AIMS Biophysics

AIMS Biophysics, 13(3): 231−254.
DOI: 10.3934/biophy.2026015
Received: 25 April 2026
Revised: 01 July 2026
Accepted: 08 July 2026
Published: 16 July 2026

http://www.aimspress.com/journal/biophysics

*Review*

# Biophysical mechanisms underlying the tumor-suppressive functions of myeloid transcription factors in acute myeloid leukemia

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**Abstract:** Acute myeloid leukemia (AML) is a hematologic malignancy characterized by impaired myeloid differentiation and uncontrolled proliferation. Central to its pathogenesis is the dysfunction of transcription factors that normally maintain hematopoietic homeostasis by directing lineage commitment and restricting cell growth. Although the genetic and epigenetic alterations that affect these factors have been extensively characterized, the biophysical mechanisms underlying their contribution to leukemogenesis remain incompletely understood. This review integrates insights from structural biology, chromatin profiling, transcriptome analyses, and pharmacological studies to delineate the biophysical principles by which key myeloid transcription factors—PU.1, IRF8, CEBPA, RUNX1, and GFI1—exert tumor-suppressive functions. We focus on how sequence-specific DNA recognition, cooperative complex assembly, chromatin accessibility, and dynamic protein–protein interactions govern transcriptional regulation in both normal and leukemic hematopoiesis. Disruption of these transcription factor networks may arise from mutations that alter the DNA-binding affinity, isoform switching that reshapes cofactor interactions, or the formation of aberrantly repressive complexes. These alterations converge on transcriptional reprogramming that favors proliferation over differentiation. Notably, the biophysical interfaces which mediate these interactions, such as the SNAG domain–lysine-specific demethylase 1 (LSD1) axis in GFI1, represent promising targets for therapeutic intervention. Elucidating these molecular mechanisms provides a framework to understand the disease heterogeneity and to develop differentiation-based therapies in AML.

**Keywords:** acute myeloid leukemia; transcription factors; hematopoietic differentiation; chromatin remodeling; epigenetic regulation

## 1. Introduction

Acute myeloid leukemia (AML) is an aggressive hematologic malignancy defined by the clonal expansion of immature myeloid blasts in the bone marrow and peripheral blood [1]. This process results in bone marrow failure and high mortality, even with recent therapeutic advances [1]. AML constitutes about 1% of new cancer cases in the United States (USA) [2]. The incidence of AML is higher in developed countries, especially across Europe and North America [3], and mainly affects older adults, with a median diagnostic age of approximately 68 years [2]. The median overall survival for AML patients under 65 years rose markedly from 8 months in 1975–1979 to 46 months in 2010–2014, whereas the overall survival in patients over 65 years remained limited [4]. According to current Surveillance, Epidemiology, and End Results (SEER) data, the 5-year relative survival is ~32% overall, with an estimated 22,010 new cases and 11,090 deaths projected for 2025 in the USA [5]. AML is characterized by recurrent genetic abnormalities that disrupt the transcriptional regulatory networks [6]. These disruptions drive clonal proliferation of immature blasts, which are arrested at specific stages of hematopoietic differentiation and acquire an abnormal self-renewal capacity [6].

Understanding the disruption of these networks in AML first requires considering the roles of key transcription factors (TFs) in normal hematopoiesis. In normal hematopoiesis, TFs form densely interconnected networks that are regulated both spatially and temporally [7]. These networks control coordinated, lineage-specific gene expression during lineage commitment, proliferation, and differentiation [7].

Purine-rich box 1 (PU.1) drives myelomonocytic fate through extensive enhancer networks [8]. CCAAT/enhancer-binding protein alpha (CEBPA) activates genes involved in granulocytic differentiation [9]. Runt-related transcription factor 1 (RUNX1) regulates the emergence of hematopoietic stem cells (HSCs) and myeloid commitment [10]. Interferon regulatory factor 8 (IRF8) integrates inflammatory signals with lineage programs [11], while growth factor independent 1 (GFI1) epigenetically represses aberrant progenitor expansion [12]. CEBPA mutations block granulocytic differentiation [9] and promote inflammatory stress tolerance [13]. RUNX1 mutations increase the susceptibility to hematological malignancies and confer resistance to chemotherapies [14]. Nucleophosmin 1 (NPM1) mutations cause cytoplasmic delocalization of PU.1, thereby disrupting the PU.1/CEBPA/RUNX1 regulatory circuit [15]. Mutations or reduced expression of GFI1, including AML-associated variants such as serine-to-asparagine substitution at residue 36 (GFI1-36N), impair myeloid regulation and are associated with increased leukemia susceptibility and poorer clinical outcomes in AML [16]. Collectively, these alterations reinforce a block to differentiation and promote aberrant self-renewal programs that drive leukemic progression [6,17,18].

