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Review

A Multi-Omics Panorama of Acute Myeloid Leukemia: From Molecular Hallmarks to Clinical Translation

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Abstract

Acute myeloid leukemia (AML) is a heterogeneous hematologic malignancy with genetic and clinical characteristics. Recent advances in multi-omic technologies, including genomics, epigenomics, transcriptomics, proteomics, metabolomics, immunomics, microbiome profiling, and both spatial and single-cell analyses, have greatly enhanced our understanding of AML

pathobiology. Substantial multi-omic studies show that recurrent driver mutations not only impart traditional genomic lesions but also participate in chromatin restructuring, transcriptional and splicing program alterations, host metabolism, and immune evasion mechanisms. Transcriptomic subclassification has improved AML classification beyond cytogenetic and mutational systems, while proteogenomic profiling has elucidated the mechanisms of chemotherapy resistance and provided new druggable targets. The use of metabolomic and immunometabolomic approaches has illuminated nutrient dependencies and metabolic vulnerabilities, while spatial/single-cell multi-omics has revealed unprecedented detail about leukemic heterogeneity and bone marrow niche organization. Multi-omics has also helped establish or refine prognostic models, identify candidate biomarkers, develop patient stratification strategies, and design targeted and immune-based therapies. The multi-omics approach provides a mechanism to rationalize the complex molecular, cellular, and microenvironmental nature of AML and represents a pathway for precision medicine, provided that methodological harmonization, large-scale rigorous validation, and equitable clinical adoption of these approaches can be achieved.

Keywords
Acute myeloid leukemia; multi-omics; biomarker discovery; leukemic microenvironment

1. Introduction

Acute myeloid leukemia (AML) is the most prevalent acute leukemia among adults, with an annual incidence of about 3 to 5 cases per 100,000 and a median age at diagnosis of 68 years [1]. Despite considerable progress in the field of molecular characterization, the standard induction chemotherapy option with targeted agents has only provided limited long-term survival for the majority of patients, especially those older adults or patients with adverse genetic characteristics. AML is characterized by considerable heterogeneity in genetic lesions, epigenetic states, and microenvironmental interactions, all of which contribute to clinical presentation and disease progression, and therapy resistance [2, 3]. Traditional classification schemas, which began with morphology-based classification such as the French–American–British classification and later incorporated cytogenetics and select molecular markers, only capture a small fraction of the complexity of the disease [4].

Current AML multi-omics now includes genomic sequencing, epigenomic sequencing (DNA methylation, histone modifications, chromatin accessibility), transcriptomic sequencing (mRNA, non-coding RNAs, alternative splicing), proteomic sequencing, metabolomic sequencing, immunomic sequencing, and an increasing number of single-cell and spatial multi-omics. By reporting these multi-omic levels, researchers not only discover new disease mechanisms but also create predictive models for prognosis and therapeutic response [5, 6]. Importantly, interpretation of multi-omics findings requires consideration of study design, cohort size, assay platform, and validation strategy.

Throughout this review, we distinguish between exploratory findings derived from preclinical models or retrospective datasets and biomarkers that have been validated across independent

cohorts or in clinical settings. This distinction is critical for interpreting the translational relevance of multi-omics discoveries in AML.

2. Genomics and Epigenomics in AML

2.1 Mutation-Specific Epigenetic Reprogramming

High-resolution multi-omics profiling has demonstrated that recurrent AML driver mutations behave not only as static genomic lesions, but also serve as active modulators of the epigenetic landscape. However, many of these findings are derived from model systems or selected patient cohorts, and their generalizability across genetically diverse AML populations remains incompletely established. For example, chronic FLT3-ITD signaling reconfigures chromatin states by selectively enriching activating histone marks at the proliferation-associated genes while eliminating repressive marks at the cytokine-responsive loci. This epigenetic reprogramming effectively maintains active signaling from transcription factors and survival pathways, identifying chromatin modulation as a downstream hallmark of cancer-promoting, enduring FLT3 signaling [7].

The *DNMT3A*^{R882H} hotspot mutation is associated with focal DNA hypomethylation, particularly in retrotransposon-rich regions of the genome. This conclusion is supported by integrative epigenomic and transcriptomic analyses performed in *DNMT3A*-mutant clonal hematopoiesis and AML models, with functional validation using hypomethylating-agent exposure. However, the viral-mimicry-like interferon response should be interpreted as a context-dependent mechanism observed in specific experimental settings rather than a universal feature of all *DNMT3A*-mutant AML cases. In these models, azacitidine further enhanced retrotransposon derepression, interferon-stimulated gene expression, translation suppression, and apoptosis. The *DNMT3A*^{R882H} hotspot mutation is associated with focal DNA hypomethylation, especially at retrotransposon-rich genomic regions [8]. However, rather than being a passive byproduct of enzymatic loss, DNA hypomethylation has been associated with activation of a viral-mimicry–like interferon (IFN) response via exposure to double-stranded RNA in certain experimental contexts. Integrative genomic and transcriptomic analyses, together with functional studies, suggest that *DNMT3A*-mutant AML cells may exhibit increased sensitivity to hypomethylating agents such as azacitidine, which can further derepress retrotransposons, enhance IFN signaling, and inhibit protein translation, ultimately contributing to apoptosis [9].

In mixed lineage leukemia (MLL)-rearranged AML, *SETD1B* was identified as a genotype-specific dependency through a CRISPR-tiling screen targeting known H3K4 methylation modifiers in an MLL-rearranged AML model. The study combined functional genetic screening with chromatin profiling and transcriptional readouts, showing that disruption of the *SETD1B* catalytic SET domain reduced broad H3K4me3 domains, decreased MYC expression, and impaired leukemic proliferation. Because the primary evidence was generated in model systems, broader validation across genetically diverse primary AML cohorts remains necessary. *SETD1B* maintains broad H3K4me3 domains at oncogenic regions of the genome with high transcriptional output, most notably at MYC. When *SETD1B* was inhibited, the domains collapsed, MYC was downregulated, the cell cycle was halted, and the fraction of leukemic proliferation was reduced [10]. Therefore, recurrent AML mutations are not mere oncogenic activators at the level of DNA but reshape higher-order chromatin architecture, transcription factor occupancy, and nucleosomal positioning in complex ways that can create vulnerabilities and therapeutic opportunities.

2.2 Epigenetic Biomarkers and Prognosis

In AML epigenome-wide association studies, DNA methylation patterns can have important mechanistic and prognostic implications; however, while several methylation-based biomarkers have shown prognostic value in individual cohorts, only a subset have been consistently validated across independent patient populations. In pediatric AML, methylation status at several CpG sites, mainly in *CD34*, *HOXA7*, and *CD96* regions, strongly predicts survival [11]. Each of these genes provides important connections to stem cell identity, developmental transcriptional programs, and functional interactions with immune cells, thereby linking aberrant methylation to both leukemic stemness and immune evasion.

The extent of overexpression of *B7-H3* (*CD276*), a likely product of promoter hypomethylation, was found to be associated with recent TP53 mutations and enrichment of immune-suppressive populations in the bone marrow in AML. *B7-H3* overexpression was also associated with enrichment of epithelial–mesenchymal transition–like signatures; however, its role as a clinically actionable biomarker remains exploratory and requires validation in independent cohorts [12]. One of the prominent cytogenetically normal (CN)-AML overexpressed genes for example is *CLIC4*, also driven by hypomethylation, and associated with inflammatory signaling and the tumor microenvironment [13]. Another proposed prognostic factor, *ANP32A*, is supported by integrated multi-omics associations; however, its prognostic utility has not yet been consistently validated across large independent AML cohorts [14].

2.3 Chromatin and Histone Modification Studies

Research into histone modifications highlights the bifunctional nature of epigenetic enzymes related to leukemia. A prominent example is EZH2, the catalytic component of the PRC2 complex. The evidence for EZH2 gain- and loss-of-function effects derives largely from integrative multi-omics analyses combining chromatin, transcriptomic, proteomic, and metabolomic profiling of oncogenic EZH2 mutant models. These studies provide mechanistic insight into differential H3K27me3 deposition and downstream transcriptional consequences, but their direct clinical applicability requires validation in larger AML patient cohorts with defined EZH2 mutation status. EZH2 gain-of-function mutations act to promote H3K27me3 at loci promoting differentiation, thus leading to an epigenetic blockade of differentiation, although these mutations may already subject cells to a stem-like state. In contrast, EZH2 loss-of-function mutations will actively deregulate proto-oncogenes and promote cellular proliferation [15]. These completely opposite results suggest that therapy targeting EZH2 must be tailored to the context of the mutations. Similarly, changes in the recruitment of histone acetylation/deacetylation enzymes may also alter the enhancer landscape, working with transcriptional factor mutations, and stabilize oncogenic circuits.

2.4 Functional Epigenomics and Therapeutic Implications

Epigenetic dysregulation often co-occurs with metabolic reprogramming. For example, metformin rescues teratogenic patterns of DNA methylation and even histone modifications in *DNMT3A*-mutant hematopoietic stem cells, while simultaneously reducing their oxidative phosphorylation and depleting the fitness of the mutant clone [16-18]. In immune cells, *TP53* mutations limit cytotoxicity and facilitate immune escape, although p53 reactivation pharmacologically restores effector function and improves survival in AML patient-derived xenografts [19]. Functional screens using CRISPR continue to identify mutations that confer specific dependencies on chromatin-modifying complexes, revealing context-dependent vulnerabilities (Figure 1).

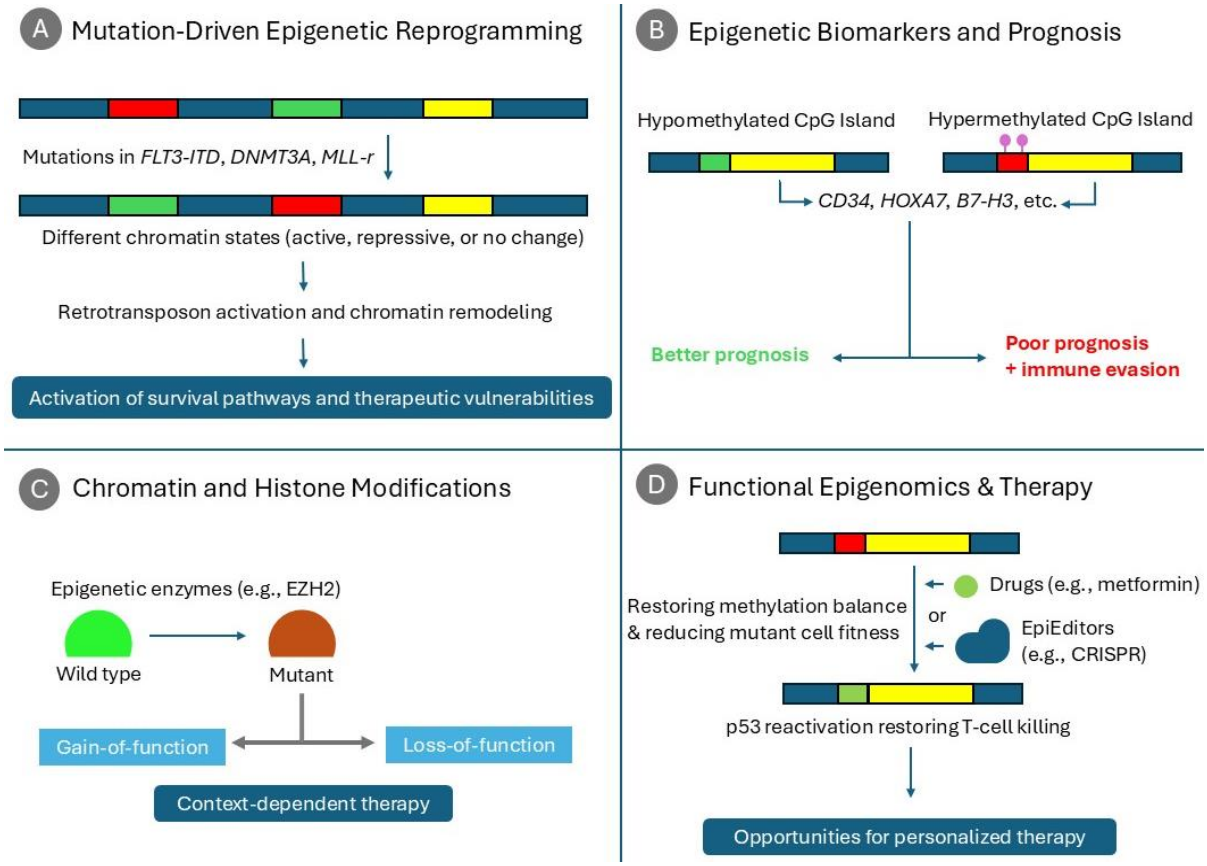

Figure 1 Genomic mutations as drivers of epigenetic dysregulation and therapeutic opportunities in AML. (A) Recurrent AML mutations (e.g., FLT3-ITD, *DNMT3A*, MLL-rearrangements) actively reprogram chromatin states by altering DNA methylation and histone modification patterns, rather than acting solely as static genomic lesions. (B) DNA methylation signatures at CpG islands provide prognostic information and reflect leukemic stemness and immune evasion programs. (C) Epigenetic regulators such as EZH2 exhibit context-dependent dual roles, underscoring the complexity of targeting chromatin-modifying pathways. (D) These convergent alterations highlight epigenetic reprogramming as a central mechanism underlying AML heterogeneity and therapy resistance, and support the use of epigenetic biomarkers for risk stratification as well as the development of targeted therapies, including hypomethylating agents and chromatin-modifying drugs.

Genomic and epigenomic studies in AML demonstrate that recurrent driver mutations extend beyond static DNA alterations to actively reprogram chromatin architecture, DNA methylation, and transcriptional regulation. These changes create context-dependent vulnerabilities, including altered differentiation states, immune evasion mechanisms, and metabolic dependencies. While large-scale cohort studies and functional genomics approaches have identified clinically relevant biomarkers and therapeutic targets, many findings remain context-specific and require validation across diverse patient populations to ensure generalizability and clinical utility.

3. Transcriptomics and Splicing Landscapes

Developments in RNA sequencing (RNA-seq), single-cell transcriptomics, and integrated computational analysis have transformed our understanding of AML's transcriptional heterogeneity. The transcriptome reflects both the underlying genetic background and the dynamic cellular state, providing a readout of differentiation hierarchy, metabolic status, immune interactions, and therapy resistance. Because transcriptomic profiles result from mutations, epigenetic reprogramming, and microenvironmental signaling, transcriptomics positions them at the center of multi-omics disease characterization [20].

3.1 Expression-Based Subclassification

Transcriptomic profiling on a massive scale has further defined subtypes of AML, enabling them to be recognized and distinguished more readily than with previous genetic or cytogenetic determinations. One important transcriptomic analysis established a large multicenter AML cohort of 655 patients in China, with RNA sequencing performed in all cases and targeted or whole-exome sequencing performed in 619 patients. Using enhanced consensus clustering, the study identified eight gene-expression subgroups (G1-G8), each associated with distinct lineage programs, transcription factor dependencies, mutational patterns, and prognostic features. Although the cohort size and integrated genomic annotation support the robustness of this classification, prospective validation and harmonization with international AML classification systems are still required before routine clinical implementation [21]. The G1 and G2 subgroups had transcriptional signatures of stem cell–like cells, with high *HOX* expression and transcription factor activity, including *MEIS1* and *PBX3*, which were associated with poor outcomes. G3 and G4 contained cells with monocytic bias, and were enriched for genes targeting *CEBPA* and inflammatory cytokines. G5 and G6 contained transcripts associated with erythroid/megakaryoblastic programs, with the gene signatures reflecting features of acute megakaryoblastic leukemia. The G7 and G8 gene sets were related to proliferation and were characterized by common cytogenetic abnormalities associated with adverse risk. Characterization of patients using this transcriptional subtyping framework with prospective mutational data can improve prognostic models and identify patient subgroups who can be sensitized to targeted options. Additionally, single-cell RNA-seq can more fully define any subgroups and explore intra-group variations/heterogeneity, including characterization of potential subclonal states with different sensitivities to standard and novel therapies [21].

3.2 Functional Transcriptomics

Transcriptomic data indicate mechanistic insights when combined with functional genomics. Oxidative stress-related expression scores have been proposed to stratify AML patients into risk categories; however, these models are primarily derived from retrospective datasets and require validation in independent prospective cohorts. Patients with high scores demonstrate enrichment of ROS defense mechanism pathways and chemotherapy resistance, while predicted sensitivity to dasatinib and cytarabine [22, 23]. Mutations can implement differential transcriptional rewiring. The *IKZF1*^{N159S} mutation was characterized in a cohort of 475 newly diagnosed non-M3 AML patients, among whom 23 carried *IKZF1* small sequence variants. RNA-sequencing–based subclassification identified three *IKZF1*-related AML classes, including nine patients with *IKZF1*^{N159S} mutations. These cases showed higher *HOXA/B* expression and native B-cell immune fractions, suggesting a distinct transcriptional and immune-associated AML subgroup. However, because the N159S subgroup was small, the finding should be considered hypothesis-generating and requires validation in larger independent cohorts [24]. Additionally, aberrant expression of NFATC4 has been associated with increased Treg infiltration and immune checkpoint activation; however, its utility as a predictive or therapeutic biomarker remains to be validated in independent patient cohorts [25]. The non-coding RNAs miR-155, miR-222, miR-424, and miR-503 act in concert to facilitate monocytic differentiation by targeting lineage-inhibitory factors [26]. Interestingly, retroelement expression from *HERV-K9* is associated with improved prognosis, potentially through immune activation via IFN signaling [27].

3.3 Splicing Regulation

Alternative splicing (AS) is an important driver of functional diversity within AML. Integrated splicing-mutational-immune profiling classified AML into four splicing regulation patterns associated with differences in immune function, tumor mutation profiles, signaling pathway activity, prognosis, and predicted treatment sensitivity. The study constructed and validated a splicing-related risk score as an independent prognostic factor using retrospective transcriptomic datasets. Therefore, while the analysis provides a useful computational framework for linking alternative splicing with AML biology, prospective validation and functional confirmation of the predicted therapeutic vulnerabilities remain necessary [28]. For example, *SRSF2*-mutant AML demonstrates immune-suppressive myeloid infiltration, while other AS patterns with higher spliceosomal protein levels are associated with improved outcomes.

RBM17 is expressed at high levels in leukemic stem cell–enriched AML populations and prevents inclusion of “poison exons” that trigger nonsense-mediated decay, thereby sustaining pro-leukemic proteins such as EIF4A2. This conclusion was supported by integrative multi-omics analyses combined with functional perturbation experiments, including *RBM17* repression, splicing analysis, proteomic validation, differentiation assays, and clonogenic assays. Although these data provide strong mechanistic support for *RBM17* as a leukemic stem cell dependency, therapeutic translation will require pharmacologic targeting strategies and validation in larger primary AML cohorts [29]. Dysregulation of AS also alters oncogenic pathways like PI3K-AKT, resulting in malignancy-specific spliced variants that could serve as neoantigens or therapeutic targets (Figure 2).

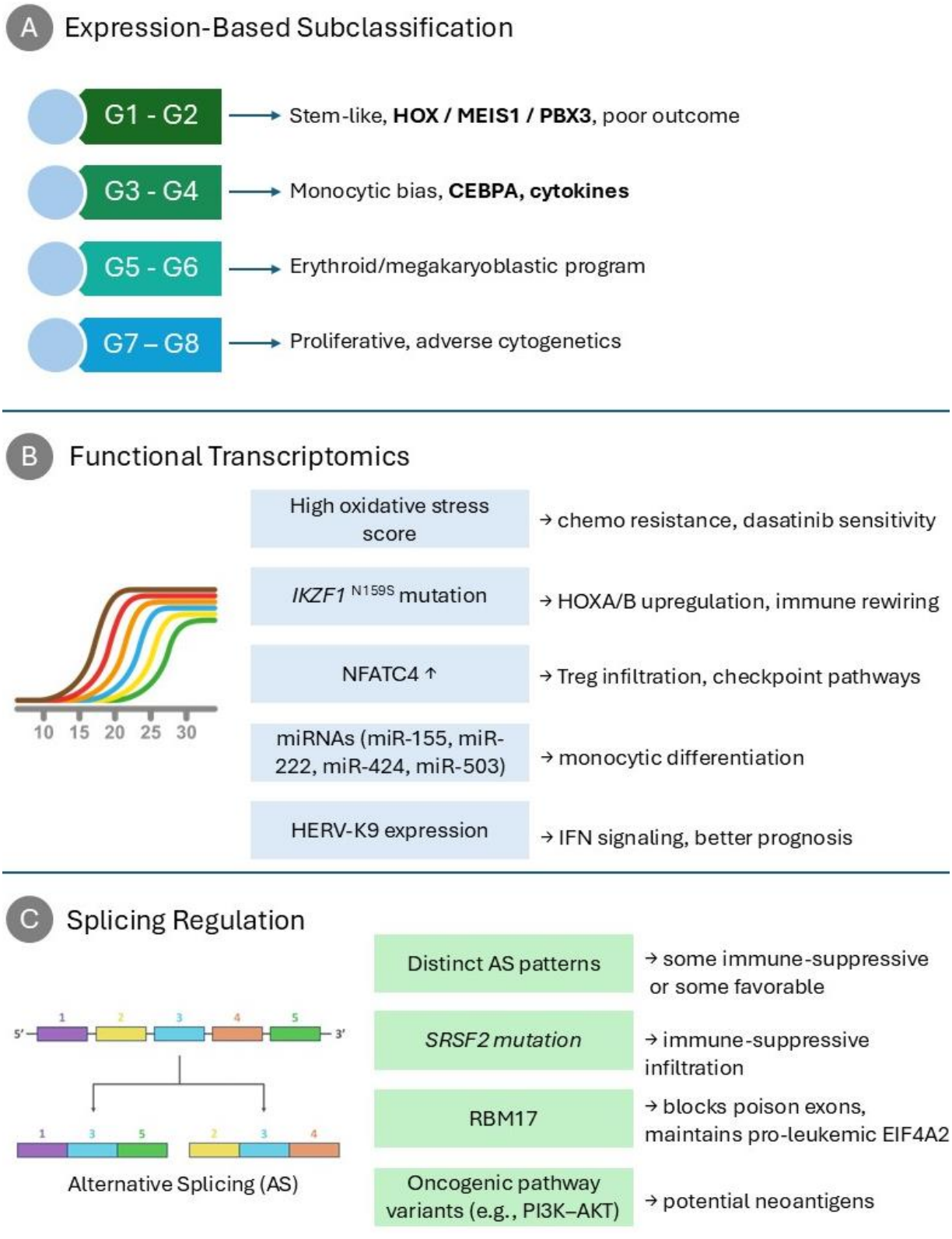

Figure 2 Transcriptomic and splicing landscapes define AML heterogeneity, mechanisms, and therapeutic opportunities. (A) Large-scale transcriptomic profiling identifies eight AML subgroups (G1-G8), each reflecting distinct lineage programs, transcription factor dependencies, and prognostic features. Stem-like groups (G1-G2) are characterized by *HOX*, *MEIS1*, and *PBX3* activity and poor outcome; G3-G4 show monocytic bias with *CEBPA* and cytokine signatures; G5-G6 reflect erythroid/megakaryoblastic programs;

and G7-G8 exhibit proliferative signatures and adverse cytogenetic associations. (B) Transcriptomic signatures provide mechanistic insights into therapy resistance and immune modulation. A high oxidative stress score predicts chemoresistance but sensitivity to dasatinib. The *IKZF1*^{N159S} mutation drives *HOXA/B* upregulation and immune rewiring. Aberrant *NFATC4* expression promotes Treg infiltration and immune checkpoint activation. MicroRNAs (miR-155, miR-222, miR-424, miR-503) cooperate to promote monocytic differentiation, while retroelement *HERV-K9* expression activates IFN signaling and correlates with a favorable prognosis. (C) Alternative splicing (AS) patterns stratify AML into distinct subgroups with different immune and mutational landscapes. *SRSF2*-mutant AML is associated with immune-suppressive infiltration, whereas elevated spliceosomal activity is associated with improved outcome. *RBM17* suppresses inclusion of poison exons, stabilizing pro-leukemic proteins such as EIF4A2. AS-driven variants of oncogenic pathways, including PI3K-AKT, can act as AML-specific neoantigens, representing potential therapeutic targets.

Transcriptomic and splicing analyses provide a central integrative layer in AML, capturing the combined effects of genomic mutations, epigenetic regulation, and microenvironmental signaling. Large-scale RNA-sequencing studies have refined AML classification into biologically and clinically meaningful subgroups, while single-cell and splicing analyses reveal intra-tumoral heterogeneity and regulatory mechanisms such as alternative splicing and non-coding RNA activity. Despite these advances, challenges remain in standardizing classification frameworks and achieving consistent validation across independent cohorts, limiting immediate clinical translation.

4. Proteomics and Proteogenomics

Proteomics and proteogenomics offer a means of connecting genomic changes to phenotypic outcomes by accounting for the functional state of the proteome, which executes cellular processes. Transcriptomic data provide valuable information on gene expression, but mRNA levels vary independently from protein abundance and do not account for how PTMs regulate protein activity, localization, and interactions. In AML, large-scale proteomic studies, in combination with other data, including genomic and transcriptomic data, have identified candidate molecular subtypes, mechanisms of therapy resistance, targets for immunotherapy, and signaling vulnerabilities; however, most of these findings are derived from moderately sized cohorts and require validation in independent datasets before clinical translation [30].

4.1 Large-Scale Proteogenomic Profiling and Chemoresistance Mechanisms

A landmark proteogenomic study analyzed bone marrow biopsies from 252 uniformly treated AML patients, integrating in-depth quantitative mass-spectrometry proteomics with cytogenetic profiling, mutation profiling, and RNA sequencing. This design enabled the identification of proteogenomic AML subtypes linked to metabolic states, DNA repair programs, and kinase signaling. Importantly, the uniformly treated cohort enhances clinical interpretability, but the technical complexity of mass-spectrometry workflows and the need for independent prospective validation remain barriers to immediate clinical implementation [30]. There were proteomic clusters contingent on mitochondrial oxidative phosphorylation and enriched for DNA repair proteins,

suggesting these as possible therapeutic vulnerabilities. Phosphoproteomics revealed subtype-specific activated kinases, e.g., CDK and MAPK hyperactivity in proliferative AML. In murine AML, combined transcriptome-proteome analyses confirmed mitochondrial metabolic remodeling and pointed to TCA cycle and fatty acid oxidation enzymes as drug targets [31].

Proteomic studies have also mapped drug resistance networks in AML. For example, Fierro et al. mapped the interactome and substrates of the ubiquitin ligase WWP1 and identified the histone demethylase JARID1B (KDM5B) as a major target stabilized through K63-linked polyubiquitination [32]. JARID1B removes the H3K4me3 marks at DNA damage repair-related genes that aid in the chromatin configurations needed for repair and survival after chemotherapy. Functional perturbation studies indicated that cellular inhibition of WWP1 destabilized JARID1B and led to the loss of chromatin occupancy, globally increased H3K4me3 marks at JARID1B target promoters, reduced the recruitment of the DNA repair machinery to sites of damage, and extensively sensitized AML cells to the standard chemotherapeutics like cytarabine. The WWP1-JARID1B axis demonstrates the importance of post-translational control of chromatin modifiers as a major factor in chemoresistance and provides an example of how proteomic mapping of ubiquitination can expose druggable resistance mechanisms [32]. Despite these advances, proteomic studies in AML remain limited by relatively small cohort sizes, technical variability, and challenges in cross-platform reproducibility, which currently constrain their routine clinical application.

4.2 Neoantigen Discovery and Immunotherapy

Proteogenomic profiling is also broadening the landscape of tumor-associated antigens for immunotherapy. A recent AML immunopeptidomics study integrated mass-spectrometry–based identification of MHC-I-presented peptides with transcriptomic and computational neoantigen-prioritization frameworks to characterize both canonical and non-canonical MHC-associated peptides. The study prioritized 13 candidate neoantigens, six of which were derived from non-canonical MHC-associated peptides, and further developed a prognostic risk model. These findings expand the antigenic landscape of AML, but clinical translation will require immunogenicity testing, HLA-diverse validation cohorts, and functional confirmation in T-cell–based assays [33]. Interestingly, a large proportion of ncMAPs showed higher predicted immunogenicity and AML specificity than traditional mutation-derived neoantigens. This is interesting as ncMAPs are a potentially more pipeable source of targets for T cell–based therapies.

Simultaneously, cellular engineering approaches are utilizing proteomic data derived from immune evasion. In one study, the inhibitory receptor NKG2A was targeted on CD33-directed CAR-NK cells. AML inhibits NKG2A–expressing NK cytotoxicity via the non-classical MHC molecule HLA-E. In this study, when comparing cytotoxicity against HLA-E negative and HLA-E positive AML lines, CRISPR-Cas9 knockout of NKG2A in CAR-NK cells effectively eliminated this checkpoint, ultimately leading to a statistically significant increase in anti-leukaemic activity *in vitro* and in the xenotransplanted model [34]. This is an example of how proteogenomic mapping of ligand–receptor interactions can directly inform the design of immunotherapy.

4.3 Phosphoproteomics and Signaling

Post-translational modifications, such as phosphorylation, are dynamic regulators of signaling networks and phosphoproteomic profiling in AML has identified kinase-driven oncogenic circuits with prognostic and therapeutic implications. For example, increased PAK1 kinase activation was identified using phosphoproteomics and was associated with poor prognosis in primary AML cases. Functional validation was performed using PAK inhibitors, including PF-3758309, in AML cell lines and primary AML samples, where treatment reduced proliferation and induced apoptosis. These data support PAK1 as a candidate signaling vulnerability; however, the evidence remains preclinical, and clinical applicability will require validation in larger patient cohorts and assessment of inhibitor selectivity, toxicity, and biomarker-guided response [35].

Functional proteomics identified the *IFN-γ-inducible lysosomal thiol reductase* (*GILT*), which encodes a modulator of redox homeostasis in chemoresistant AML. Targeting *GILT* caused an increase in mitochondrial ROS levels, oxidative damage, and cell death. This was found to synergize with conventional chemotherapeutic agents, representing a ROS-priming strategy to prevent drug resistance [36]. These studies not only link phosphoproteomic signatures to drug-sensitivity assays and enable more precise kinase targeting, but they also match patients to inhibitors that have the highest probability to disrupt their dominant signaling dependencies (Figure 3). Proteomics and proteogenomics provide a functional bridge between genomic alterations and cellular phenotypes in AML by capturing protein abundance, post-translational modifications, and signaling network activity. These approaches reveal subtype-specific kinase activation, metabolic dependencies, and mechanisms of chemoresistance that are not evident at the transcriptomic level. However, their clinical application is currently limited by technical complexity, lack of standardization, and relatively modest cohort sizes. Integration with other omics layers and prospective validation will be critical for translating proteomic insights into actionable therapeutic strategies.

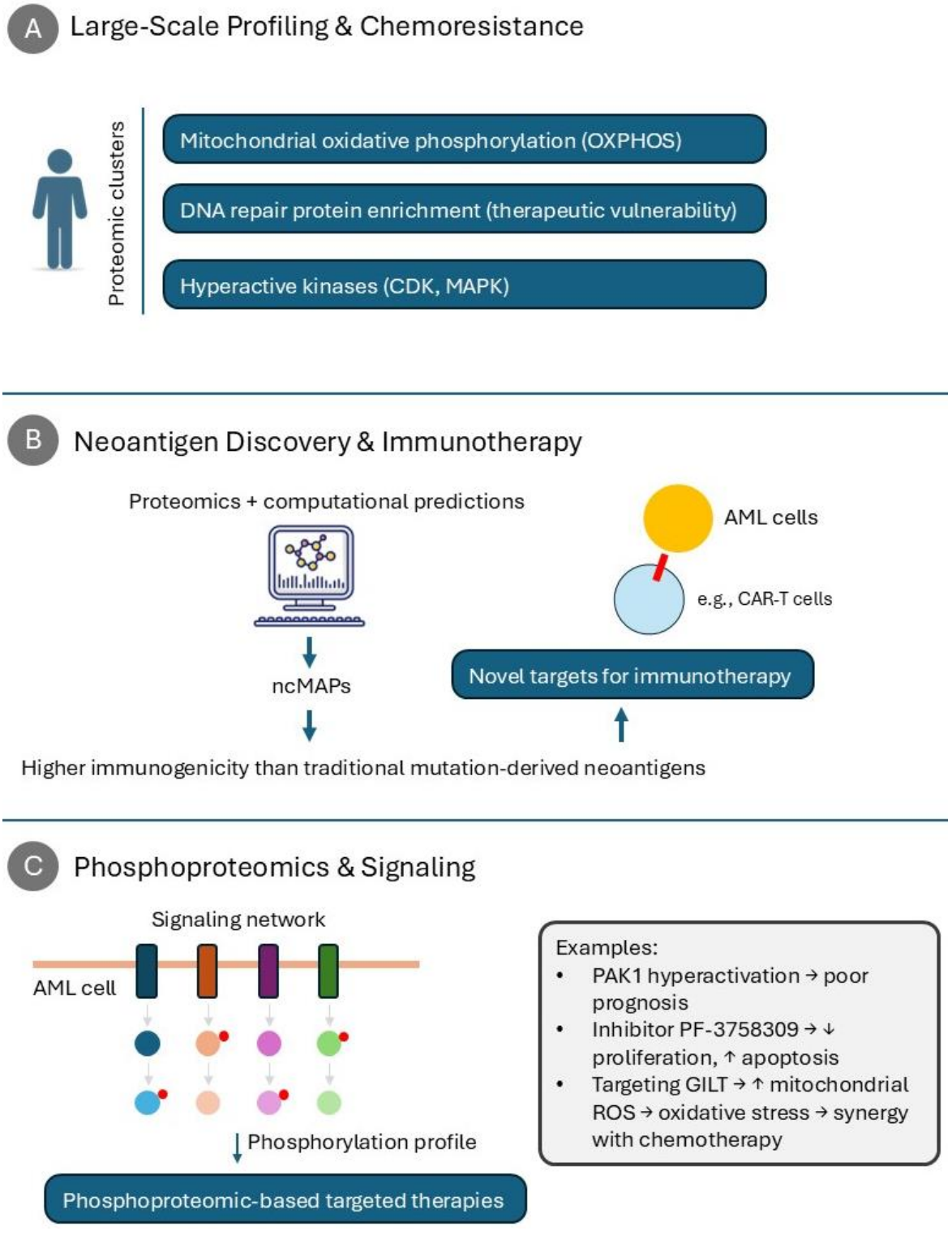

Figure 3 Proteogenomic profiling identifies molecular subtypes, therapeutic vulnerabilities, and immune targets in AML. (A) Integrated mass spectrometry–based proteomics, transcriptomics, and genomics reveal AML proteomic clusters associated with distinct metabolic and signaling states. Subgroups are enriched for mitochondrial oxidative phosphorylation (OXPHOS), DNA repair proteins representing therapeutic vulnerabilities, or hyperactive kinase signaling (e.g., CDK, MAPK). These proteomic signatures help explain chemoresistance mechanisms and point to targetable pathways. (B) Proteogenomics uncovers novel tumor-associated antigens beyond canonical

mutations. Non-canonical MHC-associated peptides (ncMAPs), identified through mass spectrometry and computational prediction, demonstrate higher immunogenicity than traditional mutation-derived antigens. These neoantigens broaden opportunities for immune-based therapies, including CAR-T and CAR-NK designs, informed by proteogenomic mapping of ligand–receptor interactions. (C) Phosphoproteomic profiling captures AML-specific signaling dependencies through post-translational modifications. PAK1 hyperactivation is associated with poor prognosis, and PF-3758309 inhibition reduces proliferation and induces apoptosis. Targeting *GILT*, a redox regulator in chemoresistant AML, elevates mitochondrial ROS and synergizes with chemotherapy, highlighting phosphoproteomic data as a guide to kinase-targeted and redox-based therapeutic interventions. These findings demonstrate that proteomics provides a functional readout of cellular activity, uncovering signaling dependencies and resistance mechanisms that can inform the precision targeting of kinase pathways, the development of immunotherapies, and the rational design of combination treatment strategies.

5. Metabolomics and Immunometabolomics

Metabolomics examines metabolites and metabolic pathways found in AML cells and the microenvironment, providing an indirect view of cellular biochemistry. Rather than tissue or cell transcriptomics or proteomics, which show potential activity, metabolomics reveals the bona fide metabolic state of the cell and ultimately reveals potential vulnerabilities to exploit therapeutically. In the context of the immune system, immunometabolomics identifies associations with specific metabolites and provides insight into how the metabolic programming of immune cells interacts with information on AML [37].

There are other important metabolic vulnerabilities, particularly including nutrient dependencies (e.g., serine biosynthesis). PSAT1 can be inhibited to create a temporary dependency upon serine, which can induce serine auxotrophy and ultimately limit nucleotide synthesis, redox balance, and one-carbon metabolism, ultimately leading to AML cell death. Targeting this pathway represents a potential therapeutic strategy; however, these findings are primarily supported by experimental models and require validation in larger and independent patient cohorts [38]. Another dependency is on FAO, with increased *CPT1A* expression associated with negative prognostics. CPT1A enhances FAO so AML cells generate ATP and NADPH, but still can cope with the oxidative stress of NRTI or daunorubicin. Using lipid profiles, AML cells could be generating increased lipid metabolism through β-oxidation compared to normal progenitors, causing dependency on CPT1A as a target [39].

Metabolic variations also influence the AML microenvironment, particularly regarding the role of bone marrow stromal cells. Observations show dysregulated circadian rhythm and lipid metabolism genes in these cells, as they encounter leukemic signals and develop a nutrient-favorable niche that supports leukemia growth, potentially reflecting the immune system and drug-delivery parameters [40].

Natural products can potentially alter the metabolism in AML. Alisol B enhances purine metabolism and intestinal microbiota by decreasing inflammatory signals. The flower Dendrobium officinale increases lipid metabolism via the PPAR/RXR pathways, altering energy dynamics and membrane lipid composition [41]. Metformin, exercises its role as an antidiabetic, yet restores

metabolic imbalances in *DNMT3A*-mutated cells, decreases their winner' superiority, and may represent a chemopreventive agent in AML [16, 17] (Figure 4).

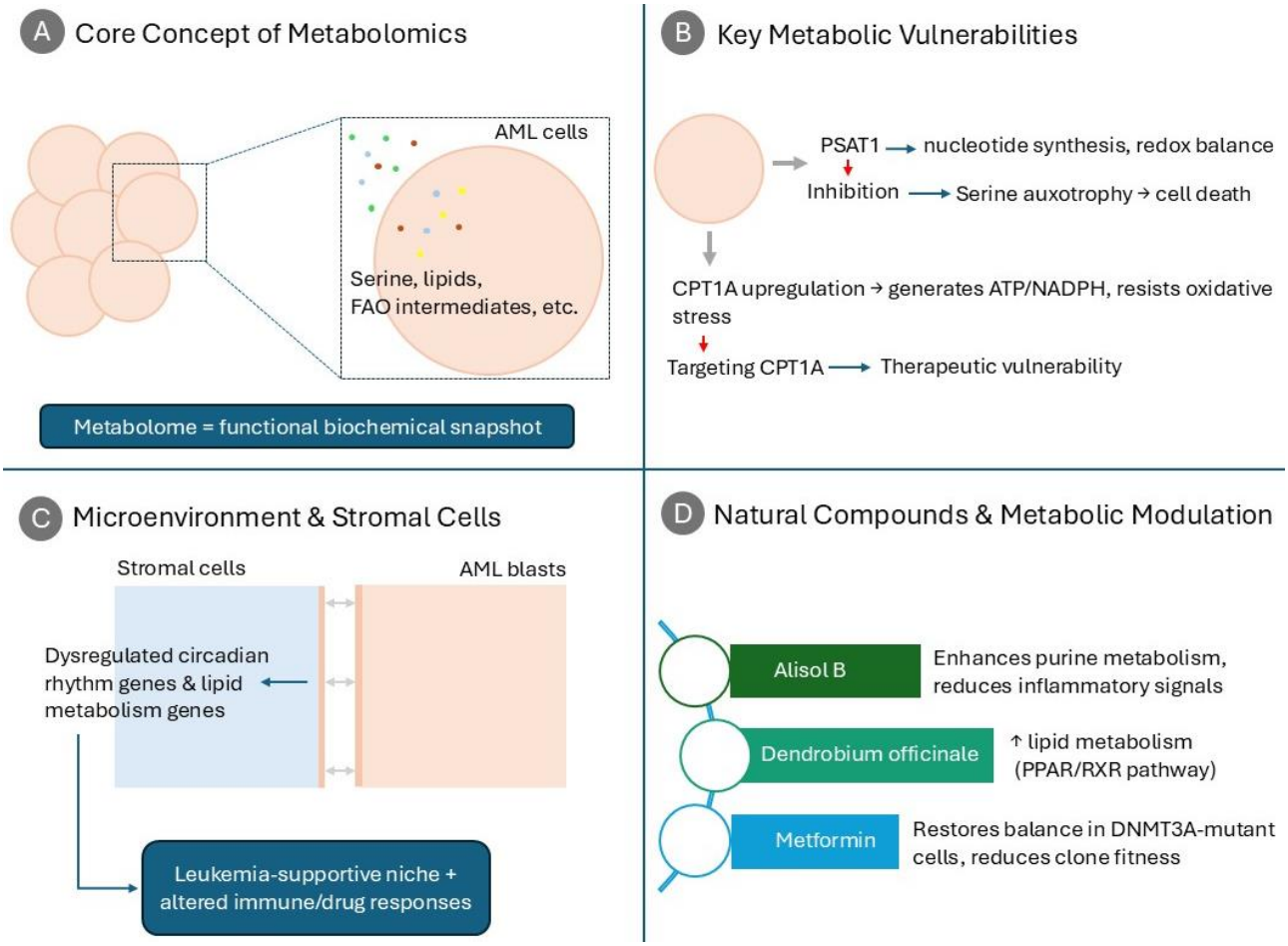

Figure 4 Metabolomic and immunometabolomic insights reveal metabolic dependencies and therapeutic opportunities in AML. (A) Metabolomic profiling captures real-time biochemical states of AML cells, reflecting active metabolic pathways. (B) AML cells exhibit specific nutrient dependencies, including serine biosynthesis and fatty acid oxidation, which support leukemic survival. (C) Leukemic cells remodel the bone marrow microenvironment, altering stromal metabolism and immune interactions. (D) These dynamic metabolic adaptations link cellular metabolism with immune regulation and disease progression, and represent critical therapeutic vulnerabilities that can be targeted alone or in combination with chemotherapy and immunotherapy. Interpretation of metabolomic data is further complicated by the dynamic and context-dependent nature of metabolic states, as well as variability introduced by sample handling, microenvironmental influences, and systemic factors, which may limit the consistency of identified metabolic biomarkers.

6. Other Multi-Omics Approaches in AML

6.1 Microbiome-Linked Multi-Omics

Microbiome-focused multi-omics studies have identified severe perturbations in the gut ecosystem during AML therapy, which have significant implications for patient immunity, metabolism, and overall treatment tolerability. In a longitudinal AML induction-chemotherapy cohort, investigators compiled amplicon sequencing data from 566 fecal samples obtained from 68 AML patients and linked these data to serum metabolomics from 260 samples collected from 36 patients, together with clinical metadata. The study validated technical quality through example analyses and provided a resource for microbiome–metabolome–clinical integration. However, interpretation of these data requires caution, as the microbiome and metabolome profiles in AML are strongly influenced by antibiotics, chemotherapy timing, hospitalization, diet, mucosal injury, and supportive-care practices [42]. This resource facilitates research into the relationships between changes in microbial composition, systemic metabolic changes, treatment response, and adverse events. The analyses revealed that therapy-related perturbations in the microbiome tend to occur very early in therapy, often leading to a loss of microbial diversity before patients experience clinical indicators of gastrointestinal dysfunction.

To support this, additional work has shown that intensive chemotherapy led to persistent dysbiosis, characterized by loss of members with beneficial commensal activity and an increase in opportunistic species that have the potential to translocate across a damaged intestinal barrier [43]. Alongside, metabolomic readouts of these patients also reflected the loss of metabolites of health importance, like short-chain fatty acids and aromatic amino acid derivatives, both of which are critical to maintaining epithelial integrity and regulating inflammatory responses. This microbiome-metabolome disruption was also associated with systemic inflammation and weight loss, contributing to cachexia. Such highlights support the therapeutic strategy of microbiome-sparing interventions, which could ameliorate toxicity and enhance resilience to treatment [41].

6.2 Single-Cell and Spatial Multi-Omics

The rise of multi-omic technologies at single-cell and spatial levels has transformed the understanding of AML by providing highly detailed insights into the heterogeneity of leukemic populations and features of the bone marrow microenvironment at single-cell resolution. In a spatial proteo-transcriptomic study that profiled bone marrow from patients with leukemia, it was found that besides blasts, the number of mesenchymal stromal cells expanded considerably and that rather than leukemia presenting randomly throughout the bone marrow, discrete blast–stromal niches were formed that facilitated only leukemia survival and immune evasion. The niches represent organized tissues that influenced the penetration and response of therapy, and not groups of cells that randomly existed [44].

The application of clonal lineage tracing through the CloneTracer platform enhanced the ability to coordinate genetic identity with human cellular behavior, reconstruct differentiation hierarchies, and identify aberrant surface markers associated with drug response. Methodologically, CloneTracer was applied to samples from 19 AML patients, thereby providing clonal resolution to single-cell RNA-sequencing data. The study showed that residual healthy and preleukemic cells dominated the dormant stem-cell compartment, whereas active leukemic stem cells and

downstream myeloid progenitors showed disease-defining transcriptional states. Although this approach provides high-resolution biological insight, the modest patient number and complexity of single-cell inference mean that validation in larger longitudinal cohorts is needed [45]. High-throughput capsule-based single-cell multi-omics is a fast and effective approach to molecularly profile many different molecular layers (genome, transcriptome, and epigenome) simultaneously in many thousands of individual cells, providing greater statistical power to study heterogeneity [46].

Longitudinal single-cell work in t(8;21) AML has demonstrated dynamic changes in immune checkpoint gene expression in the leukemic population, which suggests that the timing of immunotherapy is important [47]. Single-cell multi-omics studies of TP53-mutant leukemic evolution indicate that chronic inflammatory signaling can selectively favor expansion of TP53-mutant hematopoietic clones while suppressing wild-type progenitors. This evidence was generated using single-cell multi-omic profiling and experimental modeling of inflammatory states, supporting a non-genetic route of clonal selection. Nevertheless, because the mechanism is most directly supported in TP53-mutant contexts, it should not be generalized to all AML evolutionary trajectories without further validation [48]. Integration of advanced multi-omics approaches provides a more comprehensive picture of AML biology, therapeutic resistance, and immune interactions, uunderscoring the importance of spatial and temporal context when considering treatment strategies in the disease.

6.3 Multi-Omics Integration into the Machine Learning

Machine learning approaches have emerged as tools to integrate multi-omics datasets into clinically actionable frameworks. In parallel, functional precision medicine strategies, such as prospective tumor board-guided studies integrating genomic profiling with *ex vivo* drug testing, have demonstrated the feasibility of translating multi-omics data into individualized therapeutic recommendations in AML, further bridging the gap between omics discovery and clinical implementation. The MDREAM ensemble model integrated mutational profiles, gene-expression signatures, and large-scale *ex vivo* drug-screening data from AML resources to predict patient-specific drug responses. Its validation relied on external cohorts and performance assessment against observed *ex vivo* responses rather than prospective treatment assignment. Therefore, although MDREAM demonstrates the potential of machine learning for functional precision medicine, prospective clinical validation is still required before such models can guide therapy selection in routine AML care [49]. Generative adversarial network-based frameworks have also been successfully applied to harmonizing drug sensitivity profiles and disease phenotype as different multi-omics data modalities [50]. Besides predictive approaches, network-based integration methods are also being used to identify hidden relationships among molecular features. Multilayer network survival models consider various omic layers to examine prognostically relevant molecular interactions [51]. The Integrative Network Fusion approach that takes advantage of similarity networks of each layer of omics data generates an integrated network that improves biomarker discoverability and patient stratification [52]. Resources such as AMLdb now aggregate multi-omics data with functional screening results, providing a platform for biomarker discovery and hypothesis generation [53].

Nevertheless, machine learning-based integration approaches face challenges, including overfitting, limited external validation, and the need for large, harmonized datasets, raising concerns about their robustness and generalizability in real-world clinical settings.

6.4 Immunogenomics and Immune Profiling

Studies using immune-mediated multi-omics have further defined the molecular mechanisms of immune evasion in AML and identified additional immunotherapy targets. In post–hematopoietic stem cell transplant relapse, integrated multi-omic profiling of paired diagnosis and relapse AML samples identified loss of HLA class II expression as a mechanism of immune escape associated with PRC2-mediated epigenetic repression. The study combined transcriptomic and epigenomic analyses with functional validation, showing that pharmacological PRC2 inhibition restored HLA-II expression and improved T-cell recognition of leukemic cells. This provides mechanistic and translational support for PRC2 targeting, although clinical benefit remains to be tested prospectively [54]. This mechanistic understanding is the basis for the addition of epigenetic therapies in post-transplant relapse.

In a phase II clinical trial of hypomethylating-agent therapy combined with nivolumab for AML relapse after allogeneic hematopoietic cell transplantation, single-cell immune monitoring identified immune signatures associated with response. Responders showed activated, less senescent $CD8^+$ T-cell states and pro-inflammatory transcriptional programs in T-cell and myeloid compartments. Because this evidence derives from a phase II trial with correlative immune profiling, these signatures should be interpreted as candidate response biomarkers requiring validation in larger prospective studies [55]. Further studies have shown that *FLT3*-mutant AML harbors unique immune features that predict sensitivity to FLT3-targeted inhibitors [56]. From this integrated analysis, other immune targets, like IL1RAP in triple-mutant AML [57], are added as more potential antigens for antibody- or CAR-therapy. Large pan-cancer immunogenomic studies further identified FCN1 as an immune prognostic marker with both direct effects on leukemic proliferation and immune modulation, serving as another example of the complex relationship between innate immune pathways and leukemic cell viability (Table 1) [58].

Table 1 Multi-omics studies in the field of AML.

Authors	Year	Omics Category	Main Subject of Study	Main Findings	References
Fierro et al.	2025	Proteomics + transcriptomics	Proteomic identification of WWP1 substrates in AML and mechanistic follow-up on the WWP1–JARID1B (KDM5B) axis in chemoresistance; integration of ubiquitylome/proteome with RNA-seq and H3K4me3 ChIP-seq.	Proteomics identified JARID1B/KDM5B as a WWP1 substrate; WWP1 stabilizes JARID1B via K63 polyubiquitination. WWP1 inactivation reduces JARID1B, increases H3K4me3 at JARID1B targets, dysregulates repair-related transcription, impairs DNA-damage-repair recruitment, and sensitizes AML cells to chemotherapy—thus implicating a WWP1–JARID1B axis in AML chemoresistance.	[32]
Yiyou et al.	2025	Metabolomics + Microbiome	Studied Alisol B's effect on metabolic dysfunction-associated steatotic liver disease via purine metabolism and gut microbiota regulation.	Alisol B improved liver steatosis by regulating purine metabolism pathways and restoring gut microbiota composition, ameliorating metabolic dysfunction.	[41]
Jiang et al.	2025	Pan-cancer transcriptomics	Pan-cancer analysis identifying ectopic RUNX1T1 expression linked to lineage plasticity across cancers.	Ectopic RUNX1T1 associated with lineage plasticity and cancer progression; potential pan-cancer therapeutic target.	[59]
Sinanidis et al.	2025	Metabolomics/ Functional genomics	Investigation of serine auxotrophy in AML (driven by PSAT1 suppression) as a targetable metabolic vulnerability.	Showed that PSAT1 suppression induces serine auxotrophy in AML cells, creating a vulnerability to serine deprivation. Highlights a potential metabolic-targeting therapeutic strategy.	[38]
Lei et al.	2025	Metabolomics + Transcriptomics	Disulfidptosis pathway in pediatric AML: integrative risk analysis and therapeutic relevance.	Elevated "disulfidptosis scores" linked to poor prognosis and hypermetabolism; SLC7A11 overexpression correlates with chemoresistance, suggesting targeted therapy potential.	[60]
Song et al.	2022	Epigenomics + Transcriptomic	Comparative multi-omics of long-term survival AML patients vs healthy controls.	Differential DNA methylation and gene expression; key pathways include NK-cell cytotoxicity and amino acid metabolism; immune infiltration differences; LOXL1 and PDZRN4 as prognostic markers.	[61]

Muratoğlu et al.	2025	Transcriptomics + Metabolomics + Lipidomics	Studied bone-marrow-adipose-tissue derived MSCs (BMAT-MSCs) from healthy donors, AML, and Fanconi anemia patients with integrated multi-omics to probe AhR (aryl hydrocarbon receptor)—circadian rhythm crosstalk and effects on the leukemia microenvironment.	Revealed dysregulation of circadian genes (NPAS2, PER2, BHLHE40, PER3, CIART) and lipid metabolism genes (FABP5, CD36) in AML/FA BMAT-MSCs; identified changes in circulating lipid metabolites and suggested AhR–circadian interactions remodel the leukemia niche—potential targets for microenvironmental therapy.	[62]
Izumi et al.	2025	Epigenomics + Functional genomics	Investigated which H3K4 methylation modifier(s) sustain broad H3K4me3 domains in MLL-rearranged (MLL-r) acute myeloid leukemia (AML). Used a CRISPR-tiling screen targeting known H3K4 methyltransferases in an MLL-r model, followed by chromatin profiling to map H3K4me3 breadth and transcriptional outputs (e.g., MYC).	Disruption of the catalytic SET domain of *SETD1B* reduced the breadth of H3K4me3 at key loci (including MYC), decreased MYC expression, and impaired proliferation of MLL-r AML cells—identifying *SETD1B* catalytic activity as a dependency and potential therapeutic vulnerability in MLL-r AML.	[10]
Li et al.	2025	Immune-genomic	TP53 mutations in T and NK cells promote immune escape in AML, restoring function via small-molecule p53 reactivation.	TP53-mutant T cells showed exhaustion and impaired cytotoxicity; reactivation of p53 rescued CAR-T functionality, reduced exhaustion markers, and improved survival in AML PDX models—offering therapeutic insight.	[19]
Métois et al.	2025	Genomics + Transcriptomics	IL1RAP was identified as a potential immunotherapy target in triple-mutated AML.	Identifies IL1RAP as a potential target for immunotherapy in normal karyotype triple-mutated AML; suggests targeting IL1RAP could improve treatment outcomes.	[57]
Baronas et al.	2025	Single-cell transcriptomics	Developed a high-throughput single-cell omics platform using semi-permeable capsules to profile cells.	Demonstrated efficient single-cell multi-omics profiling with enhanced throughput, enabling comprehensive cellular heterogeneity analysis.	[46]
Yanagiya et al.	2025	Transcriptomics + retrotranscriptomics	Expression of human endogenous retrovirus K9 (*HERV-K9*)–derived elements in AML; relationship between	Aberrant (elevated) expression of *HERV-K9*–derived elements in a subset of AML cases was associated with better clinical outcome. The paper presents	[27]

			HERV-K9 expression levels and clinical outcome.	transcript-level quantification of *HERV*-derived sequences and correlates expression with survival/clinical endpoints, suggesting *HERV-K9* expression as a potential prognostic biomarker.	
Niu et al.	2025	Immunogenomics + Transcriptomics + Proteomics	Immune hallmarks and biomarkers of FLT3 inhibitor sensitivity in FLT3-mutated AML.	Identified immune-related biomarkers associated with FLT3 inhibitor responsiveness in FLT3-mutant AML, offering stratification for therapy.	[56]
Casado et al.	2025	Phosphoproteomics	PAK1 kinase activation linked to poor prognosis; inhibitor PF-3758309 reduces AML cell growth.	Identifies PAK1 activation as a poor prognosis marker in AML; PF-3758309 effectively inhibits PAK1, reducing cell proliferation and inducing apoptosis in AML cell lines and primary cells.	[35]
Xu et al.	2025	Transcriptomics + Immunogenomics	Investigation of LST1 expression in AML: expression profiling (TCGA/GEO), immune-infiltration analyses, pathway enrichment, and validation (RT-qPCR/WB); development of prognostic nomogram.	LST1 is overexpressed in AML vs normal hematopoietic tissue; higher LST1 correlates with adverse clinicopathologic features (higher WBC, non-M3 FAB, intermediate/poor cytogenetic risk) and worse overall survival across subgroups. LST1 expression associates with immune-cell infiltration patterns and immune-related pathways; the authors propose LST1 as a prognostic marker and immunologically relevant biomarker.	[63]
Song et al.	2025	Genomics	AML classification integrating mutation profiles, DNA methylation, and transcriptomics; used for predicting patient prognosis.	Built a refined classification framework significantly improving prognostic accuracy for AML patients using integrated omics.	[64]
Ajonu et al.	2024	Machine Learning + Transcriptomics	Used a high-throughput swarm-based deep neural network to identify therapeutic targets in adult AML.	SPAG5 downregulation identified as potential therapeutic target, demonstrating the power of AI-driven analysis in AML biomarker discovery.	[65]
Wu et al.	2025	Single-cell transcriptomics	Multi-omics study of HDAC1 and c-JUN in AML: single-cell RNA-seq to identify cell types with high c-JUN activity (notably HSC-Prog), MR analysis with eQTL data, bulk RNA prognostic	Identified elevated c-JUN activity in HSC-Prog cells in AML; demonstrated c-JUN interacts with HDAC1 by Co-IP; functional *in vitro* assays and mouse models suggested that combined targeting of c-JUN and	[66]

			analysis, plus biochemical validation (co-IP, Western blot) and *in vivo* drug testing (mouse models).	HDAC1 impairs AML growth—supporting c-JUN/HDAC1 as a combinatorial therapeutic target.	
Lin et al.	2024	Transcriptomics	Comparative multi-omic analysis of truncating ASXL1 variants in Bohring-Opitz syndrome (BOS) and ASXL1-mutant AML to identify shared and distinct dysregulated pathways.	Found shared molecular signatures between BOS and AML-ASXL1: de-repression of *HOXA* cluster genes, upregulated Wnt signaling, and *HOXB4*; biomarkers (VANGL2, GRIK5, GREM2) dysregulated across conditions. DNA methylation (BOS episignature) clustered AML-ASXL1 with BOS, indicating shared ASXL1 epigenetic consequences; also observed differential RUNX3 isoform usage between BOS and AML-ASXL1.	[67]
Murray et al.	2024	Proteomics + Genomics + Phosphoproteomics	Proteogenomic profiling of AML reveals biomarkers and pathways driving leukemia development.	Proteogenomic profiling reveals biomarkers and pathways driving leukemogenesis; helps identify therapeutic targets; calls for standardization before clinical proteomic assay use.	[68]
Bender et al.	2024	Transcriptomics + Epigenomics	Redistribution of transcription factor RUNX1 in AML following PU.1 downregulation.	PU.1 loss shifts survival pathways; RUNX1 redistributes to lineage-inappropriate sites, sustaining AML cell survival as a pro-oncogenic fail-safe.	[69]
Cao et al.	2024	Immunometabolomics	Developed competitive nutrient-based T-cell immunotherapy targeting the Warburg effect in AML.	Designed T-cell therapy that blocks adaptive Warburg effect, enhancing immune targeting of AML cells by metabolic competition.	[70]
Zhong et al.	2024	Comprehensive multi-omics	Pan-cancer (including AML) analysis of NCF2 (neutrophil cytosolic factor 2) to assess prognostic value and immune signatures.	Clarified NCF2's prognostic and immunological roles across cancers and defined its relevance in AML via integrative multi-omics analysis.	[71]
Bexte et al.	2024	Multi-omics + cellular engineering	CAR-NK cells targeting CD33 in AML, with CRISPR/Cas9-mediated knockout of NKG2A to overcome HLA-E–mediated inhibitory checkpoint.	Demonstrated that NKG2A knockout enhances anti-leukemic efficacy of CD33-specific CAR-NK cells by bypassing HLA-E inhibition mechanisms.	[34]

Zhang et al.	2024	Transcriptomics + bioinformatics	Bioinformatic and experimental analysis of Complement Factor D (CFD) in AML: expression profiling (TCGA, GEO, HPA, CCLE), immune infiltration analyses, drug-sensitivity correlations, and experimental validation (RT-qPCR).	CFD is differentially expressed in AML (reported overexpression in tumor datasets). Authors report associations between CFD expression and clinical/immune features and present CFD-based prognostic models—they suggest CFD has prognostic/functional relevance in AML.	[72]
Alonso-Pérez et al.	2024	Transcriptomics	Pediatric AML driven by ETO2::GLIS2 fusion: developmental context, cytokine dependency, and therapeutic targeting using primary human HSPCs & xenograft models.	ETO2::GLIS2 expression in fetal/cord blood *CD34*$^{+}$ cells led to more efficient leukemogenesis than in postnatal cells. Leukemia progression depended on cytokines (IL-3, SCF). Single-cell transcriptomics identified transformed cell states. Combined MEK + BCL2 inhibition markedly reduced leukemic progression *in vivo*.	[73]
Wang et al.	2024	Epigenomics and Genomics	AML stratification into four prognostic clusters using multi-omics data.	Four AML clusters (CS1-CS4) with distinct mutation profiles, copy number alterations, and drug sensitivity; CS4 best prognosis, CS3 worst.	[74]
Zhong et al.	2024	Genomics	Pan-cancer and AML-specific analysis of FCN1 (ficolin-1) as prognostic biomarker and immune signature; integrating transcriptomics, single-cell, epigenetic, and *in vitro* work.	Identified FCN1 as an independent prognostic indicator in AML, associated with macrophage infiltration, immune regulation; FCN1 knockdown affected proliferation, apoptosis, and cell cycle in AML cell lines.	[58]
Qin et al.	2024	Multi-omics + machine learning	Constructed a pan-programmed cell death index (PPCDI) using bulk + single-cell transcriptomics for prognosis and therapy prediction in AML.	Developed a 6-gene PPCDI signature; high PPCDI correlated with poor survival and chemotherapy resistance, while indicating sensitivity to specific drugs (dasatinib, methotrexate). Robust prognostic nomograms were built.	[75]
Cai et al.	2024	Proteomics + Transcriptomics	MHC-I-presented non-canonical antigens (ncMAPs) in AML.	ncMAPs identified as neoantigens; comparable/superior to canonical MAPs; computational framework developed for neoantigen prioritization; risk model shows clinical prognostic value.	[33]

Li et al.	2024	Single-cell multi-omics	Longitudinal single-cell multi-omics profiling of t(8;21) AML, focusing on immune cell infiltration and checkpoint expression changes over time.	Revealed heterogeneity in immune infiltration across disease progression and identified prognostic immune checkpoint signatures in t(8;21) AML.	[47]
Iida et al.	2024	Network-based trans-omics	Computational prediction and validation of synergistic AML drug combinations.	Develops SyndrumNET, a computational method to predict synergistic drug combinations; validates predictions in AML cell lines; reveals capsaicin and mitoxantrone as effective combination.	[76]
Guo et al.	2024	Single-cell transcriptomics	Single-cell RNA-seq profiling of bone marrow from MDS patients to map hematopoietic development abnormalities and immune microenvironment.	Identified abnormal hematopoietic differentiation, heterogeneity in risk profiles, and altered T-cell microenvironment in MDS at single-cell resolution.	[77]
Du et al.	2024	Single-cell omics (Statistics)	Developed ULV, a robust statistical method for clustered data, applied to multi-subject single-cell omics datasets.	ULV enables improved statistical inference for single-cell omics data with complex clustering, enhancing biological insights.	[78]
Kosvyra et al.	2024	Multi-omics + machine learning	Multi-layer network analysis integrating multi-omics to develop a survival prediction model for AML patients.	Established a multi-omics machine learning model with network feature selection to improve prognostic capabilities and guide future personalized interventions in AML.	[51]
Vinod Kumar et al.	2024	Multi-omics (database integration)	Development of AMLdb, a comprehensive multi-omics database for AML biomarker and drug target discovery.	AMLdb integrates expression, methylation, CRISPR, drug sensitivity, mutation, and biomarker data; five genes were identified as potential targets (CBFB, ENO1, IMPDH2, SEPHS2, MYH9).	[53]
Wang et al.	2024	Single-cell metabolomics	Development and testing of label-free single-cell Raman spectroscopy to identify AML1-ETO (t(8;21)) positive AML cells from patient bone-marrow; spectral classification and metabolic interpretation.	Single-cell Raman spectral fingerprints discriminated AML1-ETO (AE) positive vs negative M2 AML patient cells with >90% single-cell identification accuracy (PCA/LDA classifier). Spectral components indicated AE-associated changes consistent with lipid and nucleic-acid metabolic differences reported in genomic/metabolomic studies.	[79]

Bandyopadhyay et al.	2024	Spatial proteo-transcriptomics	Mapping cell-type and spatial organization in human bone marrow niches using single-cell RNA-seq and multiplex proteomic imaging.	Built a spatially resolved multiomic atlas; identified mesenchymal stromal cell (MSC) expansion and distinct leukemic blast–MSC neighborhoods in AML bone marrow.	[44]
Afroz et al.	2024	Multi-omics & machine learning	Integrative omics data and drug screening for AML using generative adversarial networks (GANs).	Demonstrated feasibility of using GANs to integrate multi-omic data and predict drug responses/trait phenotypes in AML.	[50]
Zou et al.	2024	Metabolomics + Transcriptomics and Proteomics	Mechanisms of Dendrobium officinale in improving hepatic lipid metabolism in diabetic mice via PPAR/RXR pathways.	DEN improved liver function, lipid profiles, and insulin sensitivity in db/db mice. Multi-omics showed modulation of lipid metabolic pathways and gene expression (e.g., Cpt1b, Scd1). Proteomics tied effects to AMPK and PPAR signaling as therapeutic mechanisms.	[80]
Hosseini et al.	2024	Metabolomics + Epigenomics	Preclinical study assessing whether metformin reverses aberrant metabolic and epigenetic states of *DNMT3A*^{R878H} hematopoietic stem/progenitor cells (HSPCs) and thereby reduces clonal fitness.	In murine HSPC models, metformin reduced the clonal fitness/competitive advantage of *DNMT3A*^{R878H} cells by reverting abnormal metabolic profiles and partially normalizing epigenetic marks, suggesting metabolic intervention could reduce the expansion of mutated clones.	[17]
Waclawiczek et al.	2024	Multi-omics (single-cell, lineage tracing)	Study of AML stem cells' lineage plasticity enabling therapy evasion and resistance mechanisms.	Discusses how AML cells exhibit lineage plasticity, allowing them to evade therapies targeting specific lineages, and the potential for lineage-specific inhibitors to overcome resistance.	[81]
Zhong et al.	2023	Immunomics	Classified AML patients based on $CD8^+$ T cell molecular subtypes with diverse immune landscapes and clinical significance.	Identified heterogeneous $CD8^+$ T cell subtypes with different immune landscapes correlating with prognosis and therapy response in AML patients.	[82]
Anthony et al.	2023	Genomics	Studied effects of radon exposure on clonal hematopoiesis and stroke susceptibility in women using multi-omics data.	Found radon exposure associated with increased clonal hematopoiesis, which in turn is linked to higher stroke risk, highlighting environmental risk factors.	[83]

Magliulo et al.	2023	Transcriptomics + Functional genomics	Investigated roles of hypoxia-inducible factors HIF1α and HIF2α in AML differentiation block and leukemogenesis using transcriptional profiling and functional assays.	Demonstrated that both HIF1α and HIF2α have oncogenic roles in AML; HIF2α in particular enforces a differentiation block by upregulating transcriptional repressors that suppress myeloid differentiation programs.	[84]
Pötgens et al.	2023	Microbiome metabolomics	Longitudinal profiling of gut microbiota, metabolome, and host gut-barrier/inflammatory markers in AML patients undergoing intensive induction chemotherapy to link microbiome changes with barrier dysfunction and cachexia.	Intensive chemotherapy transiently impaired gut barrier function and induced persistent microbiota shifts (loss of diversity; enrichment of Enterococcus faecium and Staphylococcus at discharge); reduced microbial metabolites (hippurate, branched chain metabolites); identified taxa whose loss was associated with barrier dysfunction and bodyweight loss—suggesting microbiome intervention opportunities to improve supportive care.	[43]
Kurayoshi et al.	2023	Genomics + Transcriptomics	Explored targeting of cis-regulatory elements of FOXO family transcription factors as a therapeutic differentiation strategy in AML; combined CRISPR/Cas9 screening with gene expression profiling and differentiation assays.	Showed that pharmacologic inhibition of a cis-regulatory element common to FOXO family members induced differentiation of various AML cell lines. Identified TRIB1 as an important FOXO downstream gene that maintains an undifferentiated state, linking FOXO regulation to AML differentiation status and suggesting a novel therapeutic angle.	[85]
Batten DJ et al.	2023	Multi-omics data integration	An in silico approach to identify genes contributing to patient similarity based on multi-omics profiles in AML.	Developed computational methods for integrative analysis, identifying key genes contributing to AML patient heterogeneity.	[86]
Khelfa et al.	2023	Immunomics + Transcriptomics	Compared $CD4^+$ T-cell profiles in platelet-transfused AML patients with vs without anti-HLA alloimmunization using multi-omic immune phenotyping to identify immune features associated with alloimmunization.	Found divergent $CD4^+$ T-cell signatures associated with anti-HLA alloimmunization: alloimmunized patients' $CD4^+$ cells showed activation markers (e.g., higher CD40, OX40); non-alloimmunized patients had higher PD-1 and larger/more functional Treg compartments. Multi-omic analyses supported distinct transcriptional and phenotypic programs.	[87]

Rodriguez-Meira et al.	2023	Single-cell multi-omics	Impact of chronic inflammation on TP53-mutant leukemic evolution in AML.	Chronic inflammation suppressed TP53 WT hematopoietic progenitors, promoted expansion and evolution of TP53-mutant clones, highlighting inflammation as a driver of leukemic evolution.	[48]
Apostolova et al.	2023	Immunogenomics/ single-cell transcriptomics	Phase II clinical trial of a hypomethylating agent combined with nivolumab for AML relapse after allo-HCT, coupled to single-cell RNA sequencing and single-cell immunomonitoring to define immune signatures associated with response.	Reported modest clinical activity (ORR ≈25%) and identified an immune signature correlating with response: responders showed higher frequencies of activated, less-senescent $CD8^+$ T cells and pro-inflammatory transcriptional programs in both T and myeloid compartments. These single-cell immune signatures are associated with better outcomes and may guide patient selection.	[55]
Aldana et al.	2023	Epigenomics + Genomics + Transcriptomics	Characterized oncogenic EZH2 gain- and loss-of-function mutants using a comprehensive multi-omics panel to map H3K27me3 deposition, chromatin accessibility, transcriptomic and proteomic/metabolomic consequences.	Identified discrete gene sets and downstream targets differentially affected by EZH2 GOF vs LOF mutants; mutant EZH2 reprograms chromatin, protein interaction networks, and metabolic signatures, producing distinguishable molecular signatures useful for mechanism-based biomarker/target development.	[15]
Wang et al.	2023	Multi-omics	*IKZF1*^{N159S} mutation alters gene expression and immune profiles in AML.	Describes *IKZF1*^{N159S} mutations in AML; associated with higher *HOXA/B* expression and native B-cell immune fractions; reshapes *IKZF1* binding profiles, affecting cofactor regulation.	[24]
Ma et al.	2023	Proteomics + Epigenomics	Role of super-enhancer-associated CAPG gene in AML progression.	CAPG expression correlates with poor prognosis; CAPG regulates NF-κB signaling; knockdown leads to AML cell exhaustion and prolonged survival in the murine AML model.	[88]
Beneyto-Calabuig et al.	2023	Single-cell multi-omics	Clonally resolved analysis to trace cellular differentiation trajectories in AML using CloneTracer.	Reconstructed differentiation landscape similar to healthy hematopoiesis; identified leukemic-specific misregulated surface markers predictive of therapy response.	[45]

Trac et al.	2023	Multi-omics + computational model (mutations + gene expression + drug screen integration)	Developed MDREAM, an ensemble prediction model for AML patient drug responses by integrating multi-omics (mutational profiles, gene expression) and large-scale drug-testing data (BeatAML) and validating in external cohorts.	MDREAM (122 ensemble models) predicted *ex-vivo* drug responses with good performance in validation; predictions with high confidence (>0.75) had ~77% validated proportion of good responders—model may aid personalized therapy selection.	[49]
Xia et al.	2023	Small noncoding RNA signatures	Profiling circulating sncRNAs (tsRNA, rsRNA, ysRNA) in blood/marrow of AML patients vs controls as noninvasive diagnostic biomarkers.	Identified >20 sncRNA categories; tsRNAs in serum were strongly associated with prognosis; machine learning models differentiated AML patients from controls. Supports tsRNAs as potential noninvasive biomarkers.	[89]
Blöchl et al.	2023	Glycomics, Transcriptomics	Glycomic differences define AML subtypes and relate to differentiation and gene regulation.	Identifies distinct glycomic features in AML subtypes M5 and M6; associates glycan phenotypes with differentiation status and FAB classification; explores glycosyltransferases and transcription factors involved.	[90]
Zhong et al.	2023	Transcriptomics/splicing-factor (RNA-seq based) analysis	Characterized splicing factor-mediated regulatory patterns in AML by integrating splicing factor expression, alternative splicing patterns, immune features, and clinical outcomes to identify prognostic splicing signatures.	Defined four splicing regulation patterns associated with immune function, tumor mutation landscape, and signaling pathway activity; derived splicing-factor related prognostic indicators that aid outcome prediction in AML.	[28]
Cheng et al.	2022	Transcriptomics	Subtyping AML based on transcriptomic profiling to refine classification and differentiation hierarchy frameworks.	Defined eight stable gene-expression subgroups (G1-G8), including new subgroups with clinical relevance; improved risk stratification.	[21]
Thrun et al.	2022	Bioinformatics/Omics	Bioinformatic analysis of surface molecules in AML using combined Bayesian and Approximate Bayesian Computation (ABC) approaches.	Identified key AML surface molecule patterns using Bayesian and ABC analysis—offering insights into AML immunophenotypes and potential diagnostic or therapeutic targets.	[91]
Rashidi et al.	2022	Microbiome (metagenomics/am	Compilation and release of a longitudinal dataset (fecal microbiome,	The paper provides a well-curated, validated dataset (566 fecal samples from 68 patients; 260 serum	[42]

		plicon) + serum metabolomics	serum metabolome, and clinical metadata) from AML patients undergoing induction chemotherapy—intended as a resource for integrated microbiome–metabolome–clinical analyses.	metabolome samples from 36 patients), enabling integrated multi-omics analysis. They validate data technical quality and show example integrated analyses—enabling researchers to study microbiome/metabolome changes during AML induction and their links to clinical events.	
Jin et al.	2022	Functional genomics (large-scale CRISPR-Cas9 knockout screens integrated with transcriptomics)	Integrated >1,000 *in vitro* and *in vivo* CRISPR-Cas9 knockout screens to identify AML-specific fitness genes and derived a gene-expression fitness score for prognostic stratification.	Identified AML-specific fitness genes and derived a validated 16-gene fitness score that improved risk stratification across multiple independent cohorts (training and several validation cohorts), suggesting utility as a prognostic biomarker.	[92]
Liu et al.	2022	Multi-omics (splicing/transcriptome/proteome)	Role of splicing factor *RBM17* in maintaining leukemic stem cells in AML.	*RBM17* is upregulated in LSCs, promotes survival; knockdown leads to differentiation, impaired colony formation, and inclusion of poison exons triggering NMD-sensitive transcripts of pro-leukemic factors like EIF4A2. Proteomic analysis confirmed downstream effects, suggesting therapeutic targeting potential.	[29]
Kelesoglu et al.	2022	Systems-medicine multiomics (transcriptome + proteome + metabolome integration)	Multiomics systems-medicine study that integrates RNA, protein, and metabolite data with genome-scale networks to derive novel AML molecular signatures and reporter biomolecules.	Reported new multiomics molecular signatures and candidate reporter biomolecules that may improve AML molecular classification and provide leads for diagnostic/therapeutic development.	[93]
Verma et al.	2022	Gene expression + multi-omics database analyses	Clinical and prognostic evaluation of BAALC mRNA expression in adult CN-AML (NPM1-wt/FLT3-ITD-neg subgroup); cross-reference to multi-omics databases to explore associated molecular features.	High BAALC expression correlates with *CD34* positivity, RUNX1 mutation, absence of NPM1 mutation, and worse patient outcomes (particularly in NPM1-wt/FLT3-ITD-neg CN-AML). BAALC expression is associated with promoter methylation changes and pathways (MYC targets, RAS signaling)—supporting BAALC as a prognostic marker (multi-omics support).	[94]

Gambacorta et al.	2022	Multi-omics (transcriptomics, DNA methylation, chromatin accessibility, proteomics)	Multiomic profiling of paired diagnostic/relapse AML samples after allogeneic hematopoietic cell transplant to identify mechanisms of immune escape causing relapse—with particular focus on HLA class II downregulation.	Found consistent loss of chromatin accessibility and downregulation of HLA class II genes at relapse. Identified PRC2 (Polycomb Repressive Complex 2) as an epigenetic regulator driving HLA-II repression; pharmacologic inhibition of PRC2 restored HLA class II expression and improved T-cell recognition in *ex vivo* assays—suggesting PRC2 inhibition as a strategy to counteract post-transplant immune escape.	[54]
Jayavelu et al.	2022	Proteogenomics	Proteogenomic profiling of 252 AML patient bone marrow biopsies integrating proteomics with cytogenetics and DNA/RNA sequencing.	Defined proteogenomic subtypes of AML, revealing molecular pathophysiology, diagnostic biomarkers, and therapeutic targets.	[30]
Caplan et al.	2022	Transcriptomics + proteomics (quantitative)	Mass spectrometry proteomics combined with RNA-seq in AML mouse models to identify mitochondrial metabolism proteins as drug targets.	Identified mitochondrial metabolic proteins as potential therapeutic targets in AML, bridging transcriptomic changes with proteomic expression.	[31]
Scheller et al.	2021	Epigenomics/ transcriptomics (epigenetic-focused multi-omics)	Effects of the *DNMT3A*^{R882H} hotspot mutation in clonal hematopoiesis (CH) and AML—methylation changes (retrotransposons), transcriptional (interferon/viral-mimicry) responses, and sensitivity to hypomethylating therapy, studied in patient samples and mouse models.	*DNMT3A*^{R882H} causes focal hypomethylation, particularly at retrotransposon sequences, triggering a cell-intrinsic viral-mimicry/IFN response. *DNMT3A*^{R882H} cells were selectively more sensitive to the hypomethylating agent azacytidine (AZA); AZA enhanced retrotransposon expression, ISG induction, translation suppression, and apoptosis—suggesting *DNMT3A*^{R882} status may influence AZA response.	[8]
Elsayed et al.	2022	Genomics/ Pharmacogenomics	Development of a polygenic Ara-C response score (ACS10) in pediatric AML based on SNPs in Ara-C pathway genes.	Low ACS10 scores were linked to poor outcomes on standard therapy. However, augmented chemotherapy (high-dose Ara-C or addition of gemtuzumab ozogamicin) improved event-free and overall survival in this low-score group.	[95]
Li et al.	2021	Multi-omics (transcriptomics—	Preclinical evaluation of chidamide (HDAC inhibitor) + venetoclax (BCL-2 inhibitor) in AML cell lines, primary AML	The combination produced synergistic apoptosis (combination index <1) in cell lines and primary cells and improved outcomes in mouse models.	[96]

		RNA-seq; protein-level assays noted)	cells, and mouse models; includes sequencing to probe mechanisms.	Mechanistically, venetoclax upregulated Mcl-1 while chidamide downregulated it; the combination further decreased Mcl-1. RNA/protein analyses showed enrichment/alteration of PI3K-AKT and JAK2/STAT3 pathways consistent with apoptosis enhancement.	
Nguyen et al.	2021	Multi-omics (RNA-seq, CNA)	Identification of a high-risk AML subgroup with TP53 mutations and chemotherapy resistance.	Identifies a subgroup of AML patients with poor chemotherapy response; characterized by TP53 mutations and overexpression of genes like E2F4 and MN1; over-activated pathways include immune function and DNA damage.	[97]
Dong et al.	2021	Transcriptomics on oxidative-stress gene signature (bulk RNA)	Built a prognostic multi-omic model focused on oxidative-stress related genes in AML by integrating TCGA and GEO expression datasets and clinical data to derive a prognostic risk score and explore associations with drug sensitivity, pathways and immune infiltration.	Established and validated an oxidative-stress gene prognostic risk model that stratifies AML patients; the risk score correlates with predicted drug sensitivity, immune infiltration patterns and pathway activities, suggesting oxidative-stress genes as prognostic biomarkers and potential therapeutic targets.	[22]
Zhang et al.	2021	Multi-omics (transcriptomics + methylation + immune profiling)	Integrated public multi-omics data to characterize *B7-H3* (*CD276*) expression in AML, its genomic correlates, immune landscape associations, and prognostic significance.	Found elevated *B7-H3* expression in AML vs controls; high *B7-H3* associated with older age, TP53 mutation, certain FAB subtypes and poor survival across multiple cohorts; *B7-H3* expression correlated with EMT gene signatures and immune-suppressive infiltrates (macrophages, neutrophils, DCs).	[12]
Bhadra et al.	2021	Multi-omics/ Bioinformatics	Development of an unsupervised feature selection method combining hierarchical clustering and SVD—application to biomarker discovery in AML.	The integrative clustering + SVD method successfully identified discriminative features (potential biomarkers) in AML datasets. Showcases a scalable strategy for omics-based biomarker detection.	[98]
Niu LT et al.	2021	Functional proteomics/Redox	Investigated IFN-γ-inducible lysosomal thiol reductase (*GILT*) as a target to	Targeting *GILT* increased ROS-mediated mitochondrial damage in AML cells, overcoming chemoresistance and enhancing apoptosis.	[36]

			overcome chemoresistance in AML via mitochondrial ROS regulation.		
Passaro et al.	2021	Multi-omics (RNA-seq, proteomics)	Bone marrow niche changes in AML revealed by stromal gene and protein alterations.	Analyzes bone marrow stromal components in AML xenografts; identifies early disease onset deregulated genes in the mesenchymal compartment; predicts signaling nodes involved in niche alteration.	[99]
Barresi V et al.	2021	Genomics (Cytogenetics, RNA-seq)	Investigated NUP98 gene rearrangements in pediatric AML to identify biomarkers for primary induction failure.	Identified candidate biomarkers linked to induction failure, highlighting NUP98 rearrangements as a poor prognostic factor in pediatric AML.	[100]
Kayser et al.	2021	Clinical/ clinicogenomic (cytogenetics, outcomes)	International collaborative study describing characteristics and outcomes of patients with AML harboring t(8;16)(p11;p13)/MYST3-CREBBP across centers.	Outcomes with chemotherapy alone were poor; allogeneic HCT in first complete remission (CR1) significantly improved survival in de-novo AML (less benefit in therapy-related/secondary AML or complex karyotypes)—supports considering allo-HCT in CR1 for suitable patients.	[101]
Zheng et al.	2020	Multi-omics on DNA methylation + transcriptomics (integrative)	Pediatric AML: integrated methylome and transcriptome (TARGET) to identify aberrantly methylated genes associated with prognosis and to explore mechanisms by which methylation alters gene expression.	Identified three CpG sites/genes (e.g., sites in *CD34*, *HOXA7*, *CD96*) with prognostic significance in pediatric AML and characterized their putative functional roles, proposing these methylation changes as candidate prognostic markers.	[11]
Zhao et al.	2020	Transcriptomics/ immunogenomics	Identification of immune genes linked to AML prognosis; focus on NFATC4 and its relation to immune infiltration, especially regulatory T cells (Tregs).	NFATC4 expression is increased in AML and correlates with poor prognosis. Bioinformatic immune-infiltration analyses (CIBERSORT etc.) showed NFATC4 is strongly associated with Treg abundance (positive correlation), suggesting NFATC4 may modulate AML immune microenvironment and be a candidate immunotherapy target.	[25]
Aziz et al.	2020	Systems biology (Gene regulatory networks)	Prioritized biomarkers and estimated statistical power using ensemble gene regulatory network inference.	Developed ensemble GRN inference to identify key biomarkers with improved power estimation for complex diseases like AML.	[102]

Huang et al.	2020	Multi-omics (gene expression + miRNA + DNA methylation analyses)	Role and prognostic significance of *CLIC4* (chloride intracellular channel 4) expression in cytogenetically-normal AML (CN-AML); WGCNA and integration with miRNA and methylation data.	*CLIC4* is overexpressed in CN-AML and associated with worse overall and event-free survival across multiple cohorts. Multi-omics/WGCNA linked *CLIC4*-high cases to distinct co-expression modules, immune-related pathways, dysregulated miRNAs and DNA methylation changes (CpG island/open sea and gene-region specific), supporting *CLIC4* as a potential prognostic marker and therapeutic target.	[13]
Chierici et al.	2020	Computational multi-omics methods (Integrative Network Fusion—INF framework)	Method development: a reproducible, network-based pipeline (INF) that integrates multiple omics layers (expression, methylation, CNV, etc.) using Similarity Network Fusion and ML for cancer subtyping and biomarker discovery; demonstrated on TCGA datasets.	INF (rSNF + feature selection + classifier) improved multi-omics integration, produced compact, reproducible biomarker sets, and performed well across classification tasks on TCGA datasets. The paper presents an end-to-end, reproducible framework for network-based multi-omics integration.	[52]
Zhuang et al.	2020	Multi-omics (Genomics + Transcriptomics)	Combined multi-omics analysis to identify a 10-gene signature predicting AML patient survival.	The 10-gene signature robustly predicted survival in AML, providing potential prognostic biomarkers for clinical use.	[103]
Huang et al.	2020	Multi-omics (gene expression + miRNA + DNA methylation analyses)	Prognostic significance of *ANP32A* expression in cytogenetically normal AML (CN-AML) across cohorts; follow-up multi-omics to explore associated pathways, miRNA networks, and methylation patterns.	*ANP32A* is overexpressed in CN-AML and associated with worse overall and event-free survival across cohorts and subgroups. Multi-omics analyses linked high *ANP32A* to dysregulated oncogenic/tumor-suppressor networks, altered metabolic and immune pathways, miRNA interactions, and hypomethylation at CpG/first-exon regions—proposed as an unfavorable prognostic marker and potential therapeutic target.	[14]
Hao et al.	2020	Proteomics/ Functional Genomics	Studied cereblon modulator CC-885's effect on mitophagy by targeting BNIP3L for degradation.	CC-885 inhibits mitophagy by selectively degrading BNIP3L, potentially affecting AML cell survival and providing a therapeutic angle.	[104]

Warnat-Herresthal et al.	2019	Transcriptomics + Machine Learning	Developed a scalable blood transcriptomics-based ML model for AML prediction.	The model effectively predicts AML from blood transcriptomics with high accuracy, showing potential for scalable clinical diagnostics.	[105]
Yi et al.	2019	Genomics (Transcriptomics + Epigenomics)	Examined CBFβ-MYH11 fusion impact on megakaryocyte differentiation, focusing on gene programs including GATA2 and KLF1.	CBFβ-MYH11 interferes with megakaryocyte differentiation by modulating key transcription factors GATA2 and KLF1, disrupting normal hematopoiesis.	[106]
Rappoport et al.	2019	Methods/computational multi-omics (clustering algorithm)	Presented NEMO, a neighborhood-based multi-omics clustering algorithm that handles partial datasets where some samples lack particular omics types, and demonstrated utility on cancer datasets, including AML.	NEMO achieves clustering quality comparable to top methods on full datasets and outperforms others on partial datasets; fast, simple, and useful when some samples are missing omics.	[107]
Leung et al.	2019	Multi-omics (DNA methylome, transcriptome, surface proteome)	Effects of azacitidine on AML cell lines across multi-omics layers.	Global DNA demethylation with subtle transcriptomic/proteomic changes; 5 genes commonly upregulated, including TRPM4; shifts toward decreased metabolism and increased immune response pathways.	[108]
Stuani et al.	2018	Metabolomics (Stable isotope labeling)	Used stable isotope labeling to study fatty acid and lipid metabolism alterations in AML cells.	Revealed enhanced fatty acid and lipid metabolic activity in AML, indicating metabolic adaptations supporting leukemia proliferation.	[109]
Klau et al.	2018	Multi-omics (Machine Learning)	Developed Priority-Lasso, a hierarchical method for predicting clinical outcomes from multi-omics datasets.	Priority-Lasso improved interpretability and performance in multi-omics clinical outcome prediction compared to standard methods.	[110]
Chebouba et al.	2018	Proteomics + Computational Biology	Used proteomics data and Answer Set Programming to discriminate AML patient treatment responses.	The approach effectively classified AML patients based on proteomic profiles, helping predict treatment outcomes computationally.	[111]
Na et al.	2018	Metabolomics/ Molecular signaling	Studied isoliquiritigenin's protective effect against ethanol-induced hepatic steatosis through the SIRT1-AMPK pathway.	Isoliquiritigenin activated SIRT1-AMPK signaling, reducing lipid accumulation and oxidative stress in hepatic cells.	[112]

Liu et al.	2018	Bioinformatic discovery + functional genomics	LRRC25 as a candidate leukocyte differentiation antigen identified via large-scale omics data mining; functional validation of LRRC25 in ATRA-induced granulocytic differentiation (cell lines, primary cells, CRISPR).	LRRC25 is highly expressed in mature myeloid cells, downregulated in AML cell lines/patient bone marrow, and upregulated during ATRA-induced granulocytic differentiation. Knockdown/knockout of LRRC25 impairs ATRA-induced differentiation; rescue restores differentiation—suggesting LRRC25 is a functional regulator of granulocytic differentiation and was discovered via omics data mining and bench validation.	[113]
Heo et al.	2017	Genomic (whole-exome sequencing)	WES of Korean AML patients to identify somatic mutations and compare mutation signatures with TCGA populations.	Found recurrent SNVs, indels, and CNVs. Ethnicity-specific mutation patterns emerged. Some mutations correlated with clinical features; differences compared to TCGA indicate genomic heterogeneity across populations.	[114]
Shi et al.	2016	Transcriptomics/ metabolic focus	Expression of CPT1A (carnitine palmitoyltransferase 1A) in AML - prognostic impact and rationale for targeting fatty-acid oxidation (FAO) in AML therapy.	High CPT1A expression predicted adverse outcomes in AML. The study links CPT1A expression to altered lipid metabolism in AML and suggests CPT1A as a potential therapeutic target; functional data and clinical correlations support FAO pathway relevance.	[115]
Carrabba et al.	2016	Metabolomics (NMR-based metabolomics; translational multi-omics integration)	Prospective pilot clinical trial (longitudinal sampling during induction/consolidation) and patient-derived xenografts (PDX) to trace AML-associated metabolic trajectories and identify metabolites correlating with blast clearance.	NMR metabolomics identified 7 metabolites whose trajectories mirrored AML progression/remission in both patients and PDX mice (a dynamic metabolic fingerprint). Authors propose NMR metabolomics as a translational tool to monitor treatment response and identify metabolic biomarkers.	[116]
Cauchy et al.	2015	Epigenomics (Chromatin state)	Analyzed how chronic FLT3-ITD signaling in AML links to specific chromatin signatures.	FLT3-ITD mutation correlates with unique chromatin modifications influencing gene regulation in AML, highlighting epigenetic mechanisms driving leukemogenesis.	[7]

Forrest et al.	2010	Transcriptomics (miRNA profiling)	Examined induction of miRNAs (miR-155, miR-222, miR-424, miR-503) in monocytic differentiation regulation.	These miRNAs synergistically promote monocytic differentiation through combinatorial gene regulation, which is important in hematopoiesis.	[26]
Forshed et al.	2007	Proteomics	Developed workflow to discover proteomic biomarker peaks predictive of clinical outcomes in AML patients.	Identified candidate biomarkers correlated with clinical outcomes, providing tools for prognostic assessment in AML.	[117]

Emerging multi-omics approaches, including microbiome-linked analyses, single-cell and spatial profiling, and machine learning–based integration, provide high-resolution insights into AML heterogeneity, microenvironmental interactions, and therapeutic response. These methods reveal dynamic ecosystem-level changes, including immune evolution, clonal architecture, and niche-specific signaling. However, their translation into clinical practice is constrained by small cohort sizes, technical complexity, computational demands, and limited prospective validation. Continued development of standardized pipelines and clinically interpretable models will be essential to harness their full potential in precision medicine (Table 2).

Table 2 Integrative synthesis of multi-omics findings in AML with methodological context and translational relevance.

