A REVIEW ON THE RELATIONSHIP BETWEEN MATERNAL ENVIRONMENT AND PEDIATRIC ALL INITIATION AND PROGRESSION: THE ROLE OF EARLY-LIFE EPIGENETIC MODIFICATIONS

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ABSTRACT

Acute lymphoblastic leukemia (ALL) is the most common pediatric cancer, yet its etiology remains incompletely understood, particularly regarding the interplay between genetic, epigenetic, and environmental factors. This review explores how early-life epigenetic modifications contribute to ALL initiation and progression, with a focus on maternal influences. Unlike genetic mutations, epigenetic changes are reversible and shaped by environmental exposures, making them critical in leukemia risk and prognosis.

Maternal folate levels and metabolic conditions can alter fetal DNA methylation, influencing hematopoietic development. Folate provides methyl groups necessary for maintaining genomic stability, and its deficiency during pregnancy can lead to DNA hypomethylation, disrupting gene regulation and potentially fostering leukemogenesis, the process by which normal hematopoietic cells transform into malignant leukemia cells. Similarly, maternal diabetes, through hyperglycemia and insulin-like growth factor 1 overproduction, induces oxidative stress and epigenetic changes that may predispose offspring to ALL.

Epigenetic alterations, such as DNA methylation changes, can have distinct signatures linked to prognosis and therapeutic response. These findings highlight their potential as early biomarkers and targets for intervention. However, the field lacks longitudinal studies tracking epigenetic changes from birth to diagnosis.

By integrating research on maternal environmental factors and leukemia-associated epigenetic modifications, this review underscores the need for further investigation into potential pathways linking maternal exposures to epigenetic programming and subsequent leukemogenesis. Understanding these mechanisms could improve early detection, predict prognosis, and inform targeted therapies for pediatric ALL.

ABBREVIATIONS

Epigenetic signatures are abbreviated as the following:
i.e. H3K9me3: histone 3, lysine 9, trimethylation

INTRODUCTION

Acute lymphoblastic leukemia (ALL) is the most commonly diagnosed cancer in children [1]. ALL occurs when immature lymphoid stem or progenitor cells replicate uncontrollably, undergoing clonal proliferation. These malignant cells use more resources and take up more space in the patient's bone marrow, preventing healthy stem cells from maturing properly [2]. As a result, blood cell counts decrease leading to a range of symptoms including tiredness, bruising, swollen lymph nodes, and pain. Approximately 80% of childhood cases of ALL involve B-cell progenitor cells (B-ALL) [1].

The majority of pediatric ALL cases do not have well-established causes but may result from a genetic and/or environmental factors, such as familial cancer syndromes [1]. Several mutations have been identified in ALL subtypes defined by the World Health Organization (WHO) classification of leukemia [2]. These mutations

often involve aberrant activity of transcription factors, chromosomal gains or losses, and hyperactivity of tyrosine kinase genes, affecting growth, metabolism, and differentiation. Less commonly, genetic mutations may be inherited from parents and increase the child's risk of cancer. For instance, Li-Fraumeni syndrome occurs when a child inherits a mutated version of the TP53 tumor suppressor gene, increasing their risk of leukemia [3]. However, mutations are often acquired, developing after conception. Lifestyle-related risk factors such as body weight, physical exercise, tobacco use, and diet play a larger role in adult cancers but have a limited influence on childhood cancers as it takes several years for these factors to influence risk [4]. Ultimately, the cause of the majority of mutations in childhood ALL remain unknown, are thought to arise from chance mutations in lymphoblasts, which are mutations that occur randomly and without external influence [5].

Beyond genetic mutations, growing evidence highlights the role of epigenetic modifications in pediatric cancers [6]. Epigenetics is an emerging and evolving field of research which refers to heritable changes in gene expression that occur without altering the underlying DNA sequence [7]. Unlike inherited genetic mutations, epigenetic changes can be reversible [7]. These changes are regulated by mechanisms such as DNA methylation and histone modification, as well as microRNAs (miRNA), which influence how genes are expressed or silenced [7]. Epigenetic processes are crucial for normal development, but their dysregulation can contribute to cancer initiation and progression [8]. In pediatric ALL, epigenetic modifications can influence key processes such as cell differentiation, proliferation, and apoptosis. Typical hematopoietic cell development relies on precise regulation and control of these modifications. During leukemogenesis, these may also be deregulated. These epigenetic alterations may be triggered by environmental exposures in early life, such as maternal diet, environment, or toxic substances, potentially contributing to the initiation and progression of leukemia. Understanding the role of early-life epigenetic modifications in pediatric ALL offers valuable insights into disease mechanisms and can help inform therapeutic interventions and treatment.

While epigenetic mechanisms are well-documented at the time of ALL diagnosis, their potential role in predisposing children to the disease or contributing to its early development remains underexplored and not yet established [9]. The following review will investigate maternal environmental factors that contribute to early-life epigenetic changes. Then, it will demonstrate how these epigenetic changes are implicated in the initiation and progression of pediatric ALL. Through this exploration, the review will highlight potential mechanisms linking early-life epigenetic changes to increased susceptibility to pediatric ALL. Early-life is defined as the prenatal period.

