggests that expression of miR-497 and miR-195 is downregulated in BCP-ALL. Moreover, lower expression of both miRNAs is associated with early relapse and shorter relapse-free survival, whereas higher expression of both miRNAs suppressed in vivo growth of leukemia [48]. Lower expression of miR-223 is also characteristic for ALL. Moreover, the level of miR-223 can be used as a possible predictor of ALL relapse and in the monitoring of the treatment: its expression increases in parallel with successful treatment [49]. Because miR-223 inhibits cell proliferation and promotes apoptosis in ALLm upregulation of this miRNA may be a potential therapeutic target [50]. Expression of miR-125b can be decreased in pediatric patients with ALL and is associated with poor disease outcome and malignancy progression. In addition, miR-125b has a regulatory role in B-cell lymphoma 2 (Bcl-2). An expression of miR-125b is related to an expression of Bcl-2: a downregulation of miR-125b is related to Bcl-2 upregulation. The miR-125b Bcl-2 combination can be used to monitor response to therapy [51]. Additionally, the study by Piatopoulou D et al. showed that an expression of miR-125b in bone marrow can be used for monitoring the efficiency of Berlin–Frankfurt–Münster (BFM) therapy. The research was carried out on 125 childhood patients: 88.0% (*n* = 110) of patients had B-ALL, whereas 12.0% T-ALL. 17.6% (*n* = 22) of patients presented high hyperdiploidy (>50 chromosomes) type of ALL, 3,2% (*n* = 4) Hypodiploidy (≤45 chromosomes) type of ALL. Additionally, 1.6% (*n* = 2) were Philadelphia chromosome BCR-ABL1 positive, 24.8% (*n* = 31) had TEL-AML1 (ETV6-RUMX1) fusion gene. A reduced level of miR-125b on diagnosis day and higher 33 day after BFM induction/diagnosis day expression ratio correlate with unfavorable clinicopathological prognostic features: higher risk for disease recurrence and poor survival outcome [52]. A study by Yadav M et al. showed that an evaluation of an expression of circulating miR150 may help in assessing the effectiveness of bone marrow ablation and reconstitution of marrow after transplantation [53]. Expression levels of other miRNAs can be used as diagnostic and multidrug-resistant biomarkers in ALL. MiR-324-3p and miR-508-5p regulate ATP Binding Cassette Subfamily A Member 3 protein coding gene (ABCA3) expression. Overexpression of this gene is associated with increased chemoresistance in ALL. There is a negative correlation between the expression of these two miRNAs and ABCA3 expression. For this reason, an underexpression of these miRNAs suggests multidrug-resistant ALL. Additionally, expression is lower compared to the non-cancer control group [54]. MiRNAs can also influence the effectiveness of glucocorticoids in ALL treatment. Since miR-124 decreased Nuclear Receptor Subfamily 3 Group C Member 1 protein (NR3C) protein expression, which is the receptor for glucocorticoids, expression of miR-124 is significantly higher in children with glucocorticoids-insensitive ALL compared to children with glucocorticoids-sensitive ALL. Moreover, miR-124 is a possible therapeutic target in ALL with glucocorticoids resistance [55]. Whereas a study by Tian C et al. revealed that miR-503 is downregulated in glucocorticoid-resistant leukemic cells and overexpression of miR-503 promotes sensitization to dexamethasone [56].

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