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Multi-omics approaches for deciphering disease evolution and identifying therapeutic targets in acute myeloid leukemia

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Abstract

Acute myeloid leukemia (AML) is a highly heterogeneous hematologic malignancy characterized by dynamic clonal evolution, diverse molecular alterations, and variable therapeutic responses. Although advances in genomic profiling have substantially improved disease classification and risk stratification, many patients continue to experience relapse and treatment resistance, highlighting the need for a more comprehensive understanding of AML biology. Recent developments in multi-omics technologies, including genomics, epigenomics, transcriptomics, proteomics, metabolomics, and single-cell approaches, have enabled unprecedented insights into the molecular mechanisms underlying AML initiation, progression, and therapeutic failure. Integrative multi-omics analyses have revealed complex interactions among genetic mutations, epigenetic remodeling, metabolic reprogramming, and leukemia microenvironmental adaptations that collectively drive disease evolution. These approaches have also facilitated the identification of novel biomarkers, lineage-specific dependencies, and therapeutically actionable vulnerabilities that are not apparent from single-layer analyses. Furthermore, multi-omics-guided studies are accelerating the development of precision medicine strategies by improving patient stratification and uncovering mechanisms of drug resistance. In this review, we summarize recent advances in multi-omics technologies and discuss how integrative analyses are reshaping our understanding of AML evolution. We highlight emerging therapeutic targets identified through multi-omics investigations and examine their translational potential for innovative drug development. Finally, we discuss current challenges and future opportunities for implementing multi-omics-guided precision medicine in AML.

Keywords: Acute myeloid leukemia; Multi-omics; Disease evolution; Therapeutic targets

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1. Introduction

Acute myeloid leukemia (AML) is an aggressive and genetically diverse hematologic malignancy characterized by the uncontrolled expansion of abnormal myeloid progenitor cells in the bone marrow, peripheral blood, and other hematopoietic tissues.[1] Despite significant advances in understanding the molecular basis of AML and the introduction

of several targeted therapies, the disease remains associated with high relapse rates and poor long-term survival, particularly among older patients. AML accounts for the majority of acute leukemias in adults and represents a major clinical challenge due to its remarkable biological complexity, heterogeneous clinical manifestations, and highly variable responses to therapy.

One of the defining features of AML is its extensive interpatient and intrapatient heterogeneity.[2] Comprehensive genomic studies have revealed a diverse spectrum of recurrent mutations affecting signaling pathways, transcription factors, epigenetic regulators, RNA splicing machinery, and tumor suppressor genes. Mutations in genes such as *FLT3*, *NPM1*, *DNMT3A*, *IDH1/2*, *RUNX1*, *ASXL1*, and *TP53* contribute to distinct biological subtypes and clinical outcomes. However, AML is not merely a collection of static genetic abnormalities. Instead, it is increasingly recognized as a dynamic evolutionary disease in which leukemia cells continuously acquire molecular alterations, adapt to environmental pressures, and undergo clonal selection during disease progression and therapeutic intervention. The emergence of treatment-resistant subclones and the persistence of leukemia stem cells (LSCs) are major drivers of relapse and remain significant obstacles to curative therapy.

Over the past decade, advances in next-generation sequencing technologies have transformed our understanding of AML biology. Large-scale genomic and transcriptomic studies have facilitated the identification of recurrent driver mutations and have substantially improved disease classification and risk stratification.[3] These discoveries have led to the successful development of several molecularly targeted therapies, including inhibitors of Fms-related receptor tyrosine kinase 3 (FLT3), isocitrate dehydrogenase (IDH) 1, and IDH 2. Nevertheless, clinical responses to these agents are often incomplete or transient, suggesting that genetic alterations alone cannot fully explain disease behavior or therapeutic outcomes. Increasing evidence indicates that AML evolution is governed by complex interactions among genetic mutations, epigenetic remodeling, transcriptional reprogramming, metabolic adaptation, proteomic alterations, and microenvironmental influences.

The emergence of multi-omics technologies has provided unprecedented opportunities to investigate AML from a systems-level perspective.[4] Multi-omics approaches integrate information derived from multiple molecular layers, including genomics, epigenomics, transcriptomics, proteomics, metabolomics, and single-cell profiling technologies. By simultaneously interrogating these complementary biological dimensions, multi-omics analyses enable a more comprehensive characterization of leukemia biology than any individual platform alone. Such integrative strategies have revealed previously unrecognized regulatory networks, identified novel disease-driving mechanisms, and uncovered critical molecular dependencies that may serve as therapeutic targets.

Importantly, multi-omics investigations have substantially advanced our understanding of disease evolution in AML.[5] Integrative analyses have demonstrated how genomic lesions interact with epigenetic programs to shape transcriptional states, influence cellular differentiation trajectories, and promote the emergence of therapy-resistant populations. Furthermore, the application of single-cell and spatial omics technologies has provided unprecedented resolution for dissecting intratumoral heterogeneity and tracking clonal evolution over time. These approaches have uncovered complex cellular ecosystems within the bone marrow microenvironment and revealed how interactions between leukemia cells and surrounding stromal, immune, and endothelial compartments contribute to disease progression and treatment resistance.

Beyond mechanistic insights, multi-omics technologies are increasingly facilitating the discovery of therapeutically actionable vulnerabilities.[6] Integrated molecular profiling has identified metabolic dependencies, epigenetic susceptibilities, stress-response pathways, and microenvironmental interactions that are not readily apparent through genomic analyses alone. These findings have expanded the repertoire of potential therapeutic targets and are accelerating the development of innovative treatment strategies. In parallel, multi-omics-derived biomarkers are improving patient stratification, enabling more accurate prediction of treatment response, and supporting the implementation of precision medicine approaches in AML.

In this review, we discuss how integrative multi-omics approaches are reshaping our understanding of AML biology (Figure 1). We first summarize recent advances in applying multi-omics technologies to elucidate disease evolution and cellular heterogeneity. We then examine how these approaches have facilitated the identification of novel therapeutic vulnerabilities and molecular targets. Finally, we highlight emerging opportunities and challenges in translating multi-omics discoveries into precision therapeutic strategies for AML, emphasizing future directions for innovative drug development and personalized patient management.