METHODS

A comprehensive search was conducted concerning epigenetics, environmental influences, and their implications in pediatric ALL. Databases used included OVID, PubMed and ScienceDirect. Our inclusion criteria encompassed several study types such as systematic reviews, prospective and retrospective studies. However, case studies were excluded from our search to explore broader trends rather than focused examples. The literature included came from regions in North America, Europe and Asia as epigenetics involvement in pediatric ALL is an emerging field, resulting in a limited amount of research focused in North America alone. Thus, this article pulled from a variety of sources to have a well-rounded understanding of the relationship between epigenetics and pediatric ALL and produce more rigorous evidence-based conclusions.

ENVIRONMENTAL FACTORS

While there are several environmental factors that have been associated with the risk of developing childhood ALL, this review will focus on maternal folate intake, maternal diabetes, and maternal diet. The selection of these factors was based on their consistency in recent epidemiological studies, their biological relevance in fetal development and immune function, and the availability of peer-reviewed literature. With this refined scope, we aim to provide a detailed analysis of how these factors may influence the development of ALL in children.

3.1 Folate

Maternal folate intake plays an important role in DNA methylation. Folate is involved in the 1-carbon metabolism pathway. A metabolic pathway which utilizes folate as a carrier to synthesize methyl group donors [10]. This pathway specifically generates S-adenosylmethionine (SAM), a universal methyl donor integral methylation reaction such as histone and DNA methylation [10]. In this process, dietary folate is metabolized into 5-methyltetrahydrofolate (5-methylTHF) and subsequently converted into tetrahydrofolate (THF), a coenzyme. THF is used to produce 5,10-methyleneTHF and then 5-methylTHF via the methylenetetrahydrofolate reductase (MTHFR) enzyme. This reaction provides remethylation of homocysteine into methionine, a precursor of SAM [11]. As illustrated in Figure 1, limited folates as a methyl group source can disrupt the maintenance of proper methylation processes leading to genomic DNA hypomethylation [12]. A study examined the link between maternal folate intake and ALL [13]. They analyzed bone marrow from children with ALL and saliva from their mothers. By assessing genetic variations in folate metabolism and DNA methylation patterns,

researchers found that some leukemia cases exhibited abnormal DNA hypermethylation in genes regulating cell growth. Since folate influences DNA methylation, these findings suggest that maternal folate status during pregnancy may contribute to epigenetic changes in utero, potentially increasing ALL risk in offspring [13].

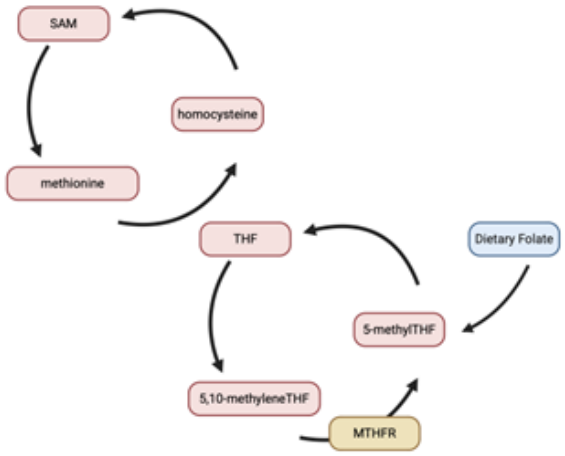

Figure 1. 1-carbon metabolism pathway: Adapted from [10,11]

3.2 Diabetes

Maternal diabetes has been identified as one of the numerous in-utero factors associated with an increased risk of childhood ALL [14]. This risk is linked to two categories of maternal diabetes: pregestational diabetes mellitus and gestational diabetes mellitus (GDM). Several primary and secondary studies have explored this relationship.

A register-based study conducted in Denmark by Søegaard et al. examined this association in children born between 1996 and 2015 [14]. The findings revealed that children of mothers with pregestational diabetes had a 2.91-fold higher risk of developing ALL, with the strongest associations observed in genetic subtypes such as ETV6-RUNX1-positive and high-hyperdiploidy. GDM also elevated the risk, although to a lesser extent, with a 1.75-fold increase compared to children of non-diabetic mothers. No significant association was found between paternal diabetes and the risk of ALL. However, higher birth weight, a common outcome in babies of mothers with diabetes, was loosely associated with an increased risk of ALL, particularly in children of mothers with pregestational diabetes, but not in those of mothers with gestational diabetes [14].

A recent study by Marcoux et al. conducted a retrospective cohort study of 1 million children born between 2006 and 2019 in Quebec, Canada, to assess the risk of childhood cancer following exposure to GDM [15]. The study found an increased risk of childhood cancers, with leukemia showing the strongest association. The findings suggested that children exposed GDM during pregnancy had a 1.74-fold increase in the risk of developing ALL within the first two years of life compared to children who were not exposed to GDM [15].

The association between GDM and childhood cancer is thought to be driven by maternal hyperglycemia and hyperinsulinemia [16]. Hyperglycemia is associated with the production of reactive oxygen species, which can cause DNA damage in fetal cells, potentially increasing cancer risk later in life. GDM also alters fetal growth through overproduction of insulin (IGF-1), which promotes cellular growth. Elevated insulin levels are associated with fetal macrosomia (higher birth weight), and have been linked to a greater risk of leukemia, particularly ALL. Hematopoietic cells may be especially sensitive to high IGF-1 levels, increasing the risk of blood cancers [15].

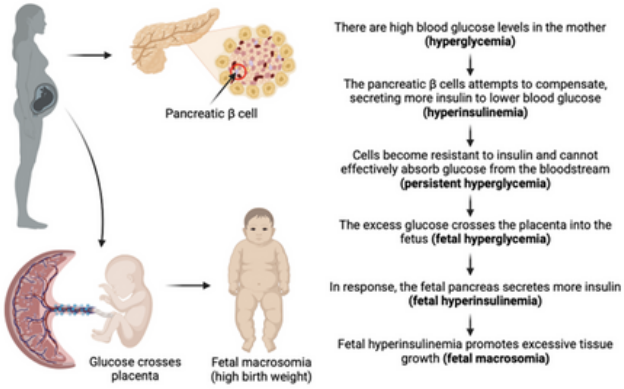

Figure 2. The mechanism of GDM: Adapted from [17]

3.3 Diet

The maternal diet shapes the risk of a child developing ALL. Two key systematic reviews have examined this relationship, revealing both protective and harmful effects of certain foods and nutrients.

Several foods have protective effects, such as certain fruits, vegetables, protein sources, folic acid, and multivitamins [18,19]. Children whose mothers eat a diet rich in fruits and vegetables during pregnancy may have a lower risk of developing ALL. Foods abundant in antioxidants such as carotenoids, vitamin A, and vitamin C, help prevent DNA damage. Glutathione is an antioxidant tripeptide found in meat and vegetables. It plays a key role in cellular functions such as cell differentiation, proliferation, and apoptosis. These processes help promote DNA repair and maintain cellular health, potentially lowering the risk of leukemogenesis [19]. The decreased risk of ALL associated with the maternal use of vitamin formulations as supplements can be explained by the capacities of the components, including folate and iron, to protect against oxidative damage to lipids, lipoproteins and DNA [19].

In contrast, some foods may have harmful effects, such as caffeine. Maternal coffee consumption, more than two cups per day, is linked to an increased risk of childhood ALL [19]. Caffeine can inhibit Topoisomerase I and Topoisomerase II, which are nuclear enzymes that solve the topological problems associated with DNA replication, transcription, recombination and chromatin remodeling. This can potentially cause DNA damage and increased leukemia risk.

MECHANISMS

This review explores DNA methylation, histone modifications, and miRNAs as they are among the most well-studied epigenetic mechanisms with established roles in gene regulation and relevance to leukemia [7,8].

4.1 DNA Methylation

DNA methylation is a key epigenetic mechanism that can contribute to the initiation and progression of many cancers, including pediatric ALL by altering gene expression patterns crucial for normal hematopoiesis [9]. In particular, aberrant methylation can disrupt cellular differentiation and tumor suppression, potentially driving leukemogenesis.

DNA methylation involves the addition of methyl groups to cytosine residues in CpG dinucleotides, often leading to transcriptional silencing of critical regulatory genes [20]. One of the most extensively studied forms of aberrant DNA methylation in ALL is the hypermethylation of CpG-rich regions, known as CpG islands (CGIs), which are commonly found in gene promoter regions. A review by Nourlund & Syvänen revealed that ALL cells consistently exhibit higher levels of methylation at CpG sites within CGIs compared to both normal bone marrow cells and cells in remission [21]. This means that the hypermethylation of CGIs is associated with the disease. This modification can silence tumor suppressor genes and differentiation factors, contributing to malignant transformation [21].

DNA methylation patterns are largely established during early embryogenesis and are influenced by genetic and environmental factors [9,22]. Hence, the prenatal period represents a critical window for the establishment of DNA methylation patterns which can influence disease susceptibility. Specifically, emerging evidence suggests that aberrant methylation patterns associated with pediatric ALL may originate in utero [9]. For example, a study by Nickels et al. examined twins discordant for ALL and identified differential DNA methylation at birth, using archived neonatal blood spots [9]. They identified that DNA hypomethylation may contribute more generally to ALL risk. Thus, these epigenetic alterations may occur prenatally and precede disease onset, supporting the hypothesis that early-life methylation changes may serve as a priming event for leukemogenesis, predisposing hematopoietic cells to malignant transformation later in life.

Beyond general DNA methylation dysregulation, specific methylation markers associated with pediatric ALL have been detected years before clinical diagnosis, suggesting a role in disease initiation. One well-documented example is the hypermethylation of VTRNA2-1, a gene involved in cellular mechanisms like Protein Kinase R-mediated cell death and immune regulation [23]. A large-scale birth cohort study analyzing neonatal blood spots found that VTRNA2 -1 hypermethylation was detectable at birth in infants who later developed ALL [23] . This study, as well as Nickels et al. [9] , provide evidence that this epigenetic alteration occurs in utero rather than as a secondary consequence of leukemia progression. Hypermethylation of this gene was significantly associated with reduced VTRNA2 -1 expression and worse survival outcomes in pre-B ALL patients [23] . These findings were validated across multiple independent populations and ethnicities and remained stable across different tissues, suggesting a consistent and reproducible early-life methylation signature . An epigenetic signature refers to a gene-specific, genome-wide DNA methylation pattern. Further, longitudinal follow-up of leukemia patients revealed a dynamic pattern: VTRNA2 -1 hypermethylation was elevated at leukemia diagnosis, normalized during remission, and increased again at relapse. This links it to disease progression. Beyond VTRNA2 -1, other genes have also been identified as exhibiting aberrant DNA methylation in pediatric ALL, contributing to leukemogenesis. T hese findings highlight the prognostic value of epigenetic signatures. Genome-wide analyses have revealed a distinct DNA methylation signature in leukemic bone marrow, characterized by hypermethylation of genes such as TCF3 [24] , EGR4 [25] , and BTG4 [26] . These genes are integral to B-cell differentiation, cell cycle regulation, and apoptosis; their silencing promotes the dysregulation of hematopoiesis and survival of leukemic blasts.

Overall, these findings indicate that aberrant DNA methylation may precede and contribute to leukemogenesis, and that once leukemia has been established, DNA methylation continues to influence its aggressiveness and progression.

4.2 Histone Modifications

Histones are recognized for their integral role in DNA packaging where they can be modified to promote or deter transcription of specific genes [8]. Negatively charged DNA wraps around positively charged histone proteins made from lysine and arginine residues. Post-translational modifications are highly specific, most often involving epigenetic changes such as methylation or acetylation at lysine residues. For instance, the following epigenetic changes suppress gene expression; H3K9me3, H3K27me3, while H3K4me3, H3K9ac, H3K14ac, H3K79me have been shown to promote gene expression [8]. The control of key enzymes balance these changes. For methylation, there are histone lysine methyltransferases (HMTs) and histone lysine demethylases (HDMs). For acetylation, there are histone acetyltransferases (HATs) and histone deacetylases (HDACs). Ultimately, research shows that the etiology of ALL may be influenced by gain or loss of function mutations of epigenetic modifying genes thus causing irregulated histone marks and subsequent malignancy [8]. The following paragraphs will discuss specific histone modifications, involving both histone acetylation

and methylation, and their mechanism of action in ALL.

4.2.1 Histone Acetylation

Several genes and proteins may be responsible for histone acetylation in ALL [27].
Loss of function mutations to the CREB binding protein (CREBBP) gene have been shown in B-ALL. The CREBBP contains HAT activity, particularly with H3K18 [27]. When this gene is mutated, oftentimes in relapsed cases, there is transcriptional dysregulation of targets including glucocorticoid responsive genes [27,28]. A 2015 next-generation sequencing study of childhood ALL found a larger incidence of CREBBP alterations in high hyperdiploidy cases of B-ALL, the most common subtype of ALL in children [29]. Moreover, a study by Gao et al. suggests that low CREBBP expression can be associated with adverse long-term risk factors in pediatric ALL and that it is an indicator of worse prognosis [30].

Additionally, several HDAC proteins have been demonstrated to be more highly expressed in ALL cases in comparison to healthy bone marrow [30]. A global loss of histone h4 acetylation has been commonly shown in pediatric B-ALL where favourable prognosis is associated with preserved acetylation [31]. Additionally, one study examining 94 pediatric ALL cases found that higher expression of HDAC7 and HDAC9 genes resulted in worse prognosis [30]. Thus, HDAC inhibitors have become appealing pharmaceutical targets to prevent relapse. Furthermore, protocadherin 17 protein coding gene is a tumour suppressor gene that may be involved in ALL. Repression of deacetylation has been shown to upregulate this gene's transcription, thus making this a potential therapeutic mechanism to treat ALL [32].

4.2.2 Histone Methylation

Histone methylation occurs when a methyl group is added to histone proteins, which can either activate or repress gene expression, depending on the specific histone residue [33]. Histone methylation may be involved in the KMT2A rearrangement B-ALL [34]. This is the most prevalent B-ALL subtype among children, accounting for 70% of infant leukemias [35]. KMT2A is a H3K4, HMT protein that activates transcription of mapped genes [35]. When this gene is rearranged it commonly results in fusion proteins. These fusion proteins can interact with epigenetic regulators, subsequently dysregulating gene expression [36]. For example, histone 3 lysine 79 methyltransferase (DOT1L), may be recruited by MLL-fusion proteins causing overexpression of the HOXA homeobox gene [27,33]. This can result in leukemia as this gene is normally tightly regulated by hematopoietic progenitors.

