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Molecular Mechanism of LSD1 Inhibition-mediated Selective Chromatin Opening: Specific Regulation of Tumor Differentiation-related Loci and Clinical Implications

Zhihan Yang*

Northeastern Agriculture University, Harbin, China

**Corresponding author: Zhihan Yang.*

Abstract

Acute Myeloid Leukemia (AML) is characterized by a differentiation block of hematopoietic cells, with Lysine-Specific Demethylase 1 (LSD1) emerging as a key epigenetic regulator that silences myeloid differentiation genes to maintain leukemic stem cell stemness. This review elucidates the molecular mechanisms of LSD1 inhibition-mediated selective chromatin opening in AML therapy, including LSD1's structural basis and its assembly in CoREST and NuRD repressive complexes. LSD1 inhibitors act by disrupting the LSD1-GFI1 interaction via steric hindrance, triggering NuRD-to-SWI/SNF chromatin remodeling switch, and reactivating PU.1/C/EBPα-dependent myeloid enhancers. Beyond histone demethylation, LSD1 modulates non-histone substrates (p53, DNMT1, E2F1, STAT3) to regulate cell apoptosis, DNA methylation, and the cell cycle. We further discuss translational advances, such as PROTAC degraders and combination regimens, as well as clinical challenges, including hematologic toxicities and drug resistance. This review highlights LSD1 as a promising epigenetic target and mechanistically informed combination therapies as the future direction for unlocking the AML differentiation block and improving clinical outcomes.

Keywords

LSD1, acute myeloid leukemia (AML), chromatin remodeling, differentiation therapy, epigenetic regulation

1. Introduction

Acute Myeloid Leukemia (AML) is a highly heterogeneous malignant clonal disorder characterized by a fundamental defect in the hematopoietic hierarchy. Its primary pathological hallmark is a differentiation block at the stage of hematopoietic stem or progenitor cells, leading to the massive accumulation of immature myeloid blasts in the bone marrow and peripheral circulation [1]. This arrest is not merely a morphological anomaly but the manifestation of a profoundly dysregulated gene expression program. While genetic driver mutations—such as those involving *IDH1/2*, *NPM1*, or *FLT3*—propel aberrant proliferation and initial arrest [2], it is often the epigenetic landscape that reinforces and stabilizes this undifferentiated, stem-like state.

Among the myriad of epigenetic regulators, Lysine-Specific Demethylase 1 (LSD1, also known as KDM1A) has emerged as a central arbiter of cell fate. Discovered in 2004 as the first histone demethylase identified, LSD1 is a flavin adenine dinucleotide (FAD)-dependent amine oxidase. It specifically catalyzes the removal of mono- and di-methyl groups from lysine 4 of histone H3 (H3K4me1/2) [3]. In the context of AML, these marks are typically associated with active enhancers and promoters; thus, LSD1-mediated demethylation acts as a molecular "off-switch" for transcriptional activity. Clinical data have consistently linked high LSD1 expression with poor prognosis, as the enzyme silences critical myeloid differentiation genes—such as *ITGAM* (CD11b) and *CD86* [4]—thereby preserving the self-renewal capacity and "stemness" of Leukemia Stem Cells (LSCs).

Differentiation therapy represents a paradigm shift in oncology, aiming to drive malignant cells toward a mature phenotype, leading them to lose proliferative potential and eventually undergo apoptosis. This strategy achieved landmark success in Acute Promyelocytic Leukemia (APL) through the synergistic use of All-Trans Retinoic Acid (ATRA) and arsenic trioxide [5]. However, replicating this therapeutic success in non-APL subtypes of AML has remained a significant clinical hurdle. Recently, a deeper mechanical understanding of LSD1 has revealed that its pharmacological inhibition can uniquely "unlock" the differentiation block across various AML genomic subtypes. Consequently, LSD1 inhibitors have transitioned from laboratory tools to high-priority candidates in the landscape of epigenetic therapeutics.

This review will comprehensively elucidate the mechanisms underlying LSD1-mediated chromatin-selective opening across multiple dimensions, including higher-order chromatin structures, polyprotein complex assembly, and non-histone substrate modifications, while exploring its translational potential and challenges for clinical applications.

2. Theoretical Background

To understand how LSD1 specifically regulates chromatin accessibility, one must examine its intricate molecular structure and its assembly into multiprotein complexes. LSD1 functions not as an isolated enzyme but as a multidomain scaffold that integrates diverse epigenetic activities. Comprising 852 amino acids, the crystal structure of LSD1 reveals three critical functional domains.

2.1 Structure and Function of the Three Critical Domains in LSD1

The SWIRM domain is a small α-helical domain highly conserved in chromatin remodeling proteins. Although many SWIRM domains possess DNA-binding capability, the SWIRM domain of LSD1 does not directly bind to DNA. Instead, it serves as a structural anchor, stabilizing the protein conformation by forming a tight hydrophobic interface with the amine oxidase (AOL) domain. This close packing is crucial for maintaining the overall folding of LSD1. Additionally, the SWIRM domain participates in protein-protein interactions, such as being recognized as one of the interfaces for LSD1's interaction with the androgen receptor (AR), which may alter LSD1's substrate specificity, shifting its modification site from H3K4 to H3K9 [6]. Nuclear magnetic resonance (NMR) studies have demonstrated that the isolated LSD1 SWIRM domain exhibits a certain binding affinity for the H3 peptide (disassociation constant Kd ≈ 2.3 × 10^-4 M), suggesting its potential auxiliary role in the initial stages of substrate recognition.

The AOL domain serves as the catalytic core of LSD1 and exhibits sequence homology with monoamine oxidases (MAO-A and MAO-B). This domain contains a FAD cofactor binding site and a deeply recessed substrate-binding cavity [7]. The geometry and electrostatic properties of this cavity determine LSD1's substrate specificity: it accommodates the N-terminal tail of histone H3 and positions the H3K4 methyl group precisely near the FAD cofactor's active site. The catalytic reaction is an FAD-dependent oxidation process that consumes oxygen and generates formaldehyde and hydrogen peroxide. LSD1 can catalyze the demethylation of monomethyl (me1) and dimethyl (me2) lysine but cannot act on trimethylated (me3) lysine because it lacks the lone-pair electrons required to form the imine intermediate [8].

The Tower domain is the most distinctive structural feature of LSD1, extending from the AOL domain to form a "tower-like" antiparallel coiled-helix structure approximately 90 Å in length. This domain is absent in the homologous protein LSD2, conferring LSD1 with its unique function. The primary role of the Tower domain is to serve as a docking site for the co-inhibitor CoREST (RCOR1) [9]. The binding of CoREST is

critical for LSD1's function at the nucleosome level. Without CoREST, LSD1 can only modify free histone peptides but cannot effectively modify histones within nucleosomes [10]. The tower domain achieves spatial coordination between enzymatic activity and chromatin localization by physically isolating the catalytic center from the DNA-binding module.

2.2 The LSD1-CoREST Complex and Its Transcriptional Repression Mechanism

LSD1 primarily exists as a heterodimer with CoREST, which acts as a functional amplifier. CoREST's SANT2 domain binds nucleosomal DNA, while the LSD1 AOL domain engages the histone H3 tail [10]. This "bivalent binding" increases the complex's residency time and catalytic efficiency on nucleosomes. The LSD1-CoREST complex can also recruit histone deacetylases (HDAC1/2). This synergistic interaction forms a potent transcriptional repression mechanism: HDACs first remove acetylation modifications on histone H3K27 and H3K9 (which mark active enhancers), followed by LSD1 removing methylation on H3K4 [11]. Deacetylation is often a prerequisite for demethylation, as the presence of acetyl groups may interfere with LSD1's recognition of the H3 tail through steric hindrance or charge repulsion. Consequently, the LSD1-CoREST-HDAC complex, through its dual enzymatic activities, completely erases active chromatin markers and establishes a stable heterochromatin state.

2.3 LSD1 in the NuRD Complex and Its Functional Role in AML

While the LSD1-CoREST complex represents a major and well-characterized mechanism by which LSD1 mediates transcriptional repression, LSD1 also exerts its epigenetic regulatory functions through association with other large chromatin-modifying complexes. Notably, unlike the LSD1-CoREST complex, which acts primarily through coordinated histone demethylation and deacetylation to compact chromatin, LSD1 integrates into additional multi-subunit assemblies that couple demethylase activity with nucleosome remodeling. Among these, the nucleosome remodeling and deacetylation (NuRD) complex stands out as another critical functional partner.

The NuRD complex comprises ATP-dependent helicases CHD3/4, MTA proteins (MTA1/2/3), and HDAC1/2. LSD1 interacts with NuRD complex components (such as MTA proteins) through its N-terminal region, enabling it to combine its histone demethylation activity with NuRD's chromatin remodeling activity. CHD4 utilizes the energy from ATP hydrolysis to slide nucleosomes, altering their positioning to cover transcription factor binding sites, thereby physically blocking the entry of the transcription machinery [12]. The presence of LSD1 ensures that while physical compaction occurs, chromatin chemical modifications remain suppressed. In AML, the LSD1-NuRD complex is enriched in the enhancer regions of myeloid differentiation genes, thereby maintaining their repression [12].

3. Literature Review

The therapeutic effects of LSD1 inhibitors do not stem from non-specific chromatin opening across the entire genome, but rather through a highly selective mechanism that specifically reactivates suppressed myeloid differentiation enhancers. This process involves complex transcription factor displacement, changes in nucleosome localization, and a cascade of histone modifications.

3.1 Selective Reactivation of Myeloid Enhancers by LSD1 Inhibition

The most significant molecular event following LSD1 inhibition was an increase in chromatin accessibility in specific enhancer regions. Joint analysis of ATAC-seq and ChIP-seq revealed that these newly opened regions were not randomly distributed but were highly enriched with myeloid-specific transcription factor PU.1 (SPI1) and C/EBPα binding motifs [13]. In leukemia cells, these critical myeloid enhancers were poised but repressed. Pioneer factor PU.1, although capable of binding to these sites, was unable to recruit activating coactivators (such as p300) because the LSD1-CoREST-GFI1 complex also bound to the same or adjacent regions [14]. The presence of the LSD1 complex maintained a locally repressive chromatin environment by demethylating H3K4me1/2 and deacetylating H3K27, thereby preventing the assembly of the transcription machinery. When cells were treated with LSD1 inhibitors, the interaction between LSD1 and GFI1 was disrupted. This break in physical linkage led to the detachment of the repressive complex from the chromatin. Studies demonstrated that chromatin opening induced by LSD1

inhibitors was highly dependent on PU.1. In AML models with PU.1 knockout or low expression, these specific enhancer regions failed to open, and the differentiation program could not be initiated, even with LSD1 inhibitors. This demonstrates that the essential function of LSD1 inhibitors is to relieve PU.1 inhibition, i.e., to "recommission" enhancers that pioneer factors have marked. Similar to PU.1, C/EBPα is also a key cofactor in this process. In cells lacking C/EBPα, the differentiation effects induced by LSD1 inhibitors are significantly attenuated. After LSD1 inhibition, C/EBPα binding signals on enhancers tend to be more stable, forming a synergistic activation complex with PU.1 to drive the expression of downstream target genes (e.g., IRF8, KLF4, MEF2C).

3.2 GFI1-Mediated Specificity in LSD1 Target Gene Regulation

A primary challenge in understanding LSD1 function is its specificity: How does LSD1 precisely recognize and inhibit myeloid differentiation genes rather than other housekeeping genes? The answer lies in the transcription factors GFI1 (Growth Factor Independence 1) and GFI1B. Both GFI1 and GFI1B contain a conserved SNAG domain at their N-terminus. Structural biology studies have shown that the amino acid sequence and conformation of the SNAG domain are highly similar to those of the N-terminal tail of histone H3. GFI1 mimics the binding of the histone H3 tail by inserting its SNAG domain into the substrate-binding cavity of LSD1. This binding is not for demethylation (the SNAG domain typically lacks methylated lysines) but serves as a high-affinity molecular hook to recruit the LSD1-CoREST complex to the DNA sites bound by GFI1 [15]. Since GFI1 is a zinc-finger transcription factor that specifically recognizes the promoter and enhancer sequences of myeloid differentiation genes, it can accurately direct the epigenetic silencing machinery to differentiation-related sites.

Most clinical-stage LSD1 inhibitors (such as trans-phenylcyclopropylamine TCP and its derivatives) exert their effects by forming covalent adducts with the FAD cofactor at the LSD1 active site. These bulky drug molecules occupy the substrate-binding pocket, not only blocking the entry of histone H3 tails (thereby inhibiting enzymatic activity), but also, more importantly, physically repelling the SNAG domain of GFI1 through steric hindrance. This repulsion leads to the physical separation of LSD1 from GFI1 [16]. Once the suppression by the LSD1-CoREST complex is relieved, GFI1 bound to DNA loses its inhibitory function, and the enhancer subsequently transitions from an inhibited to an activated state. This mechanism explains why LSD1 inhibitors can rapidly induce the deactivation of GFI1 target genes. In leukemia states, LSD1 assists in recruiting the NuRD complex (containing CHD4). CHD4 uses ATP energy to slide nucleosomes toward the core region of enhancers, thereby compacting chromatin. Following treatment with LSD1 inhibitors, as LSD1 dissociates from GFI1, the NuRD complex also dissociates from these sites, releasing physical compaction. The departure of NuRD creates a spatial window for the binding of the SWI/SNF (BAF) complex [16]. The SWI/SNF complex is an ATP-dependent chromatin remodeling factor with the opposite function of NuRD, capable of exposing DNA sequences through nucleosome ejection or sliding. With the replacement of NuRD by SWI/SNF, nucleosome density decreases in enhancer regions, exposing DNA and allowing the assembly of RNA polymerase II and transcription coactivators (such as the Mediator complex), thereby initiating transcription. This "NuRD-to-SWI/SNF" transition is a critical physical step in chromatin opening.

In addition to direct physical displacement, LSD1 inhibition also alters the abundance of components of the repressive complex. Studies have found that GSE1 (Genetic Suppressor Element 1, a subunit of the CoREST complex) is significantly downregulated after LSD1 inhibition. This downregulation does not result from reduced gene transcription but rather occurs at the post-translational or protein stability levels. LSD1 appears to stabilize GSE1. GSE1 is rich in proline and plays a crucial role in stabilizing the binding of the CoREST complex to specific promoters (particularly those involved in immune responses and cytokine signaling). The decline in GSE1 protein levels further weakens the repressive complex's ability to bind to chromatin, accelerating the derepression of myeloid differentiation genes [17].

3.3 Non-Histone Substrates and Multi-Pathway Effects of LSD1

The substrate spectrum of LSD1 extends far beyond histones. Its demethylation of non-histone substrates constitutes another complex network regulating tumor cell survival, proliferation, and apoptosis. In AML, these non-classical interactions synergize with histone modifications to maintain the malignant phenotype. LSD1 serves as a critical negative regulator of the tumor suppressor p53, targeting lysine 370 (K370) in its

C-terminal domain. Under normal conditions, dimethylation of p53K370 (p53K370me2) promotes p53 binding to the co-activator 53BP1, thereby enhancing p53's transcriptional activity and upregulating pro-apoptotic genes such as PUMA and NOXA [17]. LSD1 specifically removes the p53K370me2 modification, leading to the dissociation of p53 from 53BP1 and inhibiting its transcriptional activity. In AML cells, LSD1 inhibition restores p53K370me2 levels and reactivates the p53 pathway. This explains why LSD1 inhibitors not only induce differentiation but also directly induce apoptosis in certain cells.

LSD1 exhibits a close interdependence with DNA methyltransferase 1 (DNMT1). LSD1's demethylation of DNMT1 enhances its protein stability, preventing proteasomal degradation [17]. In AML, high LSD1 levels maintain elevated DNMT1 levels, thereby sustaining the high methylation status of tumor suppressor gene promoters across the genome. LSD1 inhibition leads to the instability and degradation of DNMT1, thereby inducing passive DNA demethylation. This crosstalk mechanism, “histone demethylase inhibition leading to DNA demethylase degradation,” provides a solid molecular basis for combining LSD1 inhibitors with demethylating agents (e.g., azacitidine, decitabine).

E2F1 is a key transcription factor regulating the G1/S transition in the cell cycle. It acts on lysine 185 of E2F1. Methylation at this site leads to the ubiquitination and degradation of E2F1. LSD1 removes this methylation modification, stabilizes the E2F1 protein, and promotes cell entry into the S phase for DNA replication. LSD1 inhibition destabilizes E2F1, leading to reduced protein levels and G1 cell cycle arrest. This is consistent with the requirement for cell cycle exit for differentiation induction, as terminally differentiated cells typically cease further division.

LSD1 has also been reported to demethylate lysine 140 of STAT3, inhibiting its phosphorylation and dimerization. LSD1 inhibition may lead to aberrant activation of the STAT3 pathway [17]. Although STAT3 promotes tumorigenesis in certain contexts, in the differentiation context induced by LSD1 inhibition, STAT3 activation may participate in the interferon response and the secretion of inflammatory cytokines, helping reshape the immune microenvironment but also potentially serving as a mechanism of drug resistance.

3.4 Synergy between LSD1 and Signaling Pathways in Leukemia Differentiation

The most profound insights arise from the recent discovery of synergy between LSD1 and signaling pathways like WNT/GSK3 [4]. This synergy suggests that differentiation is not merely a localized chromatin event but requires a systemic “rewiring” of the cell's transcriptional programs. By combining LSD1 inhibition (which provides chromatin accessibility) with GSK3 inhibition (which provides the activating signals, such as β-catenin), the cell is forced to adopt an immune-responsive, mature phenotype through co-occupancy of IRF7 and β-catenin at key loci.

3.5 Therapeutic Potential and Clinical Challenges of Targeting LSD1 in AML

From a translational perspective, the transition toward PROTAC degraders highlights the realization that LSD1’s structural scaffolding role is as significant as its enzymatic activity in maintaining the malignant state. While catalytic inhibitors can induce differentiation, the complete removal of the protein through degradation appears to offer a more durable and robust therapeutic response, particularly in subtypes like MLL-r AML, where LSD1 serves as an essential architectural component of the Menin-MLL complex.

The challenges of clinical application, specifically dose-dependent thrombocytopenia and intrinsic resistance mediated by pathways like mTOR, suggest that the future of LSD1 therapy lies in precision combination regimens. The integration of LSD1 inhibitors with Menin inhibitors, GSK3 inhibitors, or hypomethylating agents represents a mechanistically informed strategy to overcome the multi-layered epigenetic defenses of the leukemia stem cell. Ultimately, the selective opening of the chromatin landscape through LSD1 targeting provides a unique and powerful lever to unlock the differentiation block, offering hope for a curative outcome in non-APL AML that parallels the success of the APL paradigm.

4. Discussion and Synthesis

The therapeutic potential of LSD1 inhibition in Acute Myeloid Leukemia rests upon a multifaceted mechanism of “chromatin selective opening” that operates across several regulatory dimensions.

Synthesizing the available evidence reveals that the primary mechanism is not a global epigenetic shift, but a surgical reactivation of specific myeloid enhancers that the leukemic process has decommissioned.

The first dimension of this process involves higher-order chromatin structures and physical protein-protein displacement. The core of the LSD1-mediated differentiation block is the structural “lock” formed between the SNAG domain of GFI1 and the substrate-binding cavity of LSD1. This interaction is essentially a form of molecular mimicry in which the transcription factor mimics an H3 histone tail to hijack the repressive machinery of the CoREST and NuRD complexes [16]. Pharmacological inhibition, particularly through covalent FAD adducts, acts as a physical wedge that forces the displacement of the entire co-repressor complex. This displacement is the prerequisite for the second dimension: the transition in chromatin remodeling activity. The eviction of LSD1 and its associated NuRD components allows for the immediate recruitment of the SWI/SNF complex. This “NuRD-to-SWI/SNF” transition is the physical event that reduces nucleosome density, transforming a “closed” heterochromatic state into an “open” euchromatic state.

The second dimension is defined by the “recommissioning” of pioneer factors. The newly accessible DNA provides a window for PU.1 and C/EBPα to bind and recruit coactivators such as p300 [13]. This process demonstrates that LSD1 does not create new enhancers but rather restores the function of pre-existing enhancers that were poised but silenced. This is further amplified by the third dimension: the regulation of non-histone substrates and protein stability. The degradation of DNMT1 and GSE1, along with the stabilization of p53 and E2F1, creates a cellular environment that is chemically and physically primed for maturation and cell cycle exit.

Collectively, these findings highlight the critical roles of LSD1 in both epigenetic regulation and crosstalk with signaling pathways such as WNT/GSK3 during leukemic differentiation. Targeting LSD1, especially via PROTAC-mediated degradation rather than just catalytic inhibition, shows superior therapeutic potential by disrupting both its enzymatic and scaffolding functions. Despite challenges including toxicity and resistance, rational combination regimens hold great promise for overcoming differentiation blocks in AML, supporting LSD1 as a valuable therapeutic target.

To further improve the clinical efficacy of LSD1-targeted therapy, several rational combinatorial and innovative strategies have emerged. From a therapeutic perspective, the limited success of LSD1 inhibition as a monotherapy is being addressed through three major strategies: First, the development of PROTAC degraders that eliminate the entire LSD1 scaffold, thereby preventing any residual co-repressor recruitment. Second, the exploitation of potent synergies, particularly with Menin inhibitors (to suppress stemness drivers like MEIS1) and GSK3 inhibitors (to activate the type I interferon and STAT1 maturation axes). Third, the integration of LSD1 inhibitors into established treatment backbones, such as the triplet regimen with azacitidine and venetoclax, which has shown exceptional preliminary response rates by re-priming leukemic cells for apoptosis.

5. Conclusion

The comprehensive analysis of LSD1-mediated differentiation therapy reveals a paradigm where chromatin accessibility is the gatekeeper of the myeloid maturation program. The enzymatic activity of LSD1, far from being a global silencer, is surgically deployed to maintain the stemness of leukemic blasts by decommissioning critical myeloid enhancers through molecular mimicry with the SNAG domain of GFI1. Pharmacological intervention triggers a cascade of physical and chemical transitions, most notably the “NuRD-to-SWI/SNF” switch, which provides the physical space necessary for pioneer factors like PU.1 and C/EBPα to “recommission” dormant enhancers.

The management of hematologic toxicities, especially thrombocytopenia, remains the primary hurdle for widespread clinical adoption. Future efforts must focus on optimizing marrow-sparing schedules and identifying biomarkers that predict which AML genomic subtypes are most dependent on the LSD1-GFI1 axis. By viewing differentiation as a process of systemic transcriptional rewiring rather than simple mark erasure, clinicians and researchers can better leverage LSD1 inhibitors to bridge the gap between laboratory insights and curative patient outcomes in non-APL AML.

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