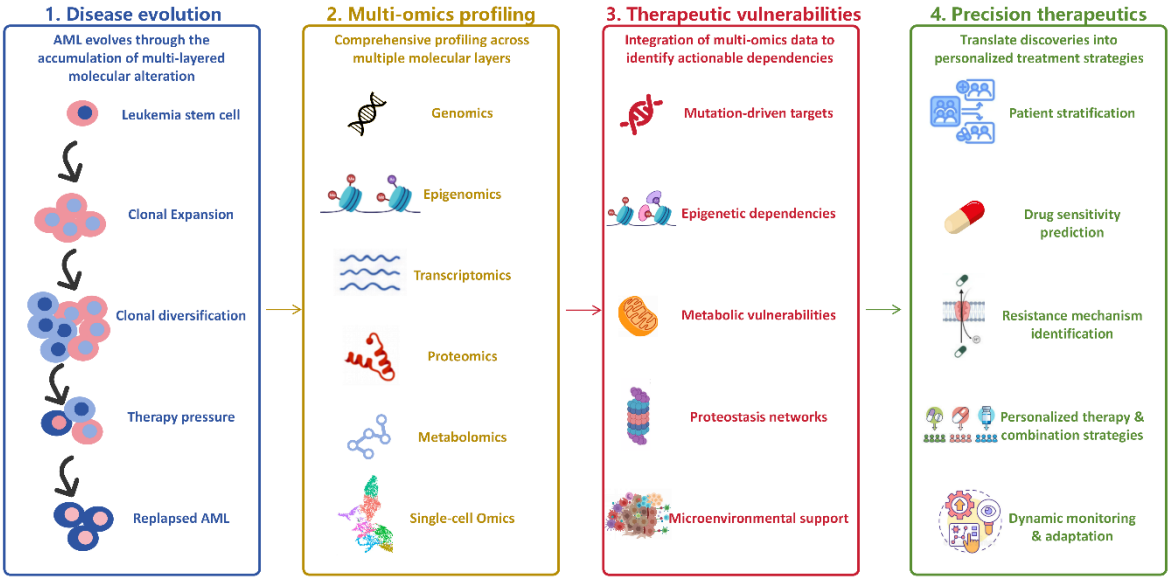

Figure 1. Multi-omics-guided framework for understanding disease evolution and advancing precision therapeutics in acute myeloid leukemia (AML). AML evolves through dynamic clonal selection and adaptation driven by multilayer molecular alterations. Comprehensive multi-omics profiling, encompassing genomics, epigenomics, transcriptomics, proteomics, metabolomics, and single-cell omics, provides a systems-level understanding of disease evolution and cellular heterogeneity. Integration of these molecular datasets enables the identification of actionable therapeutic vulnerabilities, including mutation-associated targets, epigenetic regulators, metabolic dependencies, proteostasis pathways, and microenvironmental interactions. These discoveries support biomarker development, therapeutic target identification, drug sensitivity prediction, and resistance monitoring, thereby facilitating the translation of multi-omics insights into precision medicine strategies. Figure created by the authors using Microsoft PowerPoint.

2. Multi-omics decoding of disease evolution in acute myeloid leukemia

Acute myeloid leukemia is increasingly recognized as an evolutionary disease characterized by the continuous acquisition of molecular alterations and dynamic interactions between leukemia cells and their surrounding microenvironment. Rather than arising from a single genetic event, AML develops through a multistep process involving clonal expansion, selective pressure, and adaptive remodeling across multiple biological layers.[7] Traditional genomic studies have provided valuable insights into the mutational landscape of AML; however, they are often insufficient to explain the extensive phenotypic diversity and therapeutic heterogeneity observed among patients. The integration of genomics, epigenomics, transcriptomics, proteomics, metabolomics, and single-cell technologies has transformed our understanding of AML evolution by revealing how alterations across distinct molecular dimensions cooperate to shape disease initiation, progression, and relapse.[8]

2.1. Genetic architecture of acute myeloid leukemia evolution

The evolutionary trajectory of AML is fundamentally driven by genetic alterations that accumulate in hematopoietic stem and progenitor cells. Large-scale sequencing efforts have demonstrated that AML is characterized by a complex hierarchy of founder and subclonal mutations that emerge over time. Early initiating mutations frequently occur in genes involved in epigenetic regulation and hematopoietic stem cell maintenance, including *DNMT3A*, *TET2*, and *ASXL1*. These alterations often arise years before disease diagnosis and can persist within preleukemic hematopoietic stem cells, creating a reservoir for future malignant transformation.[9]

Subsequent acquisition of mutations affecting signaling pathways and transcriptional regulators drives leukemic progression. Activating mutations in *FLT3*, *KIT*, and *RAS* genes promote uncontrolled proliferation and survival, whereas alterations in transcription factors such as *RUNX1* and *CEBPA* disrupt normal hematopoietic differentiation.[10] Importantly, AML genomes are not static. Longitudinal sequencing studies have revealed that clonal composition

evolves continuously throughout disease progression and treatment. Chemotherapy exerts strong selective pressure, eliminating sensitive populations while allowing resistant subclones to survive and expand.

Multi-region and serial sampling analyses have demonstrated several distinct evolutionary patterns in AML relapse. In some patients, relapse originates from a dominant diagnostic clone that acquires additional mutations during treatment. In others, relapse emerges from rare preexisting subclones that survive therapy and subsequently become dominant. These observations highlight the importance of clonal heterogeneity as a major determinant of therapeutic response and disease recurrence. However, genetic mutations alone cannot fully account for AML evolution, suggesting that additional regulatory mechanisms contribute to disease progression.

2.2. Epigenetic remodeling during leukemogenesis

Epigenetic dysregulation represents a central feature of AML evolution and provides a critical link between genetic alterations and cellular phenotype.[11] Epigenetic mechanisms regulate gene expression without altering DNA sequence and include DNA methylation, histone modifications, chromatin accessibility, and higher-order chromatin organization. Notably, many of the most frequently mutated genes in AML encode epigenetic regulators, underscoring the importance of epigenetic remodeling in leukemogenesis.

DNA methylation profiling has revealed extensive epigenetic heterogeneity among AML subtypes.[12] Mutations in *DNMT3A*, *TET2*, and *IDH1/2* profoundly alter methylation landscapes and disrupt normal differentiation programs. For example, mutant IDH enzymes produce the oncometabolite 2-hydroxyglutarate, which inhibits α-ketoglutarate-dependent dioxygenases and promotes widespread DNA hypermethylation. These epigenetic alterations contribute to differentiation blockade and facilitate leukemia development.

Beyond DNA methylation, histone modifications also play crucial roles in AML evolution. Aberrant activity of histone methyltransferases, histone acetyltransferases, and chromatin remodeling complexes reshapes transcriptional programs that support leukemia cell survival and self-renewal.[13] Recent chromatin accessibility studies employing assay for transposase-accessible chromatin using sequencing have further demonstrated that AML cells exhibit highly dynamic regulatory landscapes that evolve during disease progression and treatment.

Importantly, epigenetic states can change more rapidly than genetic mutations, allowing leukemia cells to adapt to environmental challenges and therapeutic pressure.[14] This plasticity contributes to phenotypic diversification and may facilitate the emergence of drug-tolerant cell populations. Integrative genomic and epigenomic analyses have therefore become essential for understanding how genetic lesions are translated into functional cellular behaviors during AML evolution.

2.3. Transcriptional and cellular heterogeneity

While genomic and epigenomic alterations establish the framework of AML evolution, transcriptional programs ultimately determine cellular phenotype and function. Transcriptomic profiling has revealed remarkable heterogeneity both between patients and within individual tumors.[15] AML samples frequently contain multiple transcriptionally distinct cell populations that coexist within the same patient, reflecting diverse differentiation states and evolutionary histories.

Bulk RNA sequencing studies have identified molecular signatures associated with prognosis, therapeutic response, and disease subtype. However, the advent of single-cell RNA sequencing has significantly expanded our understanding of AML heterogeneity by enabling the characterization of individual leukemia cells.[16] Single-cell analyses have demonstrated that AML populations comprise complex mixtures of stem-like, progenitor-like, and differentiated cell states rather than discrete homogeneous clones.

Particularly important are LSCs, a rare population with self-renewal capacity and the ability to regenerate disease following treatment.[17] Single-cell transcriptomic studies have revealed substantial heterogeneity within the LSC compartment, suggesting multiple stem-like states with distinct biological properties. Some LSC populations exhibit quiescence that enables them to evade cytotoxic therapies, whereas others display active proliferative programs associated with disease progression.

Transcriptional plasticity further complicates AML evolution. Leukemia cells can transition between cellular states in response to intrinsic signals or external stimuli, allowing adaptation to changing environmental conditions. This dynamic behavior contributes to treatment resistance and may explain why genetically similar cells often exhibit markedly different therapeutic responses. Consequently, understanding transcriptional heterogeneity has become a major focus of contemporary AML research.

2.4. Metabolic and proteomic adaptations

Emerging evidence indicates that metabolic and proteomic remodeling are critical drivers of AML evolution. Leukemia cells undergo extensive metabolic reprogramming to support rapid proliferation, maintain stemness, and survive under stressful conditions. Unlike many solid

tumors that primarily rely on glycolysis, AML cells—particularly LSCs—often exhibit a strong dependence on mitochondrial oxidative phosphorylation (OXPHOS).[18]

Metabolomic studies have identified profound alterations in amino acid metabolism, lipid utilization, and mitochondrial bioenergetics during AML progression.[19] Enhanced fatty acid oxidation, glutamine metabolism, and one-carbon metabolic pathways have been implicated in sustaining leukemia cell growth and therapeutic resistance. These metabolic adaptations are not merely consequences of oncogenic transformation but actively contribute to disease evolution by influencing epigenetic regulation, redox homeostasis, and cellular signaling.

Proteomic analyses provide another important layer of information that cannot be captured by genomic or transcriptomic studies alone.[20] Protein abundance, post-translational modifications, and signaling network activity frequently show weak correlations with mRNA expression levels. Mass spectrometry-based proteomics has revealed extensive rewiring of signaling pathways during AML progression, including alterations in kinase activity, apoptosis regulation, and stress-response pathways.

Recent studies have also highlighted the importance of protein homeostasis (proteostasis) networks in AML.[21] Leukemia cells experience elevated proteotoxic stress due to rapid proliferation and oncogenic signaling, and therefore become highly dependent on protein quality control systems, including the ubiquitin–proteasome system, molecular chaperones, autophagy, and the unfolded protein response. These adaptive mechanisms promote leukemia cell survival and may create therapeutic vulnerabilities that emerge during disease evolution.

2.5. Multi-omics integration of acute myeloid leukemia evolutionary trajectories

Although individual omics technologies have provided valuable insights into AML biology, disease evolution ultimately results from coordinated interactions among multiple molecular layers. Integrative multi-omics approaches have therefore emerged as powerful tools for reconstructing evolutionary trajectories and identifying key regulatory mechanisms underlying leukemogenesis.

By combining genomic, epigenomic, transcriptomic, proteomic, and metabolomic datasets, researchers can establish mechanistic links between genetic alterations and cellular phenotypes. For example, integrated analyses have demonstrated how specific mutations drive epigenetic remodeling, alter transcriptional networks, and reprogram metabolic pathways to promote leukemia progression.[22] Such studies have revealed that distinct AML subtypes are characterized by unique molecular ecosystems rather than isolated genetic lesions.

The development of single-cell multi-omics technologies represents a breakthrough in the study of AML evolution.[8] Simultaneous measurement of chromatin accessibility, gene expression, DNA mutations, and protein markers within individual cells allows unprecedented resolution of clonal architecture and cellular state transitions. These approaches have revealed previously unrecognized intermediate populations that connect stem-like and differentiated leukemia states, providing new insights into disease progression.

Furthermore, multi-omics integration has enhanced our understanding of interactions between leukemia cells and the bone marrow microenvironment. Spatial and single-cell analyses have demonstrated that stromal cells, immune populations, and vascular niches actively influence AML evolution by shaping selective pressures and supporting therapy-resistant states.[23] Consequently, disease progression should be viewed not only as an intrinsic property of leukemia cells but also as the result of dynamic ecosystem-level interactions.

Collectively, multi-omics studies have transformed the conceptual framework of AML evolution. Rather than a linear sequence of mutational events, AML is now understood as a multidimensional and adaptive process driven by coordinated alterations across genetic, epigenetic, transcriptional, proteomic, metabolic, and microenvironmental networks. This systems-level perspective provides the foundation for identifying therapeutically actionable vulnerabilities, which are discussed in the following section (Table 1).

3. Multi-omics identification of therapeutic vulnerabilities in acute myeloid leukemia

The growing application of multi-omics technologies has not only transformed our understanding of AML evolution but has also accelerated the identification of therapeutically actionable vulnerabilities. While conventional therapeutic strategies largely relied on cytotoxic chemotherapy and broad molecular classifications, multi-omics investigations have revealed a diverse landscape of molecular dependencies that sustain leukemia initiation, progression, and relapse. Importantly, many of these vulnerabilities extend beyond genomic mutations and involve coordinated alterations in epigenetic regulation, transcriptional programs, cellular metabolism, protein homeostasis, and microenvironmental interactions. Integrative analyses across multiple molecular layers are therefore providing unprecedented opportunities to uncover novel therapeutic targets and develop more effective precision medicine strategies for AML.

Table 1. Representative multi-omics studies revealing disease evolution and biological heterogeneity in acute myeloid leukemia

Multi-omics strategy	Major findings	Biological significance	Clinical relevance
Genomics + transcriptomics	Integrated genomic and transcriptomic profiling identified molecular subtypes and prognostic biomarkers	Improved understanding of AML molecular heterogeneity	Risk stratification and subtype classification[24]
Whole-exome sequencing + single-cell DNA sequencing	Revealed clonal evolution and subclonal architecture during AML progression	Characterized dynamic clonal evolution	Identification of relapse-associated clones[25]
Single-cell transcriptomics	Identified heterogeneous leukemia stem cell populations and differentiation trajectories	Revealed transcriptional plasticity and cellular heterogeneity	Potential biomarkers for relapse prediction[26]
DNA methylome + transcriptome	DNA methylation stochasticity correlated with transcriptional variability across AML subtypes	Demonstrated epigenetic contribution to AML evolution	Epigenetic biomarker discovery[27]
Metabolomics + transcriptomics	Identified metabolic remodeling involving amino acid and mitochondrial metabolism	Linked metabolic reprogramming with disease progression	Candidate metabolic therapeutic targets[28]
Spatial proteomics	Characterized spatial organization of leukemic cells within bone marrow microenvironment	Defined leukemia–microenvironment interactions	Improved understanding of therapy resistance[29]
Single-cell multi-omics	Simultaneously analyzed mutations, chromatin accessibility, and transcriptomes to reconstruct AML evolution	Integrated molecular mechanisms across multiple biological layers	High potential for precision medicine[30]

Abbreviation: AML: Acute myeloid leukemia.

3.1. Mutation-driven therapeutic targets

Genomic profiling has fundamentally reshaped AML treatment by enabling the identification of recurrent driver mutations that can be therapeutically targeted. Multi-omics studies have further expanded this knowledge by linking genetic alterations to downstream transcriptional, epigenetic, and metabolic consequences, thereby revealing actionable signaling networks and molecular dependencies.[31]

Among the most successful examples are activating mutations in *FLT3*, which occur in approximately one-third of AML patients and are associated with aggressive disease and poor prognosis.[32] Integrated genomic and phosphoproteomic analyses have demonstrated that constitutive FLT3 signaling activates multiple oncogenic pathways, including phosphoinositide 3-kinase/protein kinase B, mitogen-activated protein kinase, and signal transducer and activator of transcription 5 signaling, which collectively promote leukemia cell proliferation and survival. These findings facilitated the development of FLT3 inhibitors such as midostaurin, gilteritinib, and quizartinib.[33] However, multi-omics analyses have also revealed mechanisms of resistance involving secondary kinase mutations, pathway rewiring, and metabolic adaptation, highlighting the need for combination therapeutic strategies.

Mutations in *IDH1* and *IDH2* represent another paradigm of omics-guided therapeutic discovery. Through integrated genomic, epigenomic, and metabolomic studies, mutant IDH enzymes were found to produce the oncometabolite 2-hydroxyglutarate, which disrupts epigenetic regulation and impairs normal hematopoietic differentiation.[34] These mechanistic insights directly led to the development of IDH inhibitors, including ivosidenib and enasidenib. Importantly, multi-omics analyses continue to uncover determinants of response and resistance to IDH-targeted therapies, providing opportunities for rational combination approaches.

Recent studies have also identified novel mutation-associated vulnerabilities involving *TP53*, *RUNX1*, and cohesin complex mutations.[35] Although direct targeting of mutant *TP53* remains challenging, integrated transcriptomic and proteomic analyses have revealed compensatory survival pathways and stress-response mechanisms that may be therapeutically exploitable. Similarly, alterations in transcription factor networks and chromatin architecture associated with *RUNX1* and cohesin mutations have revealed unique dependencies that could be targeted through synthetic lethal approaches.

Another emerging therapeutic vulnerability involves

menin-dependent leukemias.[36] Multi-omics investigations have demonstrated that leukemias harboring *KMT2A* rearrangements or mutant *NPM1* exhibit profound dependence on menin-mediated transcriptional programs. These discoveries have led to the rapid clinical development of menin inhibitors, representing one of the most promising recent advances in AML targeted therapy.

Collectively, mutation-driven vulnerabilities exemplify how multi-omics analyses can bridge the gap between genetic lesions and therapeutic intervention by identifying critical downstream pathways that sustain leukemic growth.

3.2. Epigenetic vulnerabilities

Epigenetic dysregulation is a hallmark of AML and is among the most extensively studied therapeutic opportunities revealed by multi-omics investigations. Because epigenetic alterations are potentially reversible, they provide attractive targets for therapeutic intervention.

Integrated genomic and epigenomic studies have demonstrated that mutations affecting DNA methylation machinery, chromatin modifiers, and histone regulators contribute significantly to AML pathogenesis. DNA methyltransferases were among the earliest epigenetic targets successfully translated into clinical practice.[37] Hypomethylating agents such as azacitidine and decitabine remain important treatment options, particularly for older patients and those unfit for intensive chemotherapy. Multi-omics analyses have shown that their therapeutic effects extend beyond simple demethylation and involve widespread transcriptional reprogramming, immune modulation, and alterations in LSC function.

Histone modification pathways represent another major source of therapeutic vulnerabilities. Aberrant activity of histone deacetylases, histone methyltransferases, and bromodomain-containing proteins contributes to leukemia maintenance through the regulation of chromatin accessibility and gene expression.[38] Transcriptomic and chromatin accessibility studies have revealed that AML cells frequently depend on specific epigenetic regulators to maintain stemness-associated transcriptional programs. Consequently, histone deacetylase inhibitors, bromodomain and extra-terminal motif inhibitors, and inhibitors targeting histone methyltransferases have attracted considerable interest as potential therapeutic agents.

Recent advances in chromatin profiling technologies have further highlighted the importance of enhancer remodeling and three-dimensional genome organization in AML. Multi-omics studies integrating chromatin accessibility, chromatin conformation, and transcriptional data have identified super-enhancer-associated oncogenic networks that regulate key leukemia drivers, including *MYC*, *MEIS1*, and *HOXA* genes. Targeting these regulatory circuits may provide novel opportunities for disrupting leukemia-specific transcriptional programs.

Importantly, epigenetic plasticity also contributes to therapeutic resistance. Single-cell multi-omics analyses have demonstrated that AML cells can adopt alternative epigenetic states under treatment pressure, allowing survival despite targeted therapy. Understanding these adaptive mechanisms may facilitate the development of combination approaches that prevent the emergence of resistant cellular populations.

3.3. Metabolic dependencies

Metabolic reprogramming has emerged as a defining feature of AML biology and represents a rich source of therapeutically actionable vulnerabilities.[39] Unlike normal hematopoietic cells, leukemia cells frequently develop unique metabolic dependencies that support rapid proliferation, stem cell maintenance, and adaptation to environmental stress.

Multi-omics studies integrating metabolomics, transcriptomics, and proteomics have revealed extensive alterations in energy metabolism in AML cells. One of the most prominent features is the increased reliance of LSCs on mitochondrial OXPHOS.[40] This dependency distinguishes LSCs from many normal hematopoietic progenitors and provides a potential therapeutic window. The clinical success of venetoclax-based therapies has further highlighted the importance of mitochondrial metabolism in AML, as disruption of mitochondrial bioenergetics contributes significantly to treatment response.

In addition to OXPHOS, AML cells frequently depend on altered amino acid metabolism. Integrated metabolomic analyses have identified glutamine utilization, branched-chain amino acid metabolism, and one-carbon metabolic pathways as important regulators of leukemia cell survival.[41] These pathways influence not only bioenergetics but also epigenetic regulation and redox homeostasis, linking metabolic adaptation to broader disease evolution.

Lipid metabolism has also emerged as an important vulnerability. Multi-omics investigations have revealed elevated fatty acid oxidation activity in LSCs and therapy-resistant populations.[42] Enhanced lipid utilization provides a flexible energy source and supports survival under metabolic stress. Consequently, targeting fatty acid transport, lipid biosynthesis, or fatty acid oxidation pathways may enhance therapeutic efficacy.

Notably, metabolic dependencies are highly dynamic and can evolve during treatment. Single-cell metabolomic and transcriptomic analyses have demonstrated substantial metabolic heterogeneity within AML populations, suggesting that distinct cellular subsets may rely on different metabolic programs. Understanding this complexity will be essential for developing effective metabolism-targeted therapies and overcoming resistance mechanisms.

3.4. Proteostasis and stress-response networks

Cancer cells frequently experience elevated proteotoxic stress due to rapid proliferation, genomic instability, and aberrant oncogenic signaling. AML cells are no exception and have evolved sophisticated protein quality control systems to maintain cellular homeostasis. Recent multi-omics studies have identified proteostasis networks as critical therapeutic vulnerabilities that support leukemia survival and adaptation.[43]

Proteomic analyses have demonstrated widespread activation of molecular chaperones, unfolded protein response pathways, autophagy machinery, and ubiquitin–proteasome systems in AML.[44] These mechanisms cooperate to preserve protein integrity, remove damaged proteins, and protect leukemia cells from stress-induced apoptosis.

The endoplasmic reticulum stress response represents a particularly important adaptive pathway. Transcriptomic and proteomic studies have shown that unfolded protein response signaling contributes to LSC maintenance, metabolic adaptation, and drug resistance.[45] Similarly, autophagy plays context-dependent roles in AML by facilitating nutrient recycling, mitochondrial quality control, and survival during therapeutic stress.

The ubiquitin–proteasome system has long been recognized as a therapeutic target in hematologic malignancies. Multi-omics investigations continue to reveal previously unappreciated roles of protein degradation pathways in regulating oncogenic signaling, epigenetic factors, and metabolic enzymes.[46] Targeting components of these systems may therefore simultaneously disrupt multiple leukemia-promoting pathways.

Recent studies have also highlighted the concept of "proteostasis addiction," whereby leukemia cells become disproportionately dependent on protein quality control mechanisms compared with normal cells.[47] This dependency creates selective vulnerabilities that may be exploited therapeutically, particularly when combined with targeted or metabolic therapies.

3.5. Microenvironment-mediated therapeutic targets

Acute myeloid leukemia progression is profoundly influenced by the bone marrow microenvironment, which provides structural support, survival signals, and protective niches for leukemia cells.[48] Multi-omics technologies have significantly advanced our understanding of these complex interactions and have revealed numerous microenvironment-associated therapeutic vulnerabilities.

Single-cell transcriptomics and spatial omics studies have demonstrated that AML cells actively remodel the bone marrow ecosystem by altering stromal, immune, and vascular compartments.[49] These changes create permissive environments that support leukemia growth while suppressing antitumor immune responses. Importantly, leukemia-associated microenvironments often persist following treatment and contribute to disease recurrence.

Immune evasion has emerged as a major therapeutic challenge in AML. Multi-omics analyses have identified dysregulated immune checkpoint pathways, impaired antigen presentation, and altered cytokine networks that facilitate leukemia escape from immune surveillance.[50] These findings provide a rationale for developing immunotherapeutic strategies targeting immunosuppressive mechanisms within the bone marrow niche.

Interactions between leukemia cells and mesenchymal stromal cells also represent important therapeutic opportunities. Integrated transcriptomic and proteomic studies have revealed reciprocal signaling networks involving C-X-C motif chemokine ligand 12–C-X-C motif chemokine receptor 4[51], very late antigen-4[52], and various cytokine pathways that promote leukemia cell survival and treatment resistance. Disrupting these interactions may sensitize leukemia cells to conventional and targeted therapies.

Moreover, multi-omics investigations have shown that the microenvironment can directly influence leukemia metabolism, epigenetic regulation, and cellular state transitions.[53] Thus, therapeutic targeting of microenvironmental support mechanisms may simultaneously disrupt multiple adaptive pathways that contribute to disease persistence.

Taken together, multi-omics technologies have expanded the therapeutic landscape of AML far beyond the identification of recurrent mutations. By integrating information across genetic, epigenetic, transcriptional, proteomic, metabolic, and microenvironmental layers, these approaches have uncovered a broad spectrum of therapeutically actionable vulnerabilities (Table 2).

Table 2. Therapeutic vulnerabilities identified by multi-omics approaches in acute myeloid leukemia

Therapeutic vulnerability	Omics approach	Representative molecular targets	Current therapeutic strategy	Clinical development
Mutation-driven signaling	Genomics + phosphoproteomics	FLT3	Midostaurin, gilteritinib, quizartinib	Approved[33]
Epigenetic remodeling	Genomics + epigenomics	DNMT3A, IDH1/2, EZH2	Azacitidine, decitabine, IDH inhibitors	Approved[54]
Menin-dependent transcription	Genomics + transcriptomics	Menin–KMT2A, NPM1	Menin inhibitors	Phase II/III[55]
Mitochondrial metabolism	Metabolomics + proteomics	OXPHOS	Venetoclax-based therapy	Approved[56]
Amino acid metabolism	Metabolomics	Glutamine metabolism	Glutaminase inhibitors	Early clinical[57]
Fatty acid oxidation	Metabolomics	FAO pathway	FAO inhibitors	Preclinical[58]
Proteostasis network	Proteomics	UPR, proteasome, HSP90	Proteasome inhibitors, UPR inhibitors	Early clinical[59]
Bone marrow microenvironment	Spatial omics + single-cell transcriptomics	CXCR4/CXCL12, CD44, VLA-4	CXCR4 antagonists	Clinical trials[60]
Immune regulation	Single-cell multi-omics	Immune checkpoints	Immunotherapy combinations	Early clinical[61]

Abbreviations: AML: Acute myeloid leukemia; CXCL12: C-X-C motif chemokine ligand 12; CXCR4: C-X-C chemokine receptor 4; DNMT3A: DNA methyltransferase 3 alpha; EZH2: Enhancer of zeste homolog 2; FAO: Fatty acid oxidation; FLT3: FMS-like tyrosine kinase 3; HSP90: Heat shock protein 90; IDH1: Isocitrate dehydrogenase 1; IDH2: Isocitrate dehydrogenase 2; KMT2A: Lysine methyltransferase 2A; NPM1: Nucleophosmin 1; OXPHOS: Oxidative phosphorylation; UPR: Unfolded protein response; VLA-4: Very late antigen-4.

Importantly, many of these dependencies emerge from interactions among multiple biological systems and therefore cannot be fully appreciated through single-omics analyses. The translation of these discoveries into biomarker-guided treatment strategies, combination therapies, and precision medicine approaches represents the next frontier in AML therapeutics and is discussed in the following section.

4. Translation of multi-omics discoveries into precision therapeutics

The rapid expansion of multi-omics technologies has generated unprecedented insights into the molecular complexity of AML.[62] While these discoveries have significantly advanced our understanding of disease evolution and therapeutic vulnerabilities, their ultimate clinical value depends on successful translation into precision therapeutic strategies. Precision medicine seeks to tailor treatment decisions to the unique biological characteristics of individual patients, moving beyond traditional approaches that rely primarily on morphology, cytogenetics, or a limited number of genetic alterations. By integrating information across genomic, epigenomic, transcriptomic, proteomic, metabolomic, and microenvironmental layers, multi-omics approaches offer the potential to refine patient stratification, predict therapeutic response, uncover resistance mechanisms, and guide the development of more effective treatment strategies.

4.1. Biomarker-guided patient stratification

Accurate patient stratification is a fundamental requirement for precision medicine. Current AML classification systems increasingly incorporate molecular information, and the identification of recurrent genetic abnormalities has significantly improved prognostic assessment and therapeutic decision-making. Nevertheless, considerable heterogeneity remains within molecularly defined subgroups, indicating that genomic information alone is often insufficient to fully capture disease behavior.

Multi-omics analyses have substantially enhanced biomarker discovery by integrating complementary molecular datasets.[63] For example, combining genomic and transcriptomic information can identify biologically distinct patient subsets that share similar mutational profiles but exhibit divergent gene expression programs and clinical outcomes. Likewise, integration of epigenomic and transcriptomic data has revealed LSC-associated signatures that correlate with relapse risk and treatment resistance. These findings suggest that molecular states, rather than individual mutations, may provide more

accurate indicators of disease aggressiveness.

Proteomic and metabolomic biomarkers are also emerging as valuable tools for patient stratification.[64] Because proteins and metabolites represent functional outputs of cellular activity, they may more directly reflect disease status and therapeutic susceptibility than genomic alterations alone. Recent studies have identified proteomic signatures associated with treatment response, while metabolomic profiling has uncovered metabolic states linked to LSC persistence and relapse. As multi-omics datasets continue to expand, composite biomarker models integrating multiple molecular layers are expected to outperform single-parameter approaches and provide a more comprehensive framework for risk assessment and therapeutic selection.

4.2. Multi-omics-informed drug sensitivity prediction

One of the most promising applications of multi-omics technologies is the prediction of therapeutic response.[65] Despite major advances in AML treatment, substantial variability exists in patient responses to chemotherapy, targeted agents, and immunotherapies. The ability to predict drug sensitivity before treatment initiation would greatly enhance clinical decision-making and reduce unnecessary toxicity.

Traditional biomarker strategies often focus on individual genetic alterations; however, therapeutic response is typically influenced by complex interactions among multiple biological pathways. Multi-omics approaches provide a more comprehensive view of these interactions and enable the identification of molecular signatures associated with drug sensitivity or resistance. For example, integrated genomic and transcriptomic analyses have revealed expression programs that predict response to FLT3 inhibitors beyond the presence of FLT3 mutations alone.[66] Similarly, studies combining genomic, epigenomic, and metabolomic data have identified determinants of sensitivity to venetoclax-based therapies, including mitochondrial metabolic states and apoptosis-related signaling networks.