The regulatory output of these TFs is governed not only by their expression levels but also by biophysical properties, including the DNA-binding affinity and specificity, protein dimerization, the chromatin residence time, and nuclear–cytoplasmic localization [15,19]. These properties collectively determine their transcriptional activity in both normal and leukemic contexts [15,19]. Molecularly guided targeted therapies are now a cornerstone of AML treatment. Approved agents target fms-like tyrosine kinase 3 (FLT3) and menin, while therapies directed against other genomic lesions, including

TP53 mutations, are being evaluated [20]. Although these approaches can achieve substantial clinical benefits, resistance frequently emerges, which results in treatment refractoriness or relapse [20]. Therapeutic resistance in AML is driven by multiple factors, including cellular heterogeneity, interactions between leukemic stem cells (LSCs) and the bone marrow niche, chronic inflammation, and immune evasion mechanisms [21]. Although TFs were previously considered undruggable due to the lack of conventional active sites, they have recently emerged as promising therapeutic targets in AML owing to advances that enable pharmacological disruption of their regulatory functions [11]. Pharmacological inhibition of lysine-specific demethylase 1 (LSD1) [22] and redistribution of PU.1 genomic binding sites using heterocyclic diamidines are promising strategies to disrupt oncogenic TF programs and restore myeloid differentiation [23].

**Table 1.** Mutations and alterations of key myeloid TFs associated with AML.

| TF | Primary Alteration Type | Mutation Frequency in AML | Functional Consequence | Clinical Significance | Reference |
|---|---|---|---|---|---|
| PU.1 | Downregulation | Rare | Impaired myeloid gene transactivation; differentiation block. | Low levels drive a pre-leukemic state and potential for differentiation therapy. | [23–26] |
| IRF8 | Epigenetic Silencing/downregulation | Rare | Disrupted monocyte/dendritic cell program; abnormal proliferation. | Prognostic biomarker for AML and therapeutic target for restoring differentiation. | [11,27–32] |
| CEBPA | N-terminal (TAD) and C-terminal (bZIP) mutations | 7–16% | Defective granulocytic maturation; impaired cell cycle arrest. | Biallelic (double) mutations predict a favorable prognosis. | [9,33–38] |
| RUNX1 | Missense/nonsense mutations and translocations | ~10% (increases with age) | Loss of DNA binding; impaired transcriptional regulation. | Associated with poor prognosis and secondary AML. | [14,39–42] |
| GFI1 | GFI1-36N variant/downregulation | Rare | Altered recruitment of corepressors (LSD1/HDACs); lineage dysregulation. | Contributes to AML pathogenesis; altered differentiation program. | [12,43–46] |

**Table 2.** Functional and molecular characteristics of key myeloid TFs involved in AML.

| TF | Protein Family | Role in Hematopoiesis | Tumor-Suppressive Role in AML | Key Molecular/Biophysical Features | Reference |
|---|---|---|---|---|---|
| PU.1 | ETS | Controls the differentiation of HSCs into macrophages, dendritic cells, and B cells. | Reduced activity leads to blocked differentiation and leukemogenesis. | DNA binding via ETS domain; cooperative assembly with IRF8; exhibits negative cooperativity at high abundance to buffer transcriptional output | [24,25,47–52] |
| IRF8 | IRF | Essential for monocyte, macrophage, and dendritic cell development. | Loss/reduced activity impairs differentiation; promotes myeloid proliferation. | Forms cooperative DNA-binding complexes with PU.1; binds EICE/IECE motifs; preferentially binds H3K4me1/3-marked active chromatin. | [11,28–32] |
| CEBPA | bZIP | Regulates granulocytic lineage commitment and maturation. | Mutations/loss of function block differentiation; frequently seen in AML. | DNA binding via bZIP domain; obligate dimerization; mutations at R300/R297 disrupt direct DNA contact. | [33–37,53] |
| RUNX1 | RUNX | Essential regulator of definitive hematopoiesis and lineage specification. | Mutations disrupt transcriptional regulation and contribute to AML development. | DNA binding via Runt domain; interacts with CBFβ to stabilize DNA binding; recruitment to enhancers is BET/BRD4-dependent. | [39,40,54–56] |
| GFI1 | GFI | Maintains balance between self-renewal and differentiation of HSCs. | Altered expression contributes to AML pathogenesis by disrupting differentiation programs. | Binding via 6 C2H2 zinc-finger domains; N-terminal SNAG domain recruits LSD1 and HDACs to repress transcription**.** | [43–46,57–59] |

Here, we review the tumor-suppressive roles of PU.1, IRF8, CEBPA, RUNX1, and GFI1 in AML from a biophysical perspective, thereby focusing on mechanisms that underlie their function, including the DNA-binding specificity, protein–protein interactions, and chromatin occupancy. An overview of mutations and alterations in these key myeloid TFs is provided in Table 1, while their functional and

molecular characteristics are summarized in Table 2, with detailed descriptions presented in the main text. We further discuss how disruption of these properties drives leukemic transformation and how their pharmacological restoration offers a mechanistically grounded therapeutic strategy.

