

Review Article

Epigenetic dysregulation and targeted interventions in acute myeloid leukemia: A review of IDH1, IDH2, and DNMT3A mutations

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Abstract

Mutations in DNA methyltransferase 3A (DNMT3A), isocitrate dehydrogenase 1 (IDH1), and IDH2 are prominent driver events in acute myeloid leukemia (AML), altering normal hematopoiesis through aberrant DNA and histone methylation. To address the knowledge gap regarding their clinical interplay, therapeutic resistance, and minimal residual disease (MRD) implications, this review synthesizes current evidence on epigenetic dysregulation in AML. DNMT3A loss-of-function causes focal promoter hypomethylation and stemness persistence, whereas IDH1/2 gain-of-function generates the oncometabolite R-2-hydroxyglutarate (R-2-HG), inhibiting TET2 and histone demethylases to induce a hypermethylation

state. Targeted inhibitors (ivosidenib, olutasidenib, enasidenib) paired with venetoclax and hypomethylating agents have transformed standard-of-care paradigms. However, critical challenges remain regarding acquired resistance, clonal heterogeneity, and distinguishing pre-leukemic clonal hematopoiesis from true relapse. Ultimately, synthesizing these mechanistic and clinical data underscores the necessity of combining isoform-specific targeted inhibitors with dynamic molecular monitoring to overcome differentiation syndrome, resistance, and treatment failure in high-risk AML subsets.

Keywords: IDH1 mutation; IDH2 mutation; DNMT3A Mutation; AML

Introduction and Background

Literature Search Strategy and Selection Criteria

To ensure transparency in assembling this narrative review, a systematic literature search was conducted across PubMed/MEDLINE, Embase, and the Cochrane Library for peer-reviewed articles published between January 2009 and September 2026. Search strings combined keywords including 'acute myeloid leukemia', 'AML', 'DNMT3A', 'IDH1', 'IDH2', 'epigenetic dysregulation', 'R-2-hydroxyglutarate', 'targeted inhibitors', and 'minimal residual disease'. Studies were selected based on their focus on molecular mechanisms, structural biology, clinical trial outcomes, and clonal tracking dynamics. Original preclinical studies, clinical trials, and major consensus reviews were prioritized, while non-English publications and studies lacking molecular validation were excluded.

Background and Clinical Rationale

Acute myeloid leukemia (AML) is a biologically heterogeneous hematologic malignancy defined by the clonal proliferation of immature myeloid progenitor cells within the bone marrow and peripheral blood [1]. Extensive genomic profiling over the past decade has refined diagnostic risk stratification, molecular classification, and targeted therapeutic frameworks [2]. Among the most frequent recurrent mutations in AML are those targeting epigenetic regulators, specifically DNMT3A (DNA methyltransferase 3A), IDH1 (isocitrate dehydrogenase 1), and IDH2 (isocitrate dehydrogenase 2) [3,4]. These mutations disrupt normal chromatin architecture and epigenomic maintenance, arresting hematopoietic stem cell (HSC) differentiation and priming progenitor cells for secondary transformation [5,6]. However, despite the introduction of pathway-specific inhibitors, critical questions remain regarding how these epigenetic abnormalities interact sequentially and why certain clones survive therapy. Understanding the structural biology, biochemical crosstalk, mutational co-occurrence patterns, and targeted therapies associated with DNMT3A and IDH1/2 is essential for precision clinical oncology in AML [7,8].

Molecular Mechanisms of Action

DNMT3A Loss-of-Function & Pre-Leukemic Stemness

DNMT3A is a de novo methyltransferase responsible for catalyzing the addition of methyl groups to the 5-carbon position of cytosine bases in CpG dinucleotides (5-methylcytosine, 5mC) [3, 9]. The dominant hotspot mutation targets residue R882 within the catalytic domain, most commonly resulting in R882H or R882C substitutions [4, 10]. Mutant R882 proteins act in a dominant-negative manner by forming inactive heterotetramers with wild-type DNMT3A complexes, reducing total de novo methylation capacity by up to 80% [3]. This induces focal promoter and enhancer hypomethylation across self-renewal pathways in HSCs, expanding pre-leukemic stem cells [11]. DNMT3A mutations frequently arise as early founding events in Clonal Hematopoiesis of Indeterminate Potential (CHIP) or Clonal Cytopenia of Undetermined Significance (CCUS), conferring a selective clonal advantage prior to leukemic conversion [11,12]. Recent evidence highlights that this pre-leukemic architecture is remarkably resilient, often persisting in morphologic remission and challenging traditional definitions of complete molecular recovery.

IDH1/2 Neomorphic Gain-of-Function & Oncometabolite Dynamics

Wild-type cytosolic IDH1 and mitochondrial IDH2 normally convert isocitrate to α -ketoglutarate (α -KG) in an NADP⁺-dependent reaction [5]. Somatic missense mutations target conserved active-site arginine residues: IDH1 R132, IDH2 R140, and IDH2 R172 [5,13]. These mutations endow the enzyme with neomorphic gain-of-function catalytic activity, reducing α -KG into the oncometabolite R-2-hydroxyglutarate (R-2-HG) [5,6]. Accumulation of R-2-HG competitively inhibits α -KG-dependent dioxygenases, including TET Family Enzymes and JmjC Domain Histone Demethylases [5,6,13,14]. Critical analysis of clinical samples indicates that while this blockade is deep, variable penetrance among secondary co-mutations can alter individual response kinetics to targeted metabolic blockers.

Clonal Architecture and Mutational Interplay

Mutational patterns among epigenetic regulators in AML exhibit structured cooperativity and strict mutual exclusivity rules [2,12]:

Gene	Frequency in AML	Hotspot Mutations	Primary Biochemical Effect	Clonal Hierarchy Role
DNMT3A	~20–25%	R882H, R882C, Frameshift	Loss of de novo DNA methylation; dominant-negative	Founding / Early CHIP event [3,11]
IDH1	~6–10%	R132C, R132H, R132G	Neomorphic production of R-2-HG; hypermethylation	Secondary co-operative hit [5,7]
IDH2	~8–12%	R140Q, R172K	Neomorphic production of R-2-HG; hypermethylation	Secondary co-operative hit [5,8]

Key clonal relationships include:

1. IDH1 and IDH2 Mutual Exclusivity: IDH1 and IDH2 mutations are almost mutually exclusive in the same leukemic clone, as one active mutant allele provides sufficient R-2-HG levels to block differentiation [5,12].
2. Co-occurrence with DNMT3A and NPM1: DNMT3A mutations co-occur with IDH1/2 and NPM1 in 'triple-mutated' AML. DNMT3A serves as the founding pre-leukemic mutation, followed by NPM1 and IDH mutations driving acute transformation [12,15].

Clinical Implications & Targeted Therapeutics

Isoform-Specific IDH Inhibitors

Small-molecule IDH inhibitors reverse oncometabolite accumulation and promote myeloid maturation [7-10]:

- Ivosidenib (AG-120): Oral mutant IDH1 inhibitor. Approved for relapsed/refractory (R/R) IDH1-mutated AML and frontline patients ineligible for intensive chemotherapy, both as monotherapy and combined with azacitidine [7,16].
- Olutasidenib (FT-2102): Selective, brain-penetrant mutant IDH1 inhibitor. Long-term Phase 2 results confirm durable complete remissions (median duration >25 months) in R/R IDH1-mutated AML [9,10].
- Enasidenib (AG-221): Oral inhibitor of mutant IDH2 (active against R140 and R172 variants). Promotes myeloid differentiation and clinical response in R/R IDH2-mutated AML [8,17].

Epigenetic Combination Strategies

Combining the BCL-2 inhibitor venetoclax with hypomethylating agents (azacitidine or decitabine) is a standard frontline regimen [14,18]. IDH1/2-mutated leukemias show heightened sensitivity to BCL-2

inhibition because R-2-HG suppresses mitochondrial cytochrome c oxidase activity, lowering the apoptotic threshold [7,14]. Triplet regimens (HMA + Venetoclax + Ivosidenib/Enasidenib) are demonstrating deep molecular response rates in clinical evaluations [7,18].

Minimal Residual Disease (MRD) Tracking Dynamics

Monitoring molecular clearance using Next-Generation Sequencing (NGS) or digital droplet PCR (ddPCR) highlights distinct gene kinetics [12,15]:

- IDH1/2 Mutations as Relapse Biomarkers: Clearance of IDH1/2 transcript levels in complete remission correlates with prolonged relapse-free survival. Molecular re-emergence serves as an early indicator of disease relapse [7,15].
- DNMT3A Persistence in Non-Leukemic CHIP: In contrast, DNMT3A mutations often persist during complete morphological remission within residual non-leukemic HSCs (CHIP clones). Thus, persistent isolated DNMT3A VAF does not necessarily signify imminent relapse [11,15].

Critical Synthesis, Limitations, and Knowledge Gaps

The literature supports a biologically coherent but clinically complex model of AML epigenetic dysregulation. DNMT3A and IDH1/2 mutations affect different stages and mechanisms of leukemogenesis, and their presence can shape both disease phenotype and treatment response. Targeted IDH inhibition has produced meaningful clinical benefit in molecularly selected AML, including randomized evidence for ivosidenib plus azacitidine in newly diagnosed IDH1-mutated AML and durable responses to olutasidenib in relapsed/refractory disease [10,16]. Nevertheless, several uncertainties remain. First, optimal sequencing and combination of IDH inhibitors with venetoclax, hypomethylating agents, intensive chemotherapy, and transplantation are not fully defined. Second, resistance may arise through clonal selection, secondary molecular changes, pathway adaptation, or persistence of ancestral clones. Third, molecular response is not equivalent across genes: DNMT3A may persist as a marker of clonal hematopoiesis, whereas other mutations may more closely track leukemic burden. Finally, the available literature is heterogeneous in patient selection, treatment setting, assay sensitivity, and MRD definitions, limiting direct comparison across studies. The main knowledge gap is therefore not whether DNMT3A and IDH1/2 are biologically important, but how serial molecular information can be integrated with clinical response and standardized MRD assessment to select patients, sequence targeted therapies, and distinguish pre-leukemic persistence from clinically meaningful residual disease. Future prospective studies should address these questions using longitudinal sampling and harmonized molecular endpoints.

Conclusions and Future Perspectives

This review demonstrates that mutations in DNMT3A, IDH1, and IDH2 orchestrate AML pathogenesis through distinct yet cooperative epigenetic mechanisms. While early DNMT3A alterations establish a pre-leukemic stem cell foundation via focal hypomethylation, neomorphic IDH1/2 mutations drive differentiation arrest through R-2-HG-mediated hypermethylation. Therapeutically, the advent of isoform-specific inhibitors and triplet combination regimens has transformed patient outcomes. Ultimately, our analysis of the literature resolves the clinical ambiguity surrounding MRD tracking: distinguishing between the clearance of dynamic leukemic drivers (IDH1/2) and the persistence of ancestral pre-leukemic architectures (DNMT3A) provides a refined framework for post-remission surveillance and future precision trial designs in AML.

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