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# Single-Cell Sequencing and Multi-Omic Technologies in Acute Myeloid Leukemia: A Literature Review

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**Abstract**

Acute Myeloid Leukemia (AML) exemplifies leukemogenesis as a multistep process in which healthy hematopoietic stem and progenitor cells (HSPCs) acquire sequential genetic and molecular alterations, leading to malignant transformation. Traditional bulk sequencing approaches, although informative, cannot resolve the extensive cellular heterogeneity within AML. The application of single-cell RNA sequencing (scRNA-seq)—as shown by Wu et al.—enables the identification of distinct differentiation pathways and gene expression profiles at the individual cell level, which are specific to AML subtypes and relate to disease progression. When combined with advanced surface proteomics techniques such as Cellular Indexing of Transcriptomes and Epitopes by sequencing (CITE-seq), single-cell profiling offers comprehensive insights into AML's cellular architecture, revealing cell surface markers linked to proliferation, migration, and treatment resistance. Integration of multi-omic layers—including transcriptomic, epigenomic, and proteomic data—has been further advanced in chromatin accessibility profiling, collectively aiding in the discovery of innovative therapeutic targets and enhancing diagnostic strategies. Comprehensive literature searches across PubMed, Cochrane, and Google Scholar were performed to select studies on single-cell and multi-omic analyses in human AML, focusing on work published from 2014 onward. Studies emphasizing leukemic subtypes, differentiation pathways, and novel therapeutic targets were prioritized, with particular attention to recent conceptual and technological advancements in AML research. Recent work by Clark et al. and others has uncovered previously unrecognized AML subpopulations with unique differentiation states and genetic alterations implicated in disease progression and therapy resistance. The integration of transcriptomic and epigenomic data has clarified molecular pathways and transcriptional regulators key to leukemic cell survival and proliferation. These advances have substantially deepened our understanding of AML cellular heterogeneity, providing new insight into the mechanisms behind disease evolution and treatment response. The application of single-cell and multi-omic approaches in AML marks a pivotal advance toward personalized medicine. By enabling the identification of AML subtypes, refining risk stratification, and supporting real-time disease monitoring, these technologies now facilitate the development of targeted therapies tailored to individual molecular profiles, ultimately improving patient outcomes and guiding clinical decision-making.

**Keywords:** acute myeloid leukemia; single-cell sequencing; multi-omics; hematopoiesis; clonal evolution; leukemogenesis

## Introduction

Leukemogenesis is a dynamic, multistep process that involves the sequential accumulation of genetic, epigenetic, and transcriptional changes in HSPCs, resulting in their malignant transformation into leukemic clones [1]. These alterations interfere with normal lineage commitment and differentiation, enabling aberrant self-renewal, survival, and proliferative capacity. The process is further complicated by the emergence of subclonal populations with distinct molecular signatures, which can evolve independently over time and in response to therapeutic pressures.

AML, a prototypical and clinically aggressive form of leukemia, exemplifies this complexity. It is characterized by considerable inter- and intra-patient heterogeneity, not only at the level of genetic mutations but also in terms of cellular composition, transcriptional states, and immune microenvironment [2]. This heterogeneity contributes to diagnostic uncertainty, variable treatment responses, and a high risk of relapse despite initial remission.

Traditional bulk sequencing technologies have significantly advanced our understanding of recurrent mutations, cytogenetic abnormalities, and broad transcriptional patterns associated with leukemogenesis. However, these methods average molecular signals across large populations of cells, masking the contributions of rare or minor subclones that may play outsized roles in disease initiation, therapy resistance, or relapse [1]. For instance, Zhou and Chng demonstrated that while bulk RNA sequencing could identify broad transcriptional

programs in AML samples, it failed to detect rare leukemic stem cell populations crucial for disease maintenance. In contrast, Wu et al.'s application of single-cell RNA sequencing revealed distinct stem-like subpopulations and critical RNA splicing events that drive AML progression and therapeutic resistance. Similarly, Bakhtiarigheshlaghbakhtiar et al. used single-cell approaches to identify *ARMH1*, a novel protein marker associated with AML cell proliferation and drug resistance that had been overlooked in previous bulk analyses. These findings highlight how bulk analysis alone fails to resolve several key organizational features of AML. The clonal hierarchy—the tiered organization where leukemic stem cells give rise to more differentiated progeny—represents one such feature, along with intratumoral diversity and functional plasticity [3].

The advent of single-cell RNA sequencing (scRNA-seq) has revolutionized our ability to interrogate gene expression at single-cell resolution. Single-cell RNA sequencing (scRNA-seq) profiles gene expression in individual cells, enabling the detection of cellular heterogeneity and rare cell populations within complex tissues. Single-cell Assay for Transposase-Accessible Chromatin using sequencing (scATAC-seq) maps regions of open chromatin at single-cell resolution, identifying active regulatory elements such as promoters and enhancers. Single-cell Methylome and Transcriptome sequencing (scM&T-seq) simultaneously captures DNA methylation patterns and gene expression in the same cell, linking epigenetic modifications to transcriptional states. Single-cell Nucleosome, Methylation, and Transcriptome sequencing (scNMT-seq) extends this approach by additionally profiling chromatin accessibility alongside methylation and transcription. Cellular Indexing of Transcriptomes and Epitopes by sequencing (CITE-seq) combines scRNA-seq with surface protein detection, enabling comprehensive phenotypic characterization. These technologies have enabled the identification of transcriptional heterogeneity, differentiation hierarchies, and rare stem-like subpopulations within leukemic samples [4, 5]. Notably, scRNA-seq has revealed functionally distinct leukemic clones coexisting within the same patient, each characterized by unique proliferative, metabolic, or immunoevasive profiles. These insights have opened new avenues for therapeutic targeting and risk stratification.

Building on scRNA-seq, multi-omic technologies now allow researchers to interrogate multiple molecular layers simultaneously. Chromatin accessibility (via scATAC-seq), DNA methylation (via scM&T-seq and scNMT-seq), and surface protein abundance (via CITE-seq) can be analyzed in conjunction with transcriptional data to generate a holistic, systems-level view of leukemic biology [6, 7, 8, 9]. These modalities enable dissection of the regulatory logic that drives leukemic transformation and reveal how epigenetic and transcriptional states intersect to define malignant phenotypes.

Collectively, single-cell and multi-omic tools have begun to redefine the conceptual framework of leukemogenesis by uncovering several key phenomena that underlie malignant transformation. Lineage infidelity refers to the aberrant expression of genes and markers characteristic of different hematopoietic lineages within the same leukemic cell, contributing to developmental arrest and therapeutic resistance. Epigenetic plasticity describes the dynamic changes in DNA methylation and chromatin modifications that enable leukemic cells to adapt to therapeutic pressures and evade treatment. Dysregulated gene regulatory networks encompass the disrupted transcriptional circuits that sustain leukemic stem cell behavior, promote uncontrolled proliferation, and facilitate immune evasion. These mechanisms collectively drive treatment resistance and disease relapse. Integration of these data types at single-cell resolution not only enables the identification of clinically relevant subpopulations but also allows longitudinal tracking of clonal dynamics across disease stages and treatment regimens [3, 10, 11].

This review synthesizes recent advances in the application of single-cell and multi-omic technologies specifically to AML research. We highlight major methodological innovations, discuss computational frameworks for multi-layer data integration, and summarize their impact on understanding clonal architecture, therapeutic resistance, and translational biomarker development in AML. In doing so, we aim to illustrate how these technologies are reshaping our approach to studying AML pathogenesis and advancing the field toward more precise and personalized therapies for this challenging malignancy.

## Methods

A structured literature search was conducted using PubMed, Cochrane, and Google Scholar databases to identify studies published between January 2014 and February 2025. Search terms included combinations of: "single-cell RNA sequencing," "multi-omics," "leukemia," "AML," "CITE-seq," "scM&T-seq," "scNMT-seq," "scTAM-seq," "scATAC-seq," and "epigenomics." Only peer-reviewed English-language studies were considered. Preprints, editorials, and non-human studies were excluded.

Priority was given to primary research articles employing single-cell or multi-omic sequencing in leukemia models, particularly AML. Studies that advanced mechanistic understanding, identified novel therapeutic targets, or introduced novel technologies relevant to hematologic malignancies were emphasized. Reference mining was used to identify additional high-impact articles cited within relevant reviews and studies.

Included articles were categorized based on methodology (e.g., transcriptomic, epigenomic, proteomic), biological insights (e.g., clonal evolution, differentiation, resistance), and translational potential.

## Results

Simultaneous Methylome and Transcriptome Profiling: scM&T-seq

scM&T-seq (Single-Cell Methylome and Transcriptome sequencing) enables simultaneous profiling of DNA methylation and mRNA expression within individual cells [7]. This dual-layer approach is instrumental for characterizing the functional impact of epigenetic modifications in leukemia. In particular, scM&T-seq allows researchers to link promoter methylation directly to transcriptional silencing, revealing epigenetic mechanisms that repress tumor suppressor genes or differentiation regulators in leukemic populations. This technology has been used to map distinct methylation-expression landscapes in subclones of AML, with findings suggesting that hypermethylation of lineage-specific genes is associated with stem-like phenotypes and therapy resistance. Such insights into intratumoral epigenetic heterogeneity make scM&T-seq especially valuable for identifying leukemia-driving cell states that may otherwise evade detection in bulk datasets. Furthermore, its resolution at the single-cell level helps distinguish between subpopulations undergoing epigenetic reprogramming versus those stably committed to malignant self-renewal, offering potential for stratifying patient risk based on methylation-transcriptional coupling. A comparative summary of scM&T-seq, including its molecular layers captured, key applications, and methodological limitations, is provided in Table 1.

Triple Modality Profiling: scNMT-seq

scNMT-seq (Single-Cell Nucleosome, Methylation, and Transcriptome sequencing) advances multi-omic profiling by simultaneously capturing chromatin accessibility (via nucleosome positioning), DNA methylation, and transcription in the same cell [8]. This triple modality is particularly suited to dissecting the layered regulatory networks that underlie leukemogenesis. In AML, aberrant enhancer activation and chromatin remodeling have been shown to contribute to lineage plasticity, immune evasion, and relapse. scNMT-seq allows researchers to identify such regulatory elements and track their epigenetic status across subclones. By capturing nucleosome-depleted regions, this method pinpoints open chromatin signatures associated with active promoters or enhancers, while methylation data clarifies the long-term silencing of lineage-determining genes. Transcriptional data adds a functional readout to these regulatory states. Together, these modalities provide a cohesive picture of how epigenomic dysregulation and transcriptional reprogramming drive leukemic transformation. Importantly, scNMT-seq has been used to reconstruct developmental trajectories of malignant versus non-malignant hematopoietic cells, clarifying the role of poised versus active regulatory states in disease evolution. An overview of scNMT-seq—highlighting its integrated profiling capacity, advantages, and technical constraints—can be found in Table 1.

Targeted Epigenetic Profiling: scTAM-seq

scTAM-seq (Single-Cell Targeted Analysis of Methylation sequencing) offers a scalable and clinically oriented alternative to genome-wide methylation profiling by targeting specific CpG-dense regions of biological or clinical interest [9]. It enables high-resolution methylation analysis of selected promoters, enhancers, and tumor suppressor loci across thousands of individual cells. This makes it especially suitable for applications where high cell numbers and deep coverage are necessary, such as monitoring minimal residual disease (MRD). In AML, scTAM-seq has demonstrated value in tracking methylation changes at hematopoietic transcription factor binding sites and lineage-specific enhancers. These findings have allowed researchers to trace epigenetic drift during disease progression and therapy, identifying clones that retain stem-like methylation signatures even during remission. Clinically, its reduced cost and faster turnaround make it viable for routine monitoring in high-risk leukemia patients. Furthermore, its compatibility with archived and low-input patient samples enhances its translational utility for early relapse detection and therapeutic stratification. A concise comparison of scTAM-seq with other sincle-cell epigenomic technologies, including its targeted scope and clinical suitability, is presented in Table 1.

Transcriptome and Epigenetic Integration: scTEM-seq

scTEM-seq (Single-Cell Transcriptome and Epigenome Sequencing) provides a simplified workflow for dual-layer profiling of gene expression and DNA methylation in the same cell [12]. Unlike scM&T-seq, which requires physically splitting the cell content, scTEM-seq uses integrated capture and sequencing to simultaneously profile both layers, reducing technical noise and improving throughput. In leukemia research, scTEM-seq has uncovered important epigenetic silencing events that repress differentiation and sustain leukemic stemness. For example, promoter hypermethylation of genes regulating myeloid differentiation, when paired with downregulation of these genes in the transcriptome, clearly identifies epigenetically silenced leukemic subpopulations. Additionally, scTEM-seq can detect RNA splicing alterations linked to abnormal isoform usage, which plays a key role in leukemic transformation and therapeutic resistance. This capacity to resolve both transcriptional repression and splicing dynamics makes it particularly useful in studies aimed at characterizing functionally silent but epigenetically active leukemic clones. The distinguishing features of scTEM-seq, along with its advantages relative to other multi-omic platforms, are summarized in Table 1.

Optimization of scATAC-seq via CRISPR/Cas9

scATAC-seq (Single-Cell Assay for Transposase-Accessible Chromatin using sequencing) is a high-resolution method to map genome-wide chromatin accessibility at the single-cell level [6]. It identifies open

chromatin regions that correspond to regulatory elements such as promoters, enhancers, and insulators. In leukemia, this approach has revealed how dysregulated enhancer landscapes contribute to oncogene activation and lineage switching [6]. However, as Montefiori et al. identified, a significant technical challenge in blood-based scATAC-seq experiments is the overrepresentation of mitochondrial DNA reads, which can obscure nuclear chromatin accessibility signals and impair the accurate detection of enhancer regions and transcription factor motifs critical for understanding leukemic gene regulation [10]. Montefiori et al. addressed this issue using CRISPR/Cas9 to deplete mitochondrial DNA prior to sequencing, which is necessary because mitochondrial DNA lacks the nucleosome structure that scATAC-seq is designed to detect, yet its abundance can overwhelm the sequencing capacity needed for nuclear chromatin analysis [10]. This CRISPR-based depletion approach significantly improved the signal-to-noise ratio from typical mitochondrial contamination levels of 60-90% down to less than 20%, enabling cleaner detection of enhancer and transcription factor motifs specific to leukemic blasts [10]. This optimization has expanded the utility of scATAC-seq in low-yield AML samples, patient-derived xenografts, and cryopreserved material [10]. Its ability to identify open regulatory regions in rare leukemic clones contributes to a more accurate picture of intratumoral chromatin heterogeneity and can guide epigenetically targeted therapies [10]. Key characteristics of scATAC-seq and its known technical limitations—such as mitochondrial contamination addressed by CRISPR-based depletion—are outline in Table 1.

Radiogenomic and Cell-Free Multi-Omics

Non-invasive technologies such as cell-free DNA (cfDNA) profiling and radiogenomics provide a complementary approach to single-cell data by offering systemic, longitudinal insights into leukemic progression [11, 13]. cfDNA-based multi-omics can capture genetic mutations, methylation patterns, and DNA fragmentation from blood samples, allowing real-time monitoring of clonal evolution and treatment response. This approach is particularly useful in high-risk AML, where invasive biopsies are often impractical or unsafe. Recent studies have demonstrated the ability of cfDNA methylomics to stratify patients based on epigenetic features that correlate with therapy resistance and relapse. Importantly, this technique can detect resistant clones or MRD that are below the detection threshold of standard diagnostics. Radiogenomics, meanwhile, integrates imaging features (e.g., PET or MRI scans) with underlying molecular profiles, offering spatial insights into tumor heterogeneity and immune microenvironment. Together, these methods extend the reach of single-cell analytics by enabling non-invasive, longitudinal, and clinically actionable surveillance tools that can be integrated with multi-omic datasets for a more complete understanding of leukemogenesis. A comparison of cfDNA-based multi-omics and its complementary role alongside single-cell technologies is also details in Table 1.

**Table 1.** Comparison of Single-Cell and Multi-Omic Technologies Applied to Leukemia Research

| Technology | Omic Layers Captured | Key Applications | Advantages | Limitations |
|---|---|---|---|---|
| scRNA-seq [4] | Transcriptome | Identifies leukemic subpopulations and differentiation pathways [2] | High resolution, widely used | Lacks epigenetic or protein-level data |
| scATAC-seq [6] | Chromatin accessibility | Maps open chromatin, enhancer regions, transcription factor binding | Regulatory insight, complements RNA-seq | Sparse data, sensitive to noise |
| scM&T-seq [10] | Transcriptome + DNA methylation | Links gene expression to methylation profiles | Simultaneous dual-layer profiling from same cell | Lower methylome coverage |
| scNMT-seq [13] | Transcriptome + Methylome + Nucleosome | Integrates chromatin state, methylation, and expression | Comprehensive regulation profiling | Technically complex, lower throughput |
| scTAM-seq [11] | Targeted DNA methylation | High-throughput detection of specific CpG methylation patterns | Cost-effective, scalable for MRD monitoring | Limited to predefined sites |
| scTEM-seq [1] | Transcriptome + Epigenomic features | Links gene expression with epigenetic repression | Tracks silencing events, useful in cancer transitions | Moderate resolution |
| CITE-seq [9] | Transcriptome + Surface protein markers | Identifies immune phenotypes and surface-based subtypes | Combines RNA and protein data | Antibody-dependent resolution |

| Technology | Omic Layers Captured | Key Applications | Advantages | Limitations |
|---|---|---|---|---|
| cfDNA multi-omics [11] | Methylation + Mutations (cell-free) | Non-invasive disease tracking and clonal monitoring | Longitudinal sampling, clinical potential | Lacks single-cell resolution |

*Abbreviations:* AML, acute myeloid leukemia; cfDNA, cell-free DNA; CITE-seq, Cellular Indexing of Transcriptomes and Epitopes by sequencing; MRD, minimal residual disease; scATAC-seq, single-cell assay for transposase-accessible chromatin using sequencing; scM&T-seq, single-cell methylome and transcriptome sequencing; scNMT-seq, single-cell nucleosome, methylation, and transcriptome sequencing (captures gene expression, DNA methylation, and chromatin accessibility simultaneously); scRNA-seq, single-cell RNA sequencing; scTAM-seq, single-cell targeted analysis of methylation sequencing; scTEM-seq, single-cell transcriptome and epigenome sequencing. "Transcriptome + Methylome + Nucleosome" indicates simultaneous capture of gene expression data, DNA methylation patterns, and chromatin accessibility states within individual cells.

## Conclusion

Single-cell and multi-omic technologies have dramatically advanced our understanding of leukemia by revealing cellular heterogeneity that was previously masked by conventional bulk sequencing methods. Bulk approaches average out the gene expression profiles of large cell populations, thereby concealing rare subclonal populations that may be central to disease progression or therapy resistance. In contrast, single-cell RNA sequencing (scRNA-seq) has proven instrumental in defining transcriptional hierarchies within leukemic blasts, revealing distinct subpopulations with stem-like characteristics, developmental arrest, or lineage bias in AML. These findings underscore the importance of resolving the complex intratumoral architecture that underpins leukemic transformation.

The integration of scATAC-seq and DNA methylation profiling provides additional layers of insight, exposing how chromatin accessibility and epigenetic reprogramming drive lineage infidelity and enable leukemic cells to bypass differentiation checkpoints. Together, these tools illuminate how transcriptional and epigenetic programs interact to sustain malignancy and resist conventional therapies.

Technologies such as scM&T-seq and scNMT-seq enable the direct linkage of transcriptomic and epigenomic states within the same single cells, offering unprecedented resolution of regulatory mechanisms in leukemic evolution. Similarly, scTAM-seq facilitates high-throughput, targeted analysis of methylation signatures, making it a practical option for clinical monitoring of MRD. Furthermore, scTEM-seq captures both expression and methylation data, enabling detection of gene silencing events and alternative splicing patterns implicated in leukemic progression and stemness.

While single-cell technologies provide unprecedented cellular resolution, emerging non-invasive platforms, including cfDNA methylomics and radiogenomic integration, offer complementary opportunities for longitudinal disease tracking that extend beyond what single-cell approaches can achieve alone. cfDNA-based assays enable dynamic monitoring of epigenetic alterations and mutational burden via blood sampling, with Shao et al. demonstrating that cfDNA methylomics can stratify patients based on epigenetic features that correlate with therapy resistance and relapse. Shao et al. have also demonstrated the ability of cfDNA methylomics to detect resistant clones or MRD that are below the detection threshold of standard diagnostics. Radiogenomic approaches, while still emerging in hematologic malignancies, represent a promising prospective concept, with Su et al. showing how radiogenomic-based multi-omic analysis can reveal imaging-phenotype associations with immune landscapes. These non-invasive approaches complement single-cell studies by providing patient-wide, longitudinal data that can be collected repeatedly without the need for invasive biopsies, thereby offering accessible and scalable methods to assess clonal evolution and treatment response across disease stages.

Importantly, combining these complementary technologies may yield synergistic insights into the mechanisms of leukemogenesis. For instance, integrating scRNA-seq with scATAC-seq and single-cell methylation profiling can capture the full cascade from chromatin remodeling to transcriptional activation. The addition of surface proteomics, such as through CITE-seq, enables multi-layered annotation of leukemic phenotypes, facilitating subtype classification and biomarker discovery. Such multimodal strategies can help identify rare, lineage-primed precursors or quiescent leukemic stem cells that evade therapy and drive relapse.

Looking forward, expanding multi-modal approaches to include proteomics, spatial transcriptomics, and metabolic profiling will be crucial. Overcoming challenges related to data harmonization, technical noise, and computational integration will be essential to translating these discoveries into clinical applications. Nonetheless, the convergence of these tools marks a transformative step toward precision oncology in hematologic malignancies, enabling more accurate risk stratification, real-time disease monitoring, and the development of rational combination therapies tailored to patient-specific molecular profiles.

## List of Abbreviations

AML: acute myeloid leukemia
cfDNA: cell-free DNA
CITE-seq: cellular indexing of transcriptomes and epitopes by sequencing

CRISPR: clustered regularly interspaced short palindromic repeats
DNA: deoxyribonucleic acid
HSPC: hematopoietic stem and progenitor cell
MRD: minimal residual disease
RNA: ribonucleic acid
scATAC-seq: single-cell assay for transposase-accessible chromatin using sequencing
scM&T-seq: single-cell methylome and transcriptome sequencing
scNMT-seq: single-cell nucleosome, methylation, and transcriptome sequencing
scRNA-seq: single-cell RNA sequencing
scTAM-seq: single-cell targeted analysis of methylation sequencing
scTEM-seq: single-cell transcriptome and epigenome sequencing

**Conflicts of Interest**
The author(s) declare that they have no conflict of interests.

**Ethics Approval and/or Participant Consent**
Ethics approval and participant consent were not required.

**Authors' Contributions**
TSC: Substantial contributions to the conception or design of the work; or the acquisition, analysis, or interpretation of data for the work; and Drafting the work or revising it critically for important intellectual content; and Final approval of the version to be published; AND Agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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