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REVIEW

Integrating multi-omics approaches in acute myeloid leukemia (AML): Advancements and clinical implications

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Abstract

Acute myeloid leukemia (AML) is a highly heterogeneous and aggressive hematologic malignancy characterized by clonal proliferation of myeloid precursors. Despite significant advancements in genomic profiling and targeted therapies, patient outcomes remain suboptimal due to disease complexity, resistance mechanisms, and high relapse rates. The integration of multi-omics approaches—spanning genomics, epigenomics, transcriptomics, proteomics, and metabolomics—has revolutionized AML research, offering a comprehensive understanding of leukemogenesis, tumor heterogeneity, and therapeutic vulnerabilities. Recent studies leveraging high-throughput sequencing, mass spectrometry, and advanced computational tools have uncovered novel biomarkers, clonal evolution dynamics, and microenvironmental interactions that drive AML progression and resistance. For instance, single-cell multi-omics has revealed chemotherapy-resistant leukemic stem cell populations, while proteogenomic analyses have identified actionable targets such as MCL1 and metabolic dependencies like OXPHOS. Clinically, integrated omics platforms are refining risk stratification, minimal residual disease (MRD) monitoring, and personalized therapy selection. However, challenges such as data integration complexity, cost barriers, and ethical considerations remain. This review highlights the transformative potential of multi-omics in AML, emphasizing recent advancements in technology, biomarker discovery, and therapeutic innovation. By bridging the gap between molecular insights and clinical practice, multi-omics integration promises to redefine AML management, paving the way for precision oncology and improved patient outcomes.

Keywords Acute myeloid leukemia (AML) · Multi-omics integration · Precision oncology · Biomarkers · Therapeutic targets

Introduction

Acute myeloid leukemia (AML), a devastating hematologic malignancy, is characterized by the clonal expansion of undifferentiated myeloid precursors, leading to bone marrow failure and poor clinical outcomes [1, 2]. Despite advances in genomic profiling, AML remains a therapeutic challenge due to its striking molecular heterogeneity, with patients exhibiting diverse mutational landscapes, epigenetic dysregulation, and metabolic adaptations that drive relapse and resistance [3, 4]. The disease is stratified into risk categories based on mutations in genes such as FLT3, NPM1, and TP53, yet these classifications often fail to predict therapeutic responses accurately, underscoring the limitations of single-omics approaches [5, 6]. The BeatAML consortium has pioneered large-scale integration of genomics, transcriptomics, and ex vivo drug sensitivity profiling across > 800 AML samples, revealing subtype-specific therapeutic vulnerabilities and resistance mechanisms that transcend traditional genetic classifications [7]. For instance, even within NPM1-mutated AML, scRNA-seq studies reveal subclonal populations with distinct transcriptional programs that evade chemotherapy [8]. This biological complexity demands a paradigm shift toward multi-omics integration, a synergistic approach combining genomics, epigenomics, transcriptomics, proteomics, and metabolomics, to unravel the dynamic interplay of molecular layers that define AML pathogenesis and therapeutic vulnerabilities [9]. The significance of multi-omics lies in its capacity to resolve the discordance between

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genetic alterations and functional phenotypes. For example, while IDH1/2 mutations are well-characterized genomic drivers, their oncogenic effects are mediated through epigenetic remodeling and metabolic rewiring, as demonstrated by integrated methylome and metabolome analyses [10, 11]. Similarly, proteogenomic studies have uncovered post-translational modifications, such as STAT3 phosphorylation, that mediate resistance to FLT3 inhibitors despite favorable mutation profiles [12]. Recent advancements in spatial omics further highlight the role of the bone marrow microenvironment, where CXCL12-secreting mesenchymal cells shield leukemic stem cells (LSCs) from therapy, a finding only accessible through combined transcriptomic and imaging mass cytometry [13–15]. These insights underscore the necessity of multi-dimensional frameworks to identify synthetic lethal interactions, such as the co-targeting of BCL2 and MCL1 to overcome venetoclax resistance [16–18]. Clinically, multi-omics is reshaping AML management. Risk stratification now incorporates RNA-based classifiers like LSC17, which predicts relapse independent of traditional genetic markers [19, 20]. Liquid biopsy platforms integrating ctDNA genomics and methylation signatures enable ultrasensitive minimal residual disease (MRD) monitoring, achieving 90% concordance with bone marrow biopsies [21]. Furthermore, pharmacogenomic platforms such as PRISM have identified menin inhibitors as highly effective in KMT2A-rearranged AML, illustrating the translational power of omics-guided drug repurposing [22]. Despite these strides, challenges persist, including data harmonization, cost barriers, and the need for functional validation of multi-omics-derived targets [23]. In conclusion, the integration of multi-omics approaches is revolutionizing AML research and clinical care, offering unprecedented insights into disease biology and personalized therapeutic strategies. This review explores recent advancements, emphasizing how cutting-edge technologies and collaborative frameworks are poised to overcome longstanding barriers in AML treatment.

Genomic insights in AML: Unraveling complexity through multi-omics integration

AML is a genetically heterogeneous disease driven by somatic mutations that disrupt key cellular processes, including differentiation, proliferation, and apoptosis. Among the most common mutations are those in NPM1, FLT3, and DNMT3A, which collectively account for a significant proportion of AML cases [1, 2]. NPM1 mutations, found in approximately 30% of AML patients, result in cytoplasmic mislocalization of the nucleophosmin protein and are associated with a favorable prognosis when occurring in isolation [3].

Conversely, FLT3 internal tandem duplications (FLT3-ITD), present in 25–30% of cases, confer a high risk of relapse and poor overall survival, particularly when accompanied by high allelic ratios [5]. These mutations, along with others in IDH1/2, TP53, and RUNX1, underscore the genomic complexity of AML and the need for comprehensive molecular profiling to guide risk stratification and therapy. Whole genome sequencing (WGS) and whole exome sequencing (WES) have revolutionized our understanding of AML pathogenesis by identifying novel mutations and structural variants. For instance, WGS studies by Morita et al. revealed recurrent mutations in U2AF1 and SRSF2, splicing factors that contribute to leukemogenesis by altering RNA processing [24]. Beyond canonical splicing factors, recent work implicates ribosome assembly machinery in AML pathogenesis. Li et al. demonstrated that Dhx16-mediated ribosome biogenesis is essential for hematopoietic stem cell maintenance, with its dysfunction contributing to leukemogenesis and potential therapeutic vulnerability [25].

Similarly, WES has uncovered rare but clinically significant mutations in CEBPA and ASXL1, which influence disease progression and therapeutic response [26]. A pivotal study by Khouri et al. (2025) expanded this landscape by analyzing cohesin complex mutations (STAG2, RAD21, SMC1A, and SMC3) in a large clinical cohort. Their multi-omics approach revealed three key insights: 1) Cohesin mutations independently predicted adverse outcomes (median OS: 8.2 vs. 18.6 months; $p < 0.001$), particularly when co-occurring with RUNX1 or BCOR alterations, 2) Integrated chromatin accessibility (ATAC-seq) and transcriptomic data showed dysregulation of stemness pathways (HOXA/B clusters) and impaired differentiation in cohesin-mutant AML, and 3) These mutations synergized with FLT3-ITD to accelerate leukemogenesis in vivo, suggesting cohesin defects prime the bone marrow niche for clonal expansion [27]. Recent advancements in sequencing technologies, such as long-read sequencing, have further enhanced the detection of structural variants, including KMT2A rearrangements, which are critical for defining AML subtypes [20]. The integration of genomic data with other omics layers has provided deeper insights into AML biology. For example, combined genomic and transcriptomic analyses by Svea Stratmann et al. demonstrated that FLT3-ITD mutations upregulate MYC and HOX gene clusters, driving leukemic proliferation [28]. Moreover, proteogenomic studies by Pedro Casado et al. linked IDH2 mutations to dysregulated mitochondrial metabolism, highlighting potential therapeutic vulnerabilities [29]. These findings underscore the importance of multi-omics approaches in refining AML classification and identifying actionable targets.

Transcriptomics: Decoding AML heterogeneity and prognostic potential

Transcriptomics has emerged as a cornerstone in the molecular characterization of AML, offering unparalleled insights into gene expression patterns that define disease subtypes, predict outcomes, and guide therapeutic strategies. By leveraging high-throughput RNA sequencing (RNA-seq) and single-cell transcriptomics, researchers have unraveled the transcriptional landscapes of AML, enabling the identification of novel biomarkers and therapeutic targets.