Functional precision medicine approaches are further enhancing predictive capabilities. *Ex vivo* drug screening platforms combined with multi-omics profiling allow direct assessment of leukemia cell responses while simultaneously characterizing the molecular features that drive sensitivity or resistance.[67] Such strategies facilitate the identification of patient-specific therapeutic vulnerabilities and may support individualized treatment selection.

Importantly, multi-omics-guided drug prediction extends beyond currently approved therapies. Integrative analyses can uncover previously unrecognized molecular dependencies and identify candidate drug combinations capable of overcoming resistance mechanisms. These approaches are increasingly being incorporated into preclinical drug discovery pipelines and may accelerate the development of novel therapeutic strategies for AML.

4.3. Mechanisms of treatment resistance revealed by multi-omics

Treatment resistance remains one of the greatest challenges in AML management and represents a major cause of relapse and mortality. Although genetic mutations contribute to resistance, emerging evidence suggests that resistance is often driven by complex adaptive processes involving multiple molecular layers. Multi-omics technologies have therefore become indispensable tools for dissecting the mechanisms underlying therapeutic failure.[68]

Longitudinal studies comparing diagnostic and relapse samples have demonstrated that resistance can arise through diverse evolutionary pathways. In some cases, resistant clones acquire additional genetic mutations that directly impair drug efficacy. However, many patients exhibit resistance without obvious genetic explanations, highlighting the importance of non-genetic mechanisms. Multi-omics analyses have revealed that epigenetic remodeling, transcriptional reprogramming, metabolic adaptation, and microenvironment-mediated protection all contribute to the emergence of resistant disease.[69]

Single-cell technologies have been particularly transformative in this context.[70] By tracking individual cellular populations over time, researchers have identified rare preexisting subpopulations capable of surviving therapy and subsequently driving relapse. These treatment-persistent cells often exhibit stem-like characteristics, altered metabolic states, and enhanced stress-response programs. Importantly, many of these features are not detectable through bulk analyses, emphasizing the value of high-resolution multi-omics approaches.

Studies of targeted therapies have further illustrated the complexity of resistance mechanisms. Resistance to FLT3 inhibitors, IDH inhibitors, venetoclax, and menin inhibitors can involve pathway reactivation, lineage plasticity, metabolic rewiring, or microenvironmental adaptation. Multi-omics profiling enables comprehensive characterization of these processes and provides a framework for designing rational combination therapies to prevent or overcome resistance.

4.4. Emerging applications of artificial intelligence and single-cell multi-omics

The increasing complexity and scale of multi-omics datasets have created new analytical challenges that cannot be addressed through conventional statistical approaches alone. Artificial intelligence and machine learning technologies are therefore becoming essential components of modern precision medicine frameworks.[71]

Machine learning algorithms can integrate large volumes of heterogeneous molecular data and identify patterns that may not be apparent through traditional analyses.[72] These approaches have been used to improve disease classification, predict treatment response, identify prognostic biomarkers, and prioritize therapeutic targets. As larger multi-omics datasets become available, artificial intelligence-driven models are expected to provide increasingly accurate predictions of clinical outcomes and therapeutic efficacy.

Single-cell multi-omics technologies represent another transformative development. Unlike conventional bulk profiling methods, these approaches simultaneously measure multiple molecular modalities within individual cells, including gene expression, chromatin accessibility, protein abundance, and genetic alterations. This capability enables direct investigation of cellular heterogeneity, lineage relationships, and evolutionary trajectories.[73]

The integration of artificial intelligence with single-cell multi-omics is particularly promising for AML research. Computational frameworks can reconstruct clonal architectures, identify rare treatment-resistant populations, and infer regulatory networks that drive disease progression. Such approaches may ultimately enable real-time monitoring of disease evolution and facilitate adaptive therapeutic interventions tailored to individual patients.

4.5. Spatial transcriptomics and spatial multi-omics in acute myeloid leukemia

Recent advances in spatial transcriptomics and spatial multi-omics technologies have significantly expanded our ability to investigate the spatial organization of the bone marrow microenvironment in AML.[29]

Unlike conventional bulk sequencing or dissociated single-cell approaches, spatially resolved technologies preserve tissue architecture while simultaneously capturing gene expression, protein localization, and cellular interactions within their native context. This enables comprehensive characterization of leukemic niches, immune cell distribution, stromal cell composition, and cell–cell communication networks that regulate leukemia progression and therapeutic response.[74]

Emerging studies have demonstrated that spatial analyses can identify localized immune-suppressive microenvironments, reveal heterogeneous distributions of LSCs, and uncover spatially restricted signaling pathways associated with chemoresistance and disease relapse.[75]

Furthermore, the integration of spatial transcriptomics with single-cell RNA sequencing, spatial proteomics, and imaging-based approaches provides unprecedented resolution for reconstructing cellular ecosystems and lineage relationships in AML. As spatial technologies continue to improve in resolution, throughput, and analytical capabilities, they are expected to become an indispensable component of multi-omics-guided precision medicine by enabling the identification of spatial biomarkers and microenvironment-specific therapeutic targets.

4.6. Liquid biopsy as a complementary multi-omics strategy

Liquid biopsy has emerged as a promising complementary approach for the longitudinal monitoring of AML and may substantially enhance the clinical utility of multi-omics profiling. Compared with conventional bone marrow aspiration, liquid biopsy offers a minimally invasive method for repeatedly assessing disease dynamics throughout treatment.[76]

Recent technological advances have enabled comprehensive molecular characterization of circulating tumor DNA, circulating cell-free DNA, extracellular vesicles, circulating RNA, and other blood-derived biomarkers using integrated genomic, epigenomic, transcriptomic, and proteomic analyses. These approaches facilitate real-time monitoring of clonal evolution, measurable residual disease, treatment response, and the emergence of therapy-resistant subclones before clinical relapse becomes apparent.[77]

Moreover, combining liquid biopsy-derived molecular profiles with single-cell sequencing and artificial intelligence-driven multi-omics integration may improve early relapse prediction and support adaptive therapeutic decision-making. Although technical challenges related to assay sensitivity, standardization, and clinical validation remain to be addressed, liquid biopsy represents a highly promising strategy for non-invasive disease surveillance and is likely to become an important component of precision medicine frameworks for AML.

4.7. Computational integration of multi-omics data

The growing complexity of multi-omics datasets has made advanced computational methodologies indispensable for extracting biologically meaningful insights from heterogeneous molecular data. A wide range of multi-omics integration frameworks has been developed to combine genomic, epigenomic, transcriptomic, proteomic, metabolomic, and clinical information into unified analytical models.[78]

Representative approaches include matrix factorization-based methods such as iClusterPlus and Multi-Omics Factor Analysis, similarity-based methods including Similarity Network Fusion, and Bayesian probabilistic models that capture latent biological relationships across different omics layers.[79]

In parallel, network-based analyses, including gene regulatory networks, protein–protein interaction networks, metabolic networks, and knowledge graph-based frameworks, have become powerful tools for identifying disease-associated molecular modules, signaling pathways, and potential therapeutic targets.[80]

The rapid development of machine learning and deep learning algorithms has further enhanced multi-omics analyses by enabling patient stratification, biomarker discovery, drug response prediction, and survival modeling. Supervised learning algorithms such as random forests, support vector machines, and gradient boosting, together with deep neural networks, graph neural networks, and transformer-based architectures, have demonstrated remarkable capability in modeling high-dimensional multi-modal datasets.[81]

Moreover, robust statistical methods, including dimensionality reduction, feature selection, regularized regression, survival analysis, and cross-validation strategies, remain essential for minimizing overfitting, improving model interpretability, and ensuring reproducibility. As artificial intelligence continues to evolve[82], integrating explainable artificial intelligence with multi-omics analyses is expected to facilitate more transparent biological interpretation and support clinically actionable decision-making, ultimately accelerating the implementation of precision medicine for AML.

4.8. Challenges and future perspectives for clinical implementation

Despite remarkable progress, several challenges continue to limit the widespread clinical implementation of multi-omics-guided precision medicine in AML. One major obstacle is the complexity of data integration.[83] Different omics platforms generate datasets with distinct structures, scales, and technical biases, making standardized analysis difficult. Robust computational methods capable of integrating diverse molecular layers remain an active area of research.

Despite the remarkable advances in multi-omics technologies, several practical challenges continue to hinder their widespread implementation in routine clinical practice. One of the primary barriers is the high cost associated with comprehensive multi-omics profiling, including sample preparation, high-throughput sequencing, mass spectrometry, data storage, and computational infrastructure, which limits accessibility in many healthcare settings.[84]

Standardization also remains a major concern, as differences in sample collection, processing protocols, sequencing platforms, analytical pipelines, and quality-control procedures can lead to substantial variability across studies and institutions.[85]

Consequently, ensuring reproducibility of multi-omics findings remains challenging, particularly when results generated by independent laboratories are compared.[86] Furthermore, effective data interoperability is complicated by the heterogeneous formats, scales, and structures of genomic, transcriptomic, epigenomic, proteomic, metabolomic, and clinical datasets. The absence of universally accepted data standards and interoperable platforms hampers efficient data sharing and integrative analyses across institutions.

Another important consideration is clinical turnaround time.[87] Current multi-omics workflows often require extensive laboratory processing, bioinformatic analyses, and multidisciplinary interpretation, making it difficult to generate clinically actionable results within the narrow therapeutic decision-making window required for patients with AML.

Addressing these challenges will require coordinated efforts to establish standardized experimental and computational workflows, develop robust quality assurance frameworks, promote interoperable data infrastructures, reduce sequencing and computational costs, and implement automated analytical pipelines supported by artificial intelligence. Such advances will be essential for facilitating the routine clinical adoption of multi-omics-guided precision medicine in AML.[88]

Collectively, multi-omics technologies are reshaping the landscape of AML precision medicine. By enabling comprehensive characterization of disease biology, improving biomarker discovery, predicting therapeutic response, and uncovering resistance mechanisms, these approaches are creating new opportunities for

individualized patient care. Continued advances in single-cell technologies, computational analytics, and translational research will be critical for realizing the full potential of multi-omics-guided precision therapeutics in AML.

5. Conclusion

Acute myeloid leukemia remains one of the most biologically complex and clinically challenging hematologic malignancies. Despite substantial progress in genomic characterization and the development of targeted therapies, treatment resistance and disease relapse continue to limit long-term clinical outcomes. Increasing evidence indicates that AML evolution is governed by dynamic interactions among genetic, epigenetic, transcriptional, proteomic, metabolic, and microenvironmental networks.[89] Consequently, approaches focused on individual molecular alterations are often insufficient to fully capture the complexity of disease or identify the most effective therapeutic strategies.

The emergence of multi-omics technologies has fundamentally transformed the study of AML by enabling comprehensive characterization of disease biology across multiple molecular layers. Integrative analyses have provided unprecedented insights into clonal evolution, cellular heterogeneity, LSC biology, and mechanisms of therapeutic resistance. More importantly, multi-omics approaches have facilitated the discovery of diverse therapeutic vulnerabilities, including mutation-driven signaling pathways, epigenetic dependencies, metabolic adaptations, proteostasis networks, and microenvironment-mediated survival mechanisms.[90] These advances are expanding the repertoire of actionable targets and accelerating the development of innovative therapeutic strategies for AML.

Beyond mechanistic discoveries, multi-omics technologies are increasingly driving the transition toward precision medicine.[91] The integration of molecular profiling with biomarker discovery, drug sensitivity prediction, and resistance monitoring has the potential to improve patient stratification and enable more individualized therapeutic interventions. Furthermore, advances in single-cell and spatial omics are providing unprecedented resolution for dissecting cellular ecosystems and evolutionary trajectories, offering new opportunities to identify rare treatment-resistant populations and dynamic disease states that are not detectable through conventional approaches.

Looking forward, several developments are expected to further enhance the clinical impact of multi-omics research in AML. The continued integration of single-cell multi-omics, spatially resolved technologies, and longitudinal patient profiling will provide a more comprehensive understanding of disease evolution throughout treatment. At the same time, artificial intelligence and machine learning algorithms are expected to improve data integration, uncover hidden biological patterns, and facilitate clinically actionable decision-making. Combining multi-omics analyses with functional drug screening and real-time disease monitoring may ultimately enable adaptive therapeutic strategies tailored to the evolving molecular landscape of individual patients.[92]

In conclusion, multi-omics technologies are redefining our understanding of AML and creating new opportunities for precision therapeutics. Continued efforts to integrate molecular, functional, and clinical information will be essential for translating these discoveries into improved patient outcomes and realizing the full promise of precision medicine in AML.

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