Furthermore, a study by Jaffe et al. found that t(4;14) translocation induces NSD2 mutations, commonly among those with the ETV6-RUNX1 fused gene B-ALL subtype [36]. NSD2 is HMT of H3K36 [8]. Normally, H3K36 is unmethylated, whereas the epigenetic signature involving NSD2 mutations demonstrates increased H3K36me2 and lower levels of unmodified H3K36. Additionally, a whole genome sequencing of 12 cases of T-ALL, highlighted loss of function mutations in the genes that encode for components of the polycomb repressor complex 2 (PRC2), thus demonstrating this gene's tumour suppressing role [8]. As PRC2 contains H3K27 methyltransferase activity, when its expression is altered, the subsequent expression of the genes it acts on changes [37]. Studies have shown that PRC2 loss of function mutations are associated with activation of the IL7R/JAK/STAT pathway, leading to uncontrolled cell growth in T-ALL [37].

4.3 MiRNA

MiRNAs are small non-coding RNAs which play a role in regulating gene expression [38,39]. They can do this through sequence-specific binding to mRNA to promote or hinder its translation. These RNA molecules can be around 22 nucleotides long which can negatively control target gene expression post-transcriptionally. Currently, there are about 460 known human miRNAs [39]. Most MiRNAs are transcribed from DNA sequences into primary miRNAs which are then processed into precursor miRNAs, and ultimately into mature miRNAs. miRNAs can act as tumour suppressor genes as well as oncogenes [38-40]. Differentially expressed miRNAs have been seen to be associated with the initiation and progression of childhood ALL [38-40].

Oncogenic miRNAs (oncomiRs) have been seen to be involved with the progression of childhood ALL [41]. OncomiRs can promote leukemogenesis by downregulating tumor suppressor genes, enhancing oncogenic pathways [40]. There are many OncomiRs that exist, for example miR- 55 is a well-characterized oncomiRs, often overexpressed in childhood ALL patients. As seen in figure 2 miR-155 promotes ALL progression through inhibiting Casitas B-lineage lymphoma (CBL), a protein that plays a role in reducing proliferation and enhancing apoptosis of ALL cells [41]. miR-155 additionally has been seen to inhibit function of ZNF238, a tumor suppressor [41,42]. As such overexpression of miR-155 can increase cell proliferation in ALL cells [43]. miR-155 is just one type of oncomiR that plays a role in the initiation and progression of ALL specifically by promoting increased cell proliferation in ALL cells.

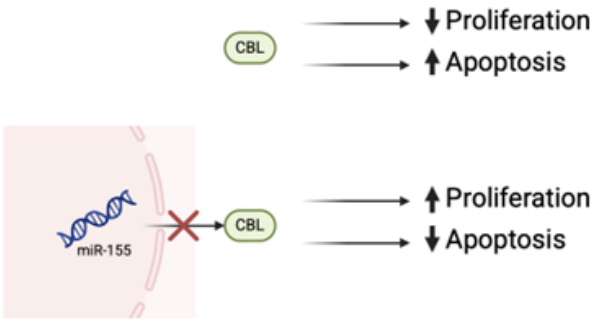

Figure 3. miR-155 promotes ALL progression by inhibiting CBL, thus leading to increased proliferation and decreased apoptosis of ALL cells. Adapted from [42]

DISCUSSION

This review underscores the growing recognition of early-life epigenetic modifications as key contributors to the initiation and progression of pediatric ALL. While previous research has focused heavily on genetic mutations, emerging evidence highlights the role of DNA methylation, histone modifications, and miRNA dysregulation in shaping the leukemic epigenome [8]. These alterations can silence tumor suppressor genes, disrupt normal hematopoiesis, and promote leukemogenesis [8]. Notably, epigenetic changes can be influenced by prenatal environmental exposures, suggesting that ALL susceptibility may, in part, be established in utero [8,9,13,14].

One of the most compelling findings is the influence of maternal factors on the epigenetic regulation of ALL risk. Studies have linked maternal folate intake and diabetes to differential DNA methylation patterns in offspring, with potential implications for disease susceptibility [13]. Maternal folate depletion has been associated with altered methylation of genes implicated in leukemogenesis, whereas maternal diabetes has been linked to increased ALL risk [13]. While these associations provide important insight, the precise mechanistic pathways remain unclear. Further research is needed to determine how these maternal exposures drive specific epigenetic modifications and whether interventions targeting these pathways could reduce disease risk.