## 2. PU.1

PU.1 is a member of the E26 transformation-specific (ETS) family of TFs, functions as a master TF governing normal hematopoietic differentiation, and is critically implicated in the pathobiology of AML [47,60]. PU.1 is composed of four major functional domains: an acidic N-terminal transactivation domain (TAD), a glutamine-rich (Gln-rich) region, a Proline, Glutamate, Serine, and Threonine (PEST) domain, and a C-terminal ETS domain (Figure 1A) [61]. The acidic and Gln-rich regions function as transactivation domains [61]. The PEST domain mediates interactions with cofactors such as IRF4 and IRF8 and contributes to the regulatory functions of PU.1 [50].

The highly conserved ETS domain, characterized by a winged helix-turn-helix structural motif, recognizes a ~10-base pair DNA sequence containing a central 5'-GGA(A/T)-3' consensus motif [60]. High-resolution structural studies revealed that PU.1–DNA recognition is governed by the ETS-specific residue Q226, which forms a key hydrogen bond with a purine at the −2 position of the target motif [60]. Disruption of this interaction reduces the binding affinity, whereas Q226 substitutions alter the base preference and broaden the motif overlap with other ETS family TFs [60]. Multiple biophysical approaches, including diffusion-ordered spectroscopy nuclear magnetic resonance (DOSY NMR), tryptophan fluorescence anisotropy, and high-precision densitometry, consistently showed that ΔN117 undergoes concentration-dependent dimerization with a dissociation constant below 10 μM [62]. The absence of a similar behavior in ΔN165 and the localization of tryptophan residues within the ETS domain suggest that dimer formation is mediated by the structured ETS region [62]. Phosphorylation of the disordered PEST domain promotes the formation and persistence of the active 1: 1 complex, thus enhancing the transcriptional function [62]. Under physiological conditions, elevated PU.1 expression drives myeloid lineage commitment by activating myeloid-specific target genes, including the macrophage colony-stimulating factor receptor (M-CSFR) [48]. Chromatin accessibility is influenced by the local DNA sequence context, as PU.1 can effectively displace nucleosomes at high-affinity binding sites by overcoming nucleosome-associated energetic barriers, thereby facilitating regulatory access [49,50]. As a pioneer TF, PU.1 promotes chromatin accessibility and cooperates with TFs such as CEBPA and IRF8 to regulate gene expression (Figure 1B) [50].

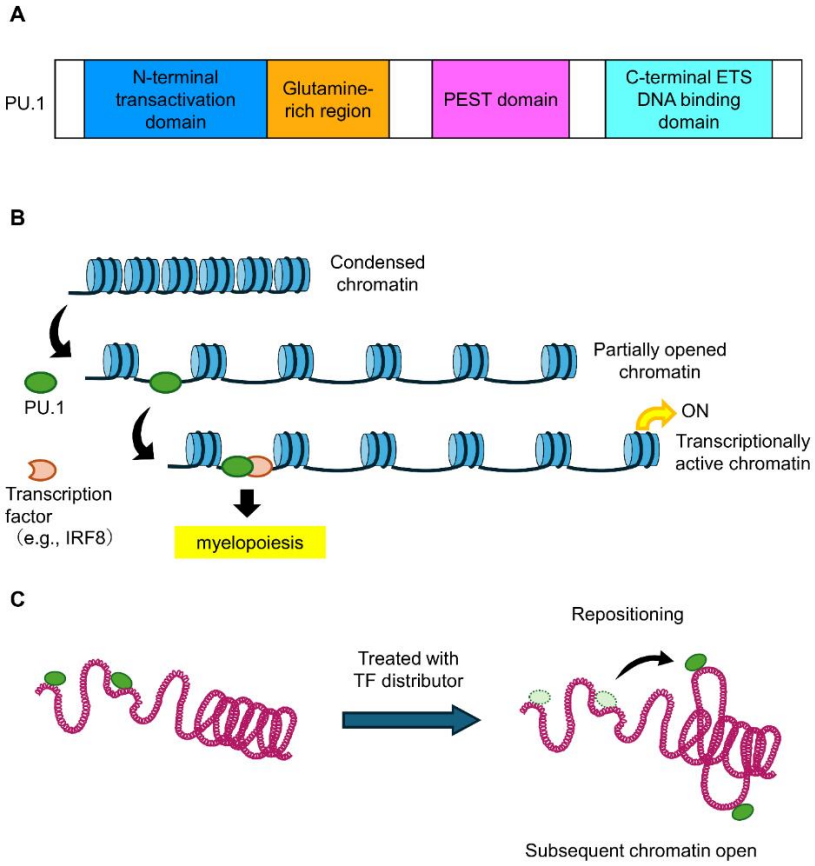


**Figure 1.** Pioneer activity and pharmacological redistribution of PU.1 at leukemic regulatory elements. (A) PU.1 is comprised of an acidic transactivation domain (TAD), a glutamine-rich region, a PEST domain, and an ETS DNA-binding domain. Blue, orange, violet, and teal boxes indicate the acidic TAD, glutamine-rich region, PEST domain, and ETS DNA-binding domain, respectively. (B) PU.1 functions as a pioneer TF and remodels chromatin for transcriptional activation. PU.1 engages condensed chromatin, displaces nucleosomes, transitions the local chromatin state to an accessible configