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New Approaches to the Identification of Epigenetic Modifications in Chronic Lymphoid Leukemia

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Abstract: Chronic Lymphoid Leukemia (CLL), one of the most common hematologic malignancies in adults in Western countries, is a disease in which epigenetic modifications play an important role in its pathogenesis. Fundamental epigenetic mechanisms include DNA methylation, histone modifications, and non-coding RNAs and are critical for normal cellular processes, including cellular growth, development, and differentiation. The identification and understanding of these modifications allows us to analyze the biology of the disease in more detail. Thanks to the technological approaches developed in recent years, it is possible to examine epigenetic changes in CLL in a more sensitive and detailed way. These methods provide a deeper understanding of the molecular mechanisms of the disease. In addition to being an important tool in the identification of epigenetic modifications in CLL, these new approaches also contribute to the development of diagnostic, prognostic, and therapeutic strategies. These developments will allow CLL to be managed more effectively.

Keywords: CLL, Epigenetic modifications, Histone modifications

Introduction

Chronic Lymphoid Leukemia (CLL), one of the most common hematologic malignancies in adults in Western countries, is a heterogeneous disease that develops with the interaction of genetic and epigenetic factors (Coll-Mulet & Gil, 2009; Chiorazzi et al., 2021). The disease has an incidence of about 4.2 cases per 100,000 people per year, with a median age at diagnosis of 70-72 years and a male prevalence of approximately 2:1 (Pérez-Carretero et al., 2021).

Epigenetic modifications include processes that alter gene expression without affecting the DNA sequence, such as DNA methylation, histone modifications and non-coding RNA (ncRNA) (Taylor et al., 2013; Prabhakaran et al., 2021). These modifications underlie many biological processes such as cell differentiation, adhesion and replication (Wu et al., 2023). Abnormal progression of epigenetic mechanisms can play an important role in the development of many diseases such as cancer. Abnormal epigenetic mechanisms may play important roles at various stages of tumor development, triggering the formation or spread of cancer (Dai et al., 2024).

In mammalian cells, DNA methylation occurs at specific sites, often called CpG islands, where CpG dinucleotides are concentrated (Tari et al., 2018). This methylation occurs mostly in gene promoter regions and often leads to gene expression arrest by repressing promoter activity (Tari et al., 2018; Hornschuh et al.,2021). Studies suggest that DNA methylation may have an important impact on the biology of CLL. (Landau & Wu, 2013; Bagacean et al., 2017).

DNA is tightly packaged with histone proteins to form the chromatin structure. In this process, DNA, approximately 147 base pairs long, is wrapped 1.7 turns around a core of 8 histone proteins (Hornschuh et

al.,2021). Histone can undergo different post-translational modifications such as acetylation, methylation, ubiquitination and phosphorylation and play important roles in the regulation of chromatin structure and expression of genes (Nie et al., 2024; Sherif et al., 2025). Abnormalities in histone modifications can lead to inhibition of tumor suppressor genes or activation of oncogenes in cancer development (Sherif et al., 2025).

Non-coding RNAs (ncRNAs) are RNA molecules that do not code for proteins but can regulate gene expression in multiple ways (Kumar et al., 2020). They are divided into two main groups: small non-coding RNAs (sncRNA) and long non-coding RNAs (lncRNA) (Sarropoulou & Fernández, 2023). MicroRNAs, small non-coding RNAs, regulate gene expression after transcription. Dysregulation of miRNAs contributes to the development of CLL (Mansouri et al., 2018).

The rapid advancement of epigenetic research has increased interest in new technologies that will enable a more detailed understanding of epigenetic changes in health and disease states (Li, 2021; Sherif et al., 2025). In this process, various methods have been developed that have the capacity to examine chromatin structures in many dimensions, from analyses focusing on specific gene regions to sequencing covering the entire genome. These advances are supported by many strategies such as advanced imaging systems, high-throughput sequencing technologies, and integration of bioinformatics tools (Li, 2021).

Emerging technologies in the field of epigenetics offer significant opportunities to better understand epigenetic modifications in CLL and translate this knowledge into clinical practice. In this study, we will focus on new approaches used to identify epigenetic modifications in CLL and their contribution to disease biology.

New Approaches to the Identification of Epigenetic Modifications

Next Generation Sequencing (NGS) Technology

In the late 1970s, DNA sequencing techniques emerged with the use of Sanger's sequencing by Edward Sanger and chemical fragmentation by Maxam-Gilbert. In 2005, Roche introduced the faster “454” technology. This technology is called “Next Generation Sequencing (NGS)” or “High Throughput Sequencing” (Mandlik et al., 2024). NGS enables the acquisition of large amounts of genetic information in a short time with high efficiency (Yin et al., 2021; Mandlik et al., 2024). The introduction of advanced NGS platforms such as Pacific Biosciences, Illumina, and Oxford Nanopore has revolutionized genomic research by enabling the parallel sequencing of large numbers (millions to billions) of DNA templates (Yin et al., 2021; Satam et al., 2023). These technologies offer new discovery opportunities to understand gene expression, genetic diversity, microbial diversity, and epigenetic modifications (Satam et al., 2023).

In recent years, with the use of next-generation sequencing technologies, significant progress has been made in understanding CLL at the molecular level. The genetic and epigenetic diversity of the disease has been revealed in detail, especially thanks to large-scale studies involving more than a thousand patients (Nagler et al., 2023). The development of NGS technologies has helped us to understand the biological complexity of CLL more comprehensively by allowing detailed examination of genomic, epigenomic and transcriptomic profiles (Nagler et al., 2023; Oder et al., 2023). NGS-based methods frequently used in epigenetic analyses are given below.

Whole Genome Bisulfite Sequencing (WGBS): WGBS is a gold standard method that can detect and quantitatively analyze DNA methylation at genome-wide base resolution (Luo et al., 2023; Yu et al., 2024). In 2009, the first human genome-wide single base resolution DNA methylation map was created using this method (Lister et al., 2009). However, WGBS has been used in basic and clinical studies to investigate the relationship between DNA methylation loci and human phenotypes (Zhou et al., 2019). Despite reductions in sequencing costs, the high cost of implementation for large genomes is an important limitation of the method (Ortega-Recalde et al., 2021; Luo et al., 2023).

Reduced Representation Bisulfite Sequencing (RRBS): RRBS, an efficient and high-throughput method for analyzing genome-wide methylation patterns, combines restriction enzymes and bisulfite sequencing to enrich regions with high CpG density (Bell &Wan, 2020; Nkongolo & Michael 2024). This technique was developed in 2005 by Meisner and colleagues to sequence a smaller representative sample of the entire genome, due to the high cost of sequencing for whole genome methylation analyses (Meissner et al., 2005). RRBS is a method for DNA methylation detection that is convenient in terms of low cost and time saving (Sun & Zhu, 2021).

Chromatin Immunoprecipitation sequencing (ChIP-seq): ChIP-seq is a method for analyzing genome-wide DNA-protein interactions in mammalian genomes, including histone modifications and transcription factors (Islam, 2021; Coskunpınar &Yıldırım, 2024). The integration of transcription factors and histone modifications provides a significant advantage for this technique in analyzing interactions between different genomic data (Coskunpınar &Yıldırım, 2024).

Assay for Transposase-Accessible Chromatin sequencing (ATAC-seq): ATAC-seq is an efficient method for mapping chromatin accessibility in the genome (Buenrostro et al., 2015). ATAC-seq has been rapidly adopted because it is more efficient in terms of cost, time and the amount of samples required compared to previous tests (Smith & Sheffield, 2020).

RNA sequencing (RNA-seq): RNA-seq is a method used to determine which genes are expressed at what level in the cells of an organism at any stage of its life cycle. Transcriptome; all of the transcript types found in cells under certain conditions are called (Darcan & Turkyılmaz, 2018). RNA-seq with NGS technology has many advantages over previous methods and has led to radical changes in our understanding of the transcriptome. This method allows for a more detailed and quantitative examination of gene expression levels, alternative splicing events and allele-specific expression (Kukurba & Montgomery, 2015).

Single-Cell Sequencing Technology

In 2009, the first single-cell RNA sequencing method was developed (Tang et al., 2009). Since then, researchers have introduced new methods to improve the accuracy, resolution and throughput of sequencing. Today, sequencing at the single cell level provides in-depth insights into cellular diversity and function, contributing to the development of new strategies for the diagnosis and treatment of diseases (Xie et al., 2024). Single cell technologies enable detailed analysis of various biological modalities such as chromatin accessibility (scATAC-seq) and gene expression (scRNA-seq) at the resolution of individual cells. These approaches provide significant advantages over bulk data analysis, particularly in determining clonal structure and cell type distribution in the tumor microenvironment (Tsagiopoulou & Gut, 2024). With the increasing number of studies on single cell technologies in CLL, the genomic, epigenetic and transcriptional landscape in CLL has begun to be elucidated at the single cell level (Gohil & Wu, 2019).

CRISPR Technology

Clustered Regularly Interspaced Short Palindromic Repeats (CRISPR) technology has been optimized for high-throughput screening, manipulation, and precise epigenome editing of epigenetic regulators. This technology allows researchers to alter specific epigenetic markers by intervening in targeted genomic regions. This method allows functional analyses of epigenetic modifications and also offers potential for therapeutic purposes by reactivating tumor suppressor genes (Sherif et al., 2025).