Beyond environmental influences, aberrant DNA methylation is a hallmark of pediatric ALL [9,21]. The hypermethylation of CpG islands in tumor suppressor genes has been detected at birth in infants who later develop ALL, indicating that epigenetic changes may precede ALL onset [23]. Similarly, histone modifications contribute to leukemogenesis, as mutations in histone-modifying genes, including CREBBP and NSD2, disrupt transcriptional regulation [8,27]. The overexpression of HDACs in ALL has also been linked to poor prognosis, supporting the rationale for HDAC inhibitors as potential therapeutic targets [30]. Furthermore, dysregulated miRNAs, such as miR-155, drive leukemic cell proliferation by downregulating tumor suppressor pathways, reinforcing the significance of post-transcriptional gene regulation in ALL pathogenesis [40-43].

Overall, this review bridges two critical aspects of pediatric ALL research;demonstrating how maternal environmental factors can drive early-life epigenetic changes and how these modifications, in turn, influence both the incidence and prognosis of the disease. By integrating evidence from recent studies, this review highlights potential connections linking maternal exposures to epigenetic changes and subsequent leukemogenesis and emphasizes the need for further longitudinal investigations.

LIMITATIONS

Several key challenges remain. A major limitation of current research is the reliance on associative and retrospective studies, which makes it difficult to establish causal relationships such as between early-life epigenetic modifications and ALL onset. While some methylation patterns have been detected at birth, more research needs to be done to confirm that these changes are primary drivers of leukemogenesis. Future studies should aim to confirm the direct role of specific epigenetic modifications in disease initiation. There were also a limited number of longitudinal studies tracking epigenetic changes from birth through leukemia diagnosis. In our review, Ghantous et al., a prospective birth cohort study, emerges as one of the first and most comprehensive studies of its kind in pediatric ALL research [23]. This study not only demonstrates that specific epigenetic markers are detectable at birth, but more notably tracks their stability and changes over the course of the disease. Other included studies have provided valuable insights by comparing epigenetic differences at birth (for instance, in twins discordant for ALL) [9], yet they do not offer the same serial follow-up across multiple disease stages. The lack of longitudinal studies highlights the urgent need for more research to track how early-life epigenetic changes develop over time and drive the onset of leukemia.

Additionally, mechanistic/functional studies are needed to determine how maternal factors, such as diet and metabolic conditions, modulate the epigenome and induce specific epigenetic changes in hematopoietic stem cells. This would help establish that maternal factors contribute to leukemia risk specifically via induction of epigenetic changes.

1. Ekpa QL, Akahara PC, Anderson AM, Adekoya OO, Ajayi OO, Alabi PO, et al. A review of acute lymphocytic leukemia (ALL) in the pediatric population: evaluating current trends and changes in guidelines in the past decade. *Cureus*. 2023. https://www.cureus.com/articles/207257-a-review-of-acute-lymphocytic-leukemia-all-in-the-pediatric-population-evaluating-current-trends-and-changes-in-guidelines-in-the-past-decade
2. National Cancer Institute. *Childhood acute lymphoblastic leukemia treatment (PDQ®)*. 2025. https://www.cancer.gov/types/leukemia/hp/child-all-treatment-pdq#_7_toc
3. Aedma SK, Kasi A. Li-fraumeni syndrome. *StatPearls*. 2025. http://www.ncbi.nlm.nih.gov/books/NBK532286/
4. Jin MW, Xu SM, An Q, Wang P. A review of risk factors for childhood leukemia. *European Review for Medical and Pharmacological Sciences*. 2016;20(18):3760-3764. https://pubmed.ncbi.nlm.nih.gov/27735044/
5. Cincinnati Children's. *Leukemia*. 2022. Available from: https://www.cincinnatichildrens.org/health/l/leukemia
6. Panditharatna E, Filbin MG. The growing role of epigenetics in childhood cancers. *Current Opinion in Pediatrics*. 2020;32(1):67–75. https://journals.lww.com/10.1097/MOP.0000000000000867
7. Farsetti A, Illi B, Gaetano C. How epigenetics impacts on human diseases. *European Journal of Internal Medicine*. 2023;114:15-22. https://linkinghub.elsevier.com/retrieve/pii/S0953620523001930

8. Burke MJ, Bhatla T. Epigenetic modifications in pediatric acute lymphoblastic leukemia. *Frontiers in Pediatrics*. 2014;2. http://journal.frontiersin.org/article/10.3389/fped.2014.00042/abstract
9. Nickels EM, Li S, Myint SS, Arroyo K, Feng Q, Siegmund KD, et al. DNA methylation at birth in monozygotic twins discordant for pediatric acute lymphoblastic leukemia. *Nature Communications*. 2022;13(1):6077. https://www.nature.com/articles/s41467-022-33677-z
10. Ducker GS, Rabinowitz JD. One-carbon metabolism in health and disease. *Cell Metabolism*. 2017;25(1):27–42. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5353360/
11. Mentch SJ, Locasale JW. One-carbon metabolism and epigenetics: understanding the specificity. *Annals of the New York Academy of Sciences*. 2016;1363(1):91–8. https://nyaspubs.onlinelibrary.wiley.com/doi/10.1111/nyas.12956
12. Crider KS, Yang TP, Berry RJ, Bailey LB. Folate and DNA methylation: a review of molecular mechanisms and the evidence for folate's role. *Advances in Nutrition*. 2012;3(1):21–38. https://linkinghub.elsevier.com/retrieve/pii/S2161831322009644
13. Schraw JM, Yiu TT, Lupo PJ, Tsavachidis S, Rau R, Bondy ML, et al. Maternal folate genes and aberrant DNA hypermethylation in pediatric acute lymphoblastic leukemia. *Public Library of Science ONE*. 2018;13(5):e0197408. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5953491/
14. Søegaard SH, Rostgaard K, Kamper-Jørgensen M, Schmiegelow K, Hjalgrim H. Maternal diabetes and risk of childhood acute lymphoblastic leukaemia in the offspring. *British Journal of Cancer*. 2018;118(1):117–20. https://www.nature.com/articles/bjc2017351
15. Marcoux S, Côté-Corriveau G, Healy-Profitós J, Auger N. Varying impact of gestational diabetes mellitus on incidence of childhood cancers: an age-stratified retrospective cohort study. *Diabetes Care*. 2022;45(5):1177–83. https://diabetesjournals.org/care/article/45/5/1177/144696/Varying-Impact-of-Gestational-Diabetes-Mellitus-on
16. Potter C, Moorman AV, Relton CL, Ford D, Mathers JC, Strathdee G, et al. Maternal red blood cell folate and infant vitamin B12 status influence methylation of genes associated with childhood acute lymphoblastic leukemia. *Molecular Nutrition & Food Research*. 2018;62(22):1800411. https://onlinelibrary.wiley.com/doi/10.1002/mnfr.201800411
17. Choudhury AA, Devi Rajeswari V. Gestational diabetes mellitus - A metabolic and reproductive disorder. *Biomedicine and Pharmacotherapy*. 2021;143:112183. https://www.sciencedirect.com/science/article/pii/S0753332221009677
18. Abiri B, Kelishadi R, Sadeghi H, Azizi-Soleiman F. Effects of maternal diet during pregnancy on the risk of childhood acute lymphoblastic leukemia: a systematic review. *Nutrition and Cancer*. 2016;68(7):1065–72. https://www.tandfonline.com/doi/full/10.1080/01635581.2016.1206581
19. Blanco-Lopez J, Iguacel I, Pisanu S, Almeida C, Steliarova-Foucher E, Sierens C, et al. Role of maternal diet in the risk of childhood acute leukemia: a systematic review and meta-analysis. *International Journal of Environmental Research and Public Health*. 2023;20(7):5428. https://www.mdpi.com/1660-4601/20/7/5428
20. Moore LD, Le T, Fan G. DNA methylation and its basic function. *Neuropsychopharmacology*. 2013;38(1):23–38. https://www.nature.com/articles/npp2012112
21. Nordlund J, Syvänen AC. Epigenetics in pediatric acute lymphoblastic leukemia. *Seminars in Cancer Biology*. 2018;51:129–38. https://linkinghub.elsevier.com/retrieve/pii/S1044579X17300913
22. Kessler NJ, Waterland RA, Prentice AM, Silver MJ. Establishment of environmentally sensitive DNA methylation states in the very early human embryo. *Science Advances*. 2018;4(7):2624. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6040841/
23. Ghantous A, Nusslé SG, Nassar FJ, Spitz N, Novoloaca A, Krali O, et al. Epigenome-wide analysis across the development span of pediatric acute lymphoblastic leukemia: backtracking to birth. *Molecular Cancer*. 2024;23(1):238. https://molecular-cancer.biomedcentral.com/articles/10.1186/s12943-024-02118-4
24. Lin YC, Jhunjhunwala S, Benner C, Heinz S, Welinder E, Mansson R, et al. A global network of transcription factors, involving E2A, EBF1 and Foxo1, that orchestrates B cell fate. *Nature Immunology*. 2010;11(7):635–43. https://www.nature.com/articles/ni.1891
25. Scholz C, Nimmrich I, Burger M, Becker E, Dörken B, Ludwig WD, et al. Distinction of acute lymphoblastic leukemia from acute myeloid leukemia through microarray-based DNA methylation analysis. *Annals of Hematology*. 2005;84(4):236–44. http://link.springer.com/10.1007/s00277-004-0969-1
26. Chaber R, Gurgul A, Wróbel G, Haus O, Tomoń A, Kowalczyk J, et al. Whole-genome DNA methylation characteristics in pediatric precursor B cell acute lymphoblastic leukemia (Bcp all). Bandapalli OR, editor. *Public Library of Science ONE*. 2017;12(11):e0187422. https://dx.plos.org/10.1371/journal.pone.0187422
27. Janczar S, Janczar K, Pastorczak A, Harb H, Paige A, Zalewska-Szewczyk B, et al. The role of histone protein modifications and mutations in histone modifiers in pediatric b-cell progenitor acute lymphoblastic leukemia. *Cancers*. 2017;9(1):2. https://www.mdpi.com/2072-6694/9/1/2
28. Mullighan CG, Zhang J, Kasper LH, Lerach S, Payne-Turner D, Phillips LA, et al. CREBBP mutations in relapsed acute lymphoblastic leukaemia. *Nature*. 2011;471(7337):235–9. https://www.nature.com/articles/nature09727
29. Paulsson K. High hyperdiploid childhood acute lymphoblastic leukemia: chromosomal gains as the main driver event. *Molecular and Cellular Oncology*. 2016;3(1):e1064555. https://www.tandfonline.com/doi/full/10.1080/23723556.2015.1064555
30. Gao C, Zhang R, Liu S, Zhao X, Cui L, Yue Z, et al. Low CREBBP expression is associated with adverse long-term outcomes in paediatric acute lymphoblastic leukaemia. *European Journal of Haematology*. 2017;99(2):150–9. https://onlinelibrary.wiley.com/doi/10.1111/ejh.12897
31. Drożak P, Bryliński Ł, Zawitkowska J. A comprehensive overview of recent advances in epigenetics in pediatric acute lymphoblastic leukemia. *Cancers*. 2022;14(21):5384. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC9659124/
32. Thanh Nha Uyen L, Amano Y, Al-Kzayer LFY, Kubota N, Kobayashi J, Nakazawa Y, et al. PCDH17 functions as a common tumor suppressor gene in acute leukemia and its transcriptional downregulation is mediated primarily by aberrant histone acetylation, not DNA methylation. International Journal of Hematology. 2020;111(3):451–62. http://link.springer.com/10.1007/s12185-019-02799-4
33. Bernt KM, Zhu N, Sinha AU, Vempati S, Faber J, Krivtsov AV, et al. Mll-rearranged leukemia is dependent on aberrant h3k79 methylation by dot1l. *Cancer Cell*. 2011;20(1):66–78. https://linkinghub.elsevier.com/retrieve/pii/S1535610811002285
34. Xu H, Yu H, Jin R, Wu X, Chen H. Genetic and epigenetic targeting therapy for pediatric acute lymphoblastic leukemia. *Cells*. 2021;10(12):3349. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8699354/
35. Górecki M, Kozioł I, Kopystecka A, Budzyńska J, Zawitkowska J, Lejman M. Updates in kmt2a gene rearrangement in pediatric acute lymphoblastic leukemia. *Biomedicines*. 2023;11(3):821. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC10045821/
36. Jaffe JD, Wang Y, Chan HM, Zhang J, Huether R, Kryukov GV, et al. Global chromatin profiling reveals NSD2 mutations in pediatric acute lymphoblastic leukemia. *Nature Genetics*. 2013;45(11):1386–91. https://www.nature.com/articles/ng.2777
37. Andrieu GP, Kohn M, Simonin M, Smith CL, Cieslak A, Dourthe MÉ, et al. PRC2 loss of function confers a targetable vulnerability to BET proteins in T-ALL. *Blood*. 2021;138(19):1855–69. https://ashpublications.org/blood/article/138/19/1855/476181/PRC2-loss-of-function-confers-a-targetable
38. Szczepanek J. Role of microRNA dysregulation in childhood acute leukemias: diagnostics, monitoring and therapeutics: A comprehensive review. *World Journal of Clinical Oncology*. 2020;11(6):348–69. https://www.wjgnet.com/2218-4333/full/v11/i6/348.htm
39. Chuang JC, Jones PA. Epigenetics and microRNAs. *Pediatric Research*. 2007;61(5):24R-29R. https://www.nature.com/doifinder/10.1203/pdr.0b013e3180457684