Gene expression profiling to classify AML subtypes

Gene expression profiling has revolutionized the classification of AML, moving beyond traditional cytogenetic and mutational criteria to incorporate transcriptional signatures. The Cancer Genome Atlas (TCGA) AML consortium laid the groundwork by identifying distinct transcriptional subtypes, such as those driven by NPM1 mutations or RUNX1 rearrangements [30]. Recent advancements have further refined these classifications. For instance, Ng et al. developed a 17-gene LSC signature (LSC17) that stratifies AML patients into high- and low-risk groups, independent of mutational status. This signature has been validated across multiple cohorts, demonstrating its robustness in predicting relapse and survival [20, 31]. Single-cell RNA sequencing (scRNA-seq) has further deepened our understanding of AML heterogeneity. Van Galen et al. utilized scRNA-seq to uncover rare chemotherapy-resistant stem-like populations within AML tumors, revealing transcriptional programs associated with treatment failure [8]. Building on this, Zeng et al. (2022) established a comprehensive cellular hierarchy framework using scRNA-seq of 40,000 cells from 16 AML patients, integrating genomic data to map mutation-specific transcriptional states across distinct subpopulations (LSCs, progenitors, blasts) [32]. Their study revealed three critical insights: (i) FLT3-ITD mutations drive OXPHOS hyperactivity in monocyte-like blasts, conferring venetoclax resistance; (ii) NPM1-mutant cells exhibit disrupted HOX expression in granulocyte–macrophage progenitors (GMPs), promoting stemness, and (iii) Co-occurring DNMT3A/RUNX1 mutations synergize to activate inflammatory pathways in LSCs (NF-κB/TNF). These findings provide a mechanistic basis for subtype-specific therapy resistance and highlight metabolic dependencies (e.g., OXPHOS inhibition to overcome venetoclax resistance) [32]. These integrated approaches underscore the importance of resolving intratumoral diversity to develop targeted therapies.

Identification of prognostic gene signatures

Transcriptomic analyses have also identified prognostic gene signatures that refine risk stratification. The LSC17 score, for example, has been widely adopted for its ability to predict outcomes in patients undergoing standard chemotherapy or allogeneic stem cell transplantation [20]. Similarly, Svea Stratmann et al. integrated transcriptomic and proteomic data to identify discordant mRNA-protein pairs, such as BCL2, which explain resistance to venetoclax [28]. These integrated approaches highlight the limitations of relying solely on mRNA levels and emphasize the need for multi-omics frameworks. Studies have also explored the role of non-coding RNAs in AML prognosis. For example, microRNA-3151 was identified as a key regulator of FLT3-ITD-driven leukemogenesis, with high expression correlating with poor outcomes [33, 34]. Such findings open new avenues for therapeutic intervention. Beyond transcriptomic signatures, proteomic inflammatory scores are emerging as powerful prognostic tools. Reville et al. (2025) recently identified an 8-protein inflammatory risk score (IL-6, IL-8, TNF-α, CXCL10, OPG, MCP-1, Galectin-9, and FLT3LG) that outperforms conventional genetic risk models in newly diagnosed AML. This score, derived from serum proteomics of 452 patients, stratifies patients into distinct risk cohorts (low vs. high: HR = 3.2, $p < 0.001$) independent of ELN 2022 criteria. Critically, it detects early relapse (AUC = 0.89) and predicts overall survival more accurately than mutation-based classifiers by capturing microenvironment-driven resistance. The inclusion of FLT3LG—a ligand for FLT3—further bridges inflammatory signaling with known AML driver pathways [35, 36].

Clinical implications and future directions

The integration of transcriptomic data with other omics layers, such as genomics and epigenomics, is transforming AML management. For instance, the BeatAML consortium applied machine learning to integrate genomic, transcriptomic, and ex vivo drug sensitivity data from 672 patients, identifying BCOR mutations as predictors of MEK inhibitor sensitivity and revealing novel resistance mechanisms in FLT3-ITD AML through RNA splicing dysregulation [5, 7]. These insights are being translated into clinical trials, such as the MyeloMATCH platform, which uses transcriptomic signatures to guide therapy selection [37, 38]. Transcriptomics has become an indispensable tool in AML research, enabling the discovery of novel subtypes, prognostic signatures, and therapeutic vulnerabilities.

Epigenomics in AML: Decoding the epigenetic landscape

Epigenetic dysregulation is a hallmark of AML, driving aberrant gene expression and contributing to disease initiation, progression, and therapeutic resistance. The integration of epigenomic data with other omics layers has unveiled critical insights into AML biology, offering new avenues for risk stratification and targeted therapy.

DNA methylation patterns and their impact on gene expression

DNA methylation, particularly at CpG islands, plays a pivotal role in AML pathogenesis. Hypermethylation of tumor suppressor gene promoters, such as CDKN2B and CEBPA, silences their expression, promoting leukemogenesis [10]. Recent studies using whole genome bisulfite sequencing (WGBS) have identified distinct methylation signatures associated with AML subtypes. For instance, NPM1-mutated AML exhibits a unique hypermethylation profile linked to favorable outcomes, while TP53-mutated AML shows global hypomethylation, correlating with poor prognosis [39, 40]. These findings underscore the prognostic value of methylation patterns in refining ELN 2022 risk categories. Therapeutic targeting of DNA methylation has transformed AML treatment. Hypomethylating agents (HMAs) like azacitidine and decitabine reverse aberrant methylation, restoring tumor suppressor expression. Studies demonstrated that IDH1/2-mutated AML, characterized by a hypermethylator phenotype, exhibits heightened sensitivity to HMAs [41–43]. However, resistance remains a challenge, prompting studies to integrate methylation data with transcriptomic and proteomic profiles. For example, Stratmann, S. et al. revealed that DNMT3A mutations disrupt methylation patterns, leading to venetoclax resistance through upregulation of anti-apoptotic proteins [28].

Histone modifications associated with AML progression

Histone modifications, including acetylation, methylation, and phosphorylation, regulate chromatin accessibility and gene expression. Dysregulation of histone-modifying enzymes, such as EZH2 (a component of PRC2) and KMT2A (a histone methyltransferase), is prevalent in AML. KMT2A-rearranged AML, for instance, exhibits aberrant H3K4 methylation, driving oncogenic gene expression programs [22, 44]. Targeting histone modifications has shown promise in preclinical and clinical settings. Menin inhibitors, which disrupt the KMT2A-menin interaction, have demonstrated efficacy in *KMT2A*-rearranged AML, with phase II trials showing durable remissions (Issa et al., 2023). Similarly, histone deacetylase inhibitors (HDACis) like vorinostat and panobinostat have been explored in combination with HMAs, revealing synergistic effects in restoring normal chromatin architecture [45].

Integrative epigenomics in AML

The integration of epigenomic data with genomic and transcriptomic layers has uncovered novel therapeutic vulnerabilities. For example, Zhang Q et al. combined ATAC-seq (chromatin accessibility) with RNA-seq to identify enhancer-promoter interactions driving *FLT3-ITD* expression [46]. Such integrative approaches are paving the way for precision epigenomic therapies, including dual targeting of DNA methylation and histone modifications. Epigenomic dysregulation is a central driver of AML pathogenesis, with DNA methylation and histone modifications offering promising therapeutic targets.

Proteomics: Decoding protein expression and post-translational modifications in AML

Proteomics has emerged as a cornerstone in AML research, providing critical insights into protein expression alterations and post-translational modifications (PTMs) that drive leukemogenesis, therapeutic resistance, and disease progression [47, 48]. Unlike genomic and transcriptomic approaches, proteomics captures the functional end-products of cellular processes, offering a direct window into the molecular mechanisms underlying AML pathogenesis [47]. Recent advancements in mass spectrometry (MS)-based technologies, such as tandem mass tag (TMT) labeling and data-independent acquisition (DIA), have enabled high-throughput profiling of AML proteomes, revealing novel biomarkers and therapeutic targets [47–49].

Protein expression alterations in AML

AML is characterized by dysregulated protein expression, often decoupled from transcriptional activity. For instance, the Clinical Proteomic Tumor Analysis Consortium (CPTAC) identified significant overexpression of mitochondrial proteins, such as NDUFS1 and COX5A, in *IDH2*-mutant AML, linking metabolic reprogramming to disease progression [47]. Similarly, Stratmann, S et al. demonstrated discordance between mRNA and protein levels of BCL2, a key apoptosis regulator, explaining why some patients with high BCL2 transcript levels fail to respond to venetoclax [28]. Clinically actionable proteomic signatures are reshaping AML risk assessment. Reville et al. demonstrated that

elevated baseline levels of IL-6 and Galectin-9—key components of their inflammatory risk score—correlate with chemotherapy resistance LSC enrichment in patient samples. Mechanistically, IL-6 activates JAK/STAT signaling in LSCs, while Galectin-9 promotes T-cell exhaustion in the bone marrow niche. This inflammatory axis, quantifiable via ELISA or mass spectrometry, offers a rapid, blood-based prognostic tool that complements genomic classifiers [35]. These findings underscore the importance of proteomic validation in biomarker discovery and therapeutic targeting.

Post-translational modifications in AML pathogenesis

PTMs, including phosphorylation, acetylation, and ubiquitination, play pivotal roles in AML signaling networks. Phosphoproteomic studies have revealed hyperactivation of kinase signaling pathways, such as FLT3-ITD-driven STAT3 and ERK1/2 phosphorylation, which mediate resistance to tyrosine kinase inhibitors (TKIs) [50, 51]. Additionally, acetylation of histones and non-histone proteins, regulated by enzymes like HDACs and KATs, has been implicated in AML stem cell maintenance. For example, Wang et al. identified hyperacetylation of p53 as a mechanism of chemoresistance in *TP53*-mutant AML, suggesting HDAC inhibitors as a potential therapeutic strategy [52, 53].

Clinical implications and future directions

Proteogenomic integration has identified actionable targets, such as HSP90, whose inhibition synergizes with venetoclax in *TP53*-mutant AML [54, 55]. Furthermore, phosphoproteomic profiling has guided the development of combination therapies targeting FLT3 and downstream effectors [5]. Moving forward, spatial proteomics and single-cell proteomics hold promise for resolving intratumoral heterogeneity and microenvironmental interactions, paving the way for precision medicine in AML.

Metabolomics: Decoding metabolic reprogramming in AML

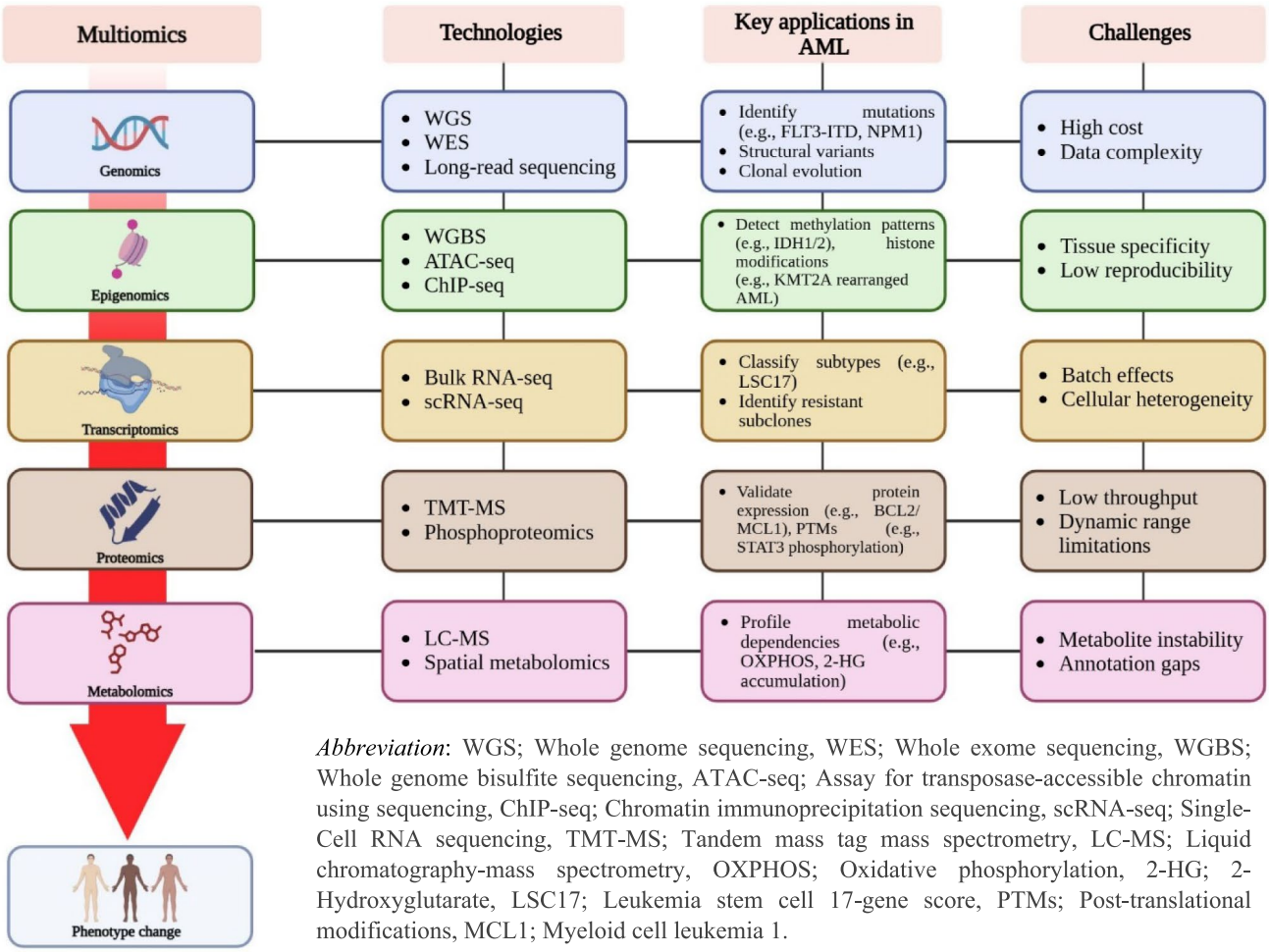
Metabolic reprogramming is a hallmark of AML, enabling leukemic cells to meet the heightened biosynthetic and bioenergetic demands of rapid proliferation. AML cells exhibit a remarkable plasticity in their metabolic pathways, shifting between glycolysis, oxidative phosphorylation (OXPHOS), and amino acid metabolism to sustain survival and evade therapeutic pressure [56, 57]. This metabolic flexibility not only supports leukemogenesis, but also contributes to therapy resistance, making metabolomics a critical component of multi-omics integration in AML research. Recent studies have highlighted the role of mitochondrial metabolism in AML pathogenesis. For instance, Jones et al. identified SLC2A1 (GLUT1) overexpression as a key driver of glucose uptake in AML cells, correlating with poor response to azacytidine [58, 59]. Also studies demonstrated that LSCs rely on fatty acid oxidation (FAO) and OXPHOS for survival, providing a rationale for targeting mitochondrial metabolism with agents like venetoclax. The integration of metabolomic and genomic data has further revealed that mutations in IDH1/2 alter the tricarboxylic acid (TCA) cycle, leading to the accumulation of the oncometabolite 2-hydroxyglutarate (2-HG), which disrupts epigenetic regulation and promotes leukemogenesis [1, 60, 61]. Metabolic vulnerabilities extend beyond OXPHOS and FAO. For instance, dihydroartemisinin sensitizes AML cells to cytarabine by modulating the Nrf2/HO-1 antioxidant pathway, suggesting redox metabolism as a targetable axis [62]. Metabolomics has also emerged as a powerful tool for identifying potential biomarkers for AML diagnosis and prognosis. Recent studies demonstrated the use of mass spectrometry-based metabolomic profiling to identify elevated levels of branched-chain amino acids (BCAAs) in AML patients, which were associated with adverse outcomes [28, 29]. Similarly, Li et al. reported that increased serum levels of lactate, a byproduct of glycolysis, correlated with resistance to induction chemotherapy [10]. These findings underscore the potential of metabolomic signatures to refine risk stratification and guide therapeutic decisions. Figure 1 compares omics methods in AML research and, Table 1 shows multi-omics biomarkers have been investigated.

Integrative multi-omics frameworks: Methods and applications

The integration of multi-omics data—spanning genomics, epigenomics, transcriptomics, proteomics, and metabolomics—has emerged as a transformative approach to decipher the molecular complexity of AML. Recent advancements in computational tools and high-throughput technologies have enabled researchers to unravel the intricate interplay between molecular layers, providing unprecedented insights into AML biology and therapeutic vulnerabilities.

Machine learning and network biology

Machine learning (ML) algorithms have become indispensable for integrating and interpreting multi-omics datasets. For instance, the BeatAML consortium applied ML to integrate genomic, transcriptomic, and drug sensitivity data, identifying *BCOR* mutations as predictors of MEK inhibitor sensitivity [5]. Recent studies employed



Abbreviation: WGS; Whole genome sequencing, WES; Whole exome sequencing, WGBS; Whole genome bisulfite sequencing, ATAC-seq; Assay for transposase-accessible chromatin using sequencing, ChIP-seq; Chromatin immunoprecipitation sequencing, scRNA-seq; Single-Cell RNA sequencing, TMT-MS; Tandem mass tag mass spectrometry, LC-MS; Liquid chromatography-mass spectrometry, OXPHOS; Oxidative phosphorylation, 2-HG; 2-Hydroxyglutarate, LSC17; Leukemia stem cell 17-gene score, PTMs; Post-translational modifications, MCL1; Myeloid cell leukemia 1.

Fig. 1 Integration of multi-omics approaches in AML research. The figure highlights key technologies across genomics, epigenomics, transcriptomics, proteomics, and metabolomics, their applications in AML (e.g., mutation detection, clonal evolution analysis, and metabolic dependency mapping), and associated challenges (e.g., data complexity, batch effects). Multi-omics insights drive the identification of molecular drivers (e.g., FLT3-ITD, NPM1 mutations), therapeutic targets (e.g., BCL2 inhibition), and phenotype changes, offering a roadmap for precision oncology

Table 1 Key multi-omics biomarkers and therapeutic targets in AML

Biomarker/Target	Omics layers involved	Clinical implication	Refs
LSC17 score	Transcriptomics + Genomics	Predicts relapse risk independent of mutations; guides therapy selection	[20]
MCL1 upregulation	Proteomics + Genomics	Drives venetoclax resistance; co-targeting with BCL2 improves outcomes	[16]
Menin inhibitors	Pharmacogenomics + Epigenomics	Effective in KMT2A-rearranged AML; repurposed via PRISM platform	[22]
2-HG accumulation	Metabolomics + Epigenomics	Links IDH1/2 mutations to epigenetic dysregulation; guides HMA therapy	[59]
Inflammatory risk score	Proteomics + Microenvironment	Predicts relapse independent of genetics; guides immunotherapy	[35]

weighted gene co-expression network analysis (WGCNA) to link *FLT3* mutations to inflammatory signaling pathways, revealing potential therapeutic targets [63, 64]. These approaches have also been extended to single-cell datasets, where ML models like MOFA + [9] have been used to deconvolute cellular heterogeneity and identify rare subpopulations, such as chemotherapy-resistant LSCs [8]. Advanced AI tools like TRAPT, which predict transcriptional regulators from epigenomic data, exemplify next-generation computational frameworks for multi-omics synthesis. Such models could resolve enhancer-driven AML subtypes (e.g., KMT2A-rearranged) and nominate epigenetic targets [65].

Spatial multi-omics and microenvironment crosstalk

Spatial transcriptomics and imaging mass cytometry (IMC) have revolutionized our understanding of AML cell interactions within the bone marrow niche. Tirado, H. A et al. integrated spatial metabolomics and proteomics to uncover metabolic crosstalk between AML cells and their microenvironment, identifying glutamine metabolism as a key vulnerability [60, 66].

Clinical applications: From biomarkers to targeted therapy

Integrative multi-omics frameworks have also been instrumental in refining AML risk stratification and MRD monitoring. Ng et al. and Kim et al. developed the LSC17 score, an RNA-based classifier that predicts relapse independent of mutation status [19, 20, 67], while Honoré, N. et al. demonstrated the utility of liquid biopsy approaches integrating ctDNA genomics and methylation for MRD detection with 90% sensitivity [68–70]. Proteomic risk scores now augment liquid biopsy platforms. The Reville inflammatory score achieves 92% specificity for relapse prediction when combined with ctDNA mutation tracking, outperforming either method alone. This integration is particularly valuable for FLT3-wild-type patients where genomic MRD monitoring has limitations. Ongoing trials (NCT05484740) are prospectively validating this multi-omics approach for adaptive therapy escalation [35]. These advancements have paved the way for personalized therapy, as exemplified by the PRISM platform, which screens > 5,000 drug combinations against patient-derived omics profiles to identify effective therapies [71, 72]. The BeatAML study further demonstrated that integrating transcriptomic signatures with drug response data could predict clinical outcomes, with a 30% improvement in relapse prediction accuracy compared to conventional genetic markers alone [7]. This highlights the translational potential of multi-omics frameworks for real-time treatment adaptation. Adoptive T-cell therapies represent a promising frontier, especially for high-risk AML. Optimizing memory T-cell persistence and function, as explored by Sun et al., could enhance the efficacy of immunotherapies targeting AML-specific antigens [73].

Overcoming resistance and drug repurposing

Multi-omics integration has also shed light on resistance mechanisms and novel therapeutic strategies. For example, Pei et al. used proteogenomic analysis to identify MCL1 upregulation as a key driver of venetoclax resistance, leading to the development of combinatorial therapies targeting BCL2 and MCL1 (NCT03797261) [16, 74]. Similarly, Issa et al. leveraged integrated pharmacogenomics to identify menin inhibitors as effective in KMT2A-rearranged AML, demonstrating the clinical potential of multi-omics-driven drug repurposing [22] (Table 2).

Challenges and future directions in integrating multi-omics approaches in AML

The integration of multi-omics approaches in AML has revolutionized our understanding of disease biology and therapeutic opportunities. However, several challenges persist, and addressing these will be critical for translating multi-omics insights into clinical practice.

Data integration complexity

One of the foremost challenges is the harmonization of multi-omics datasets, which often originate from diverse platforms with varying resolutions and biases. For instance, batch effects in RNA sequencing and mass spectrometry can obscure true biological signals [75, 76]. Advanced computational tools like MOFA + [9] have been developed to integrate genomics, transcriptomics, and proteomics data, but scalability remains an issue for large-scale studies. Furthermore, the lack of standardized pipelines for multi-omics integration limits reproducibility across research groups [77]. The Reville study exemplifies solutions to these challenges, employing harmonized multi-platform validation (Olink PEA, Luminex, and LC–MS/MS) across three independent cohorts. Their machine learning pipeline (XGBoost + SHAP analysis) resolved batch effects while prioritizing biologically interpretable proteins, providing a blueprint for scalable omics integration [35].

Functional validation of omics findings

While multi-omics studies have identified numerous candidate biomarkers and therapeutic targets, functional validation remains a bottleneck. Proteogenomic analyses revealed mitochondrial protein dysregulation in IDH2-mutant AML, but mechanistic studies are needed to confirm their role in leukemogenesis [78, 79].

Clinical trial design and implementation

Translating multi-omics insights into clinical trials requires innovative trial designs. Platform trials like NCI-MATCH and MyeloMATCH are pioneering adaptive randomization based on molecular profiling [38]. However, the high cost of multi-omics profiling poses a significant barrier to widespread adoption [80]. Additionally, regulatory frameworks

Table 2 Novel drug targets in AML identified by omics-based studies

Target	Omics Approach	Biological Role in AML	Therapeutic Strategy	Clinical Trial Phase	Refs
KMT2A/MENIN	Epigenomics	Drives leukemogenesis via chromatin remodeling	Menin inhibitors (e.g., revumenib)	Phase II/III	[22]
SRSF2	Genomics/Transcriptomics	Mutant splicing factor promoting RNA dysregulation	Splicing modulators (e.g., H3B-8800)	Preclinical/Phase I	[82]
TIM3 (HAVCR2)	Genomics/Proteomics	Immune checkpoint protein overexpressed in LSCs	Anti-TIM3 antibodies (e.g., sabatolimab)	Phase II	[83, 84]
LSD1 (KDM1A)	Epigenomics	Epigenetic eraser maintaining stemness	LSD1 inhibitors (e.g., iadademstat)	Phase II	[85]
BCL2	Metabolomics/Proteomics	Anti-apoptotic protein in mitochondrial pathways	Venetoclax (BCL2 inhibitor) + azacitidine	FDA-approved	[86]
CDK6	Transcriptomics	Regulates cell cycle in AML progenitor cells	CDK4/6 inhibitors (e.g., palbociclib)	Phase I/II	[87]
PRMT5	Proteomics	Symmetric arginine methylation for RNA splicing	PRMT5 inhibitors (e.g., JNJ-64619178)	Phase I	[88]
IDH1/2	Multi-omics	Oncometabolite (2-HG) production altering epigenetics	IDH1/2 inhibitors (e.g., ivosidenib)	FDA-approved	[89]
DOT1L	Epigenomics	Histone methyltransferase in MLL-rearranged AML	DOT1L inhibitors (e.g., pinometostat)	Phase I	[90]
TP53	Multi-omics	Tumor suppressor mutated in high-risk AML	APR-246 (eprenetapopt) + azacitidine	Phase III	[91]
FLT3-ITD splicing variants	Transcriptomics + Drug Response	Mediates resistance to FLT3 inhibitors	Splicing modulators (e.g., H3B-8800)	Phase I	[7]

for omics-driven therapies must evolve to ensure patient safety and data integrity.

Ethical and economic considerations

The ethical implications of multi-omics data, including privacy concerns and data ownership, must be addressed. Federated learning networks, which enable decentralized data analysis without sharing raw data, offer a potential solution [77]. Economically, reducing the cost of omics technologies and improving reimbursement models will be essential for equitable access.

Future directions

The future of multi-omics in AML lies in the development of scalable, user-friendly platforms for data integration and analysis. Collaborative efforts, such as the BeatAML consortium [5], provide a blueprint for large-scale, multi-institutional studies. Additionally, the incorporation of artificial intelligence and machine learning algorithms will enhance predictive modeling and biomarker discovery [21, 64]. Multi-omics frameworks must also integrate panvascular perspectives, particularly as cardio-oncology emerges as a critical discipline. Understanding vascular toxicity and metabolic crosstalk in AML therapy could mitigate complications like differentiation syndrome [81]. Finally, longitudinal multi-omics studies are needed to capture the dynamic evolution of AML under therapeutic pressure, enabling the design of adaptive treatment strategies.

Conclusion

The integration of multi-omics approaches in acute myeloid leukemia has transformed our understanding of this complex disease. By unifying insights from genomics, epigenomics, transcriptomics, proteomics, and metabolomics, researchers have revealed the intricate networks that drive leukemogenesis and therapy resistance. This comprehensive framework not only refines risk stratification and identifies novel biomarkers, but also paves the way for the development of targeted, personalized treatment strategies. As technological advances continue to overcome challenges such as data harmonization and scalability, the promise of multi-omics lies in its potential to bridge the gap between laboratory discoveries and clinical applications. Future research, supported by innovative computational models and adaptive clinical trial designs, will further elucidate the dynamic evolution of AML under therapeutic pressure. Ultimately,

this holistic approach is set to redefine precision oncology, offering renewed hope for improved patient outcomes and a more effective management of AML.

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Declarations

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Competing interests The authors declare no competing interests.

Consent for publication Not applicable.

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