Omics Layer	Study Design & Cohort	Integrative Biological Insight	Key Findings	Translational Relevance	Key Limitations	Reference
Genomics/ Epigenomics	Large cohorts (e.g., TCGA ~200 AML; BeatAML >500 patients)	Genetic mutations reshape epigenetic and transcriptional landscapes	*DNMT3A* mutations induce hypomethylation and IFN signaling; integrated genomic classification improves risk prediction	Molecular classification, prognostic stratification, targeted therapies	Cohort heterogeneity; context-dependent effects	[8, 21]
Transcriptomics	Bulk RNA-seq cohorts (hundreds) + single-cell validation	Defines AML subtypes and functional cell states	G1-G8 transcriptional subgroups; *IKZF1* mutation rewires immune and *HOX* programs	Improved classification and therapy stratification	Limited prospective validation; reproducibility issues	[21, 24]
Splicing/RNA regulation	Retrospective datasets + functional validation	Alternative splicing drives leukemic identity and immune interaction	*RBM17* maintains leukemic stem cell survival via poison exon suppression; splicing-based prognostic models	Novel therapeutic targets; prognostic biomarkers	Mostly computational or preclinical validation	[28, 29]
Proteomics/ Proteogenomics	Moderate cohorts (~200-300 AML patients; deep profiling)	Connects genomic alterations to functional protein states and signaling networks	Proteogenomic subtypes reveal metabolic and signaling dependencies; ubiquitin-mediated chemoresistance via WWP1–JARID1B axis	Identification of druggable pathways; resistance mechanisms	High cost; limited standardization; cohort size constraints	[30, 32]
Phosphoproteomics	Smaller cohorts + *in vitro*/primary AML validation	Identifies active kinase signaling dependencies	PAK1 activation linked to poor prognosis; inhibition reduces AML growth	Precision kinase targeting and combination therapies	Primarily preclinical; limited clinical validation	[35]

Metabolomics	Small–moderate cohorts; patient samples + experimental models	Captures real-time metabolic vulnerabilities and cellular states	Serine dependency via PSAT1 suppression; CPT1A-driven FAO supports AML survival	Metabolic targeting strategies; combination therapies	Highly context-dependent; sensitive to environment and handling	[38]
Immunometabolomics	Integrated metabolomic + immune datasets	Links metabolic rewiring to immune evasion and response	Metabolic competition strategies enhance T-cell therapy efficacy	Immunotherapy optimization	Complex interpretation; limited validation	[70]
Microbiome–Metabolome	Longitudinal cohorts (e.g., 68 AML patients; repeated sampling)	Therapy-induced microbiome changes alter systemic metabolism and immunity	566 fecal + 260 serum samples linked to treatment dynamics; chemotherapy-induced dysbiosis and metabolite loss	Supportive care strategies; toxicity mitigation	Strong confounders (antibiotics, diet, treatment)	[42, 43]
Single-cell/Spatial multi-omics	Small cohorts (tens of patients) with high-resolution profiling	Resolves cellular heterogeneity and microenvironmental niches	Blast–stromal niche organization; clonal tracing and differentiation mapping	Targeting microenvironment and clonal evolution	Small sample size; high cost; technical complexity	[44, 45]
Machine Learning/Integration	Retrospective datasets + external validation	Integrates multi-omics to predict outcomes and therapy response	MDREAM predicts drug response using multi-omics integration	Personalized therapy selection; biomarker discovery	Overfitting risk; lack of prospective validation	[49]

7. Translational and Clinical Perspectives

The clinical application of multi-omic-generated findings addressing the management of AML has started to make an impact, with several studies showing obvious prognostic or therapeutic value.

7.1 Clinical Outcome Relevance

One interesting outcome with potential clinical implications is the uncommon t(8;16)(p11;p13) rearrangement/MYST3-CREBBP fusion that is exceptionally rare, aggressive, with significant disease biology and poor outcomes after standard-dosing chemotherapy [101]. Using multi-omic approaches, it is suggested that this fusion disrupts transcriptional regulation through histone acetyltransferase activity in the fusion protein and widespread epigenetic deregulation, increasing the potential for leukemogenesis. The clinical observations show that these patients tend to do better if they undergo early allogeneic hematopoietic stem cell transplantation in first complete remission, implying that early recognition via genomic screening of the rearrangement can drive treatment decisions.

Microenvironmental remodeling is another domain where multi-omics is producing clinically relevant insights. Stromal transcriptional profiling shows that bone marrow niche remodeling occurs during the earliest stages of AML development, even prior to the overt presentation of hematological abnormalities [99]. The remodeling is reflected by the altered composition of the extracellular matrix, alterations in cytokine secretion, and expression of adhesion molecules, which together create a pro-leukemic niche. The notion that microenvironment-targeted therapies may circumvent leukemogenic conditioning before the establishment of fully malignant disease is intriguing, and such associations might be leveraged to improve clinical outcomes in high-risk settings where pre-leukemic clonal hematopoiesis exists.

In pediatric AML, NUP98 rearrangements have emerged as a consistent indicator of poor prognosis. Through multi-omics, NUP98 fusions also appear to be associated with dysregulated transcriptional programs involving *HOX* gene clusters, chromatin remodeling factors, and stemness signaling pathways. It is possible that the prognostic power of this rearrangements warrants its inclusion in pediatric AML therapy risk stratification system to potentially choose more aggressive initial therapy, perhaps even early transplant, for patients with NUP98 fusions [100].

Molecular biomarkers are also advancing for prognostic evaluation in CN-AML. *BAALC* (*brain and acute leukemia cytoplasmic*) gene overexpression is associated with poor survival and, mechanistically, with erroneous activation of MYC and RAS signaling pathways [94]. High BAALC expression was proposed as a candidate criterion for intensifying induction or consolidation regimens for patients with CN-AML. Finally, immune epigenetics offers a novel perspective in addressing post-transplant relapse. Investigations of immune escape mechanisms have identified that PRC2-dependent repression of HLA class II genes impairs T-cell recognition of leukemic blasts [54]. Pharmacologic inhibition of PRC2 can revive HLA-II expression and T-cell-mediated cytotoxicity and ultimately represents a new approach to treat patients with recurrent disease following allogeneic transplantation. This mechanistic insight is particularly valuable at a time of personalized immunotherapy in which the unraveling of antigen presentation may enhance synergy with checkpoint blockade or adoptive T-cell approaches [118].

7.2 Real-World Barriers to Clinical Implementation of Multi-Omics in AML

Despite the rapid expansion of multi-omics studies and their strong emphasis on clinical translation, several practical barriers continue to limit their integration into routine AML care. These challenges extend beyond biological discovery and relate to cost, infrastructure, reproducibility, scalability, and regulatory considerations. Many of the multi-omics studies described in this review rely on resource-intensive platforms, including high-depth sequencing, mass spectrometry–based proteomics, and single-cell or spatial technologies. For example, large-scale proteogenomic profiling studies involving hundreds of AML patients require complex sample preparation, advanced instrumentation, and substantial computational resources [30]. Similarly, single-cell and spatial multi-omics approaches, while highly informative, involve high per-sample costs and specialized workflows that limit scalability across clinical centers [44, 45]. These financial and technical constraints currently restrict widespread clinical implementation.

Multi-omics approaches require integrated laboratory and computational infrastructure, including sequencing platforms, high-resolution mass spectrometers, and bioinformatics pipelines capable of handling large, high-dimensional datasets. While consortia-based efforts and specialized research centers can support such infrastructure, many clinical institutions lack the resources or expertise to do so. For instance, integrative frameworks such as proteogenomic profiling [30], microbiome–metabolome datasets [42], and machine-learning–based models like MDREAM [49] depend on coordinated multi-platform data generation and advanced computational integration, which are not yet standardized in routine clinical environments.

A major limitation highlighted across the cited studies is the lack of standardized protocols for sample collection, processing, sequencing depth, and data analysis. Variability across platforms, particularly in proteomics, metabolomics, and single-cell analyses, can lead to inconsistent results between studies. For example, proteomic studies in AML have identified important signaling and metabolic subtypes, but differences in mass spectrometry workflows and analytical pipelines limit cross-study reproducibility [30, 68]. Similarly, transcriptomic and splicing-based classification systems show discrepancies across cohorts, reflecting differences in dataset composition and analytical methods [21, 28].

Many multi-omics findings are derived from retrospective datasets, experimental models, or relatively small patient cohorts, with limited prospective validation. While large datasets such as TCGA and BeatAML provide foundational insights, numerous studies cited in this review rely on functional assays in cell lines, xenograft models, or computational validation approaches rather than clinical trials. For example, kinase dependencies identified through phosphoproteomics [35], metabolic vulnerabilities such as serine auxotrophy [38, 119, 120], and splicing factor dependencies like *RBM17* [29] have strong mechanistic support but remain largely preclinical. Similarly, machine learning models such as MDREAM have demonstrated predictive performance using retrospective and *ex vivo* validation but have not yet been widely validated in prospective clinical settings [49].

Translating multi-omics into routine AML care requires rapid turnaround times and clinically interpretable outputs. However, current multi-omics workflows often involve prolonged data processing and complex interpretation, which may not align with the urgent treatment timelines in AML. Furthermore, scaling multi-layer data integration for large patient populations remains challenging due to computational demands and a lack of standardized reporting frameworks. Even

large-scale databases such as AMLdb primarily function as research tools rather than clinical decision-support systems [53].

Clinical implementation of multi-omics approaches requires compliance with regulatory standards for diagnostic accuracy, reproducibility, and clinical utility. However, regulatory frameworks for multi-parameter, high-dimensional omics assays remain underdeveloped. Challenges include validating composite biomarkers, interpreting complex datasets, and ensuring reproducibility across laboratories. In addition, ethical considerations such as data privacy, management of incidental findings, and equitable access to advanced diagnostics must be addressed before widespread adoption [47, 120].

Addressing these barriers will require coordinated efforts to standardize experimental and computational pipelines, reduce costs through technological innovation, and design large-scale prospective validation studies. Integration of multi-omics data into user-friendly clinical decision-support systems, combined with regulatory harmonization, will be essential to translate these advances into precision medicine for AML [48, 56].

8. Future Directions and Challenges

Research on AML using multi-omics comes with its own challenges. For example, there are no standardized pipelines for integrating multi-omics data because varied methods of data collection and analysis lead to inconsistent results, limiting the ability of multiple studies to reproducibly validate findings. The standardization of data collection and analysis using universally accepted computational frameworks that incorporate multi-omics is necessary in order to demonstrate robust and clinically applicable findings that must be validated across institutions [5].

A major challenge is validating candidate biomarkers identified in multi-omics studies across large, diverse, and prospectively followed patient cohorts. The methodological context summarized throughout this review shows that AML multi-omics evidence spans very different levels of validation: large discovery cohorts such as TCGA and BeatAML provide broad genomic, transcriptomic, and functional reference datasets; deeply profiled proteogenomic cohorts provide mechanistic resolution but are technically complex; single-cell and spatial studies offer high-resolution insights but are often based on smaller patient numbers; and machine-learning models frequently rely on retrospective public datasets and require external or prospective validation. Therefore, future AML multi-omics studies should routinely report cohort size, sample source, disease stage, treatment context, assay platform, validation cohort, and whether findings were supported by functional perturbation, orthogonal assay validation, independent dataset replication, or prospective clinical testing [45].

Similar to the multi-omics research model, integrating multi-omics into clinical workflows poses significant challenges related to timelines, costs, and computational infrastructure. The recent technological developments in rapid sequencing, cloud analytics, and automated interpretation of data may ultimately help bring multi-omics data into the point-of-care decision-making process [108].

From a methodological perspective, longitudinal and single-cell multi-omics will be increasingly useful in revealing the temporal nuance of clonal evolution and therapeutic responses, and machine learning will improve prognostic models toward personalized treatment paradigms. However, ethical and logistical considerations, including but not limited to patient consent, data privacy, and

equitable access to diagnostics, and therapies first require a collective global effort to achieve and to use open data to ensure that every patient benefits fairly from advances in precision AML medicine [45, 121].

9. Conclusion

The multi-omics paradigm has revolutionized our understanding of AML in so many ways by demonstrating the interconnectedness of genetic mutations, epigenetic remodeling, transcriptomic regulation, proteomic changes, metabolic functions, immune evasion, and the microenvironment. The integrative nature of multi-omics will allow us to redefine AML classification schemes, enhance prognostic models, and identify additional therapeutic targets not apparent in single-omic approaches. The integration of multimodal spatial and single-cell technologies will enable us to examine how populations of distinct leukemic clones and populations of stroma interact within a specialized niche of bone marrow. Simultaneously, ongoing computational advances in integrating multi-source data and models, especially with machine learning as a component, are creating the possibility of making clinically relevant predictions from these complex systems, outpacing the evidence this complexity provides. The challenge is not to improve our generation of the astonishingly rich facility of multi-omics but to translate its unique explanatory power into specific and precise therapeutic strategies that may enhance survival and ultimately quality of life for those suffering from AML. This will entail not only ongoing technological innovation but also collaboration to standardize methods, validate biomarkers, and implement clinical workflows that are cost-effective.

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Author Contributions

Manal Hadi Ghaffoori Kanaan: conceptualization, supervision, writing – original draft, writing – review & editing; Ahmad M. Tarek: conceptualization, investigation, writing – review & editing; Beom-Jin Lee: writing – original draft, investigation, writing – review & editing; Sura Saad Abdullah: writing – original draft, investigation; Chulhun Park: writing – review & editing; Abdolmajid Ghasemian: writing – review & editing; Steward Mudenda: writing – review & editing. All the authors critically revised and approved the final version of the manuscript.

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