40. Otmani K, Rouas R, Lewalle P. OncomiRs as noncoding RNAs having functions in cancer: Their role in immune suppression and clinical implications. *Frontiers in Immunology*. 2022;13:913951. https://www.frontiersin.org/articles/10.3389/fimmu.2022.913951/full
41. Sun X, Guan G, Dai Y, Zhao P, Liu L, Wang Q, et al. MicroRNA-155-5p initiates childhood acute lymphoblastic leukemia by regulating the irf4/cdk6/cbl axis. *Laboratory Investigation*. 2022;102(4):411–21. https://linkinghub.elsevier.com/retrieve/pii/S002368372200054X
42. Kyriakidis I, Kyriakidis K, Tsezou A. MicroRNAs and the diagnosis of childhood acute lymphoblastic leukemia: systematic review, meta-analysis and re-analysis with novel small RNA-seq tools. *Cancers*. 2022;14(16):3976. https://www.mdpi.com/2072-6694/14/16/3976
43. Barrios-Palacios D, Organista-Nava J, Balandrán JC, Alarcón-Romero LDC, Zubillaga-Guerrero MI, Illades-Aguiar B, et al. The role of miRNAs in childhood acute lymphoblastic leukemia relapse and the associated molecular mechanisms. *International Journal of Molecular Sciences*. 2023;25(1):119. https://www.mdpi.com/1422-0067/25/1/119