CRISPR associated protein 9 (Cas9) system functions as an RNA-dependent nuclease and is known by its abbreviation as CRISPR/Cas9 (Dalai & Sar, 2021). In 2013, this technology was used for the first time for genome editing in mammalian cells and spread rapidly. Thanks to its ability to regulate gene expression, ranging from genome sequence changes to epigenetic and transcriptional modifications, this technology has found significant application (Hernández-Sánchez, 2022).

Artificial Intelligence Technology

Artificial intelligence, in its most basic form, is a technology that enables computer systems to perform tasks that require human intelligence. These tasks include complex processes such as speech recognition, natural language understanding, and decision making. Deep learning (DL) and Machine Learning (ML) are subcategories of artificial intelligence (Ozcelik et al., 2024).

Artificial intelligence enables significant advances in precision medicine related to cancer. AI technologies can save time by automating the initial analysis of images, as well as extracting features by examining stained tumor slices or radiological data. These systems can distinguish cancerous and non-cancerous cells with high accuracy and can be effective in defining tumor morphology, dimensions, subtype, and level of spread (Yu et al., 2024).

Machine learning is a branch of artificial intelligence that makes predictions about future events by analyzing large data sets (Rauschert et al., 2020). Deep Learning is a subset of machine learning that uses neural networks to process large data sets to gain insights (Ozcelik et al., 2024). ML applications have significantly contributed to the investigation of many questions regarding the basic biological functions of epigenetic elements, their contributions to gene regulation processes, and the potential benefits of the epigenome in cancer diagnosis and treatment (Arslan et al., 2021).

Examples of Literature Studies Conducted with Epigenetic Methods in CLL

Epigenetic modifications such as promoter hypermethylation can drive cancer by causing tumor suppressor genes to lose their function. Pan et al. (2021) reported DNA methylation driver cells in CLL by regulating DNA methylation with CRISPR. They suppressed the expression of three candidate drivers, DUSP22, RPRM and SASH1, in the HG3 cell line and changed promoter methylation with the dCas9 system (Pan et al., 2021).

Pastore and colleagues conducted a comprehensive study to delve deeper into the epigenetic aspect of cancer evolution. To this end, they used bulk reduced representation bisulfite sequencing (RRBS) analysis, a chromatin immunoprecipitation sequencing (ChIP-seq) method of histone post-translational modifications and gene expression, and performed joint DNA methylation and transcriptome single-cell analysis. The study found that coordination between different layers of the CLL epigenome was significantly reduced. This ongoing epigenetic diversification has reportedly led to a mixture of cells with different epigenetic profiles, providing new insight into the epigenetic dimension of cancer evolution (Pastore et al., 2019). By applying multiplex single-cell reduced representation bisulfite sequencing (MscRRBS) to B cells from CLL patients and healthy donors, Gaiti and colleagues showed that epigenetic information enables mapping of CLL lineage history and prediction of its evolution after therapy (Gaiti et al., 2019).

Knisbacher and colleagues conducted a study integrating genomic, transcriptomic and epigenomic data to create a map of CLL. Combining existing and new data, the largest dataset to date, including WES/WGS, RNA-seq and DNA methylation analyses, was generated from samples of 1095 CLL and 54 MBL patients. These comprehensive data have contributed to a better definition of the molecular subtypes and biological features of CLL.This study provides new insights into CLL oncogenesis and prognosis in general (Knisbacher et al., 2022).

Mallm and colleagues performed a comprehensive analysis of chromatin modifications, comparing aberrant epigenetic mechanisms in primary CLL cells with NBCs. This research predicts new molecular connections to targets of CLL therapies and provides an important resource for further studies on the epigenetic contribution to the disease (Mallm et al., 2019)

Grimm et al performed a study of 79 German patients to evaluate the clinical utility of an epigenetic marker set for CLL patient stratification. The study used pyrosequencing and support vector machine learning tool following bisulfite treatment. Researchers have confirmed the prognostic value of epigenetic classification in CLL and reported that it is useful for patient stratification in the clinic (Grimm et al., 2022).

Conclusion

Identification and understanding of epigenetic modifications in CLL allows for a deeper understanding of the biological mechanisms of the disease. The use of new technologies allows these modifications to be studied in more detail, contributing to significant advances in the diagnosis, prognosis and treatment of CLL In the future, further advancement of epigenetic research will pave the way for the development of more targeted, personalized treatment strategies for CLL, enabling more effective management of CLL.

Scientific Ethics Declaration

* The authors declare that the scientific ethical and legal responsibility of this article published in EPHELS Journal belongs to the authors.

Conflict of Interest

* The authors declare that they have no conflicts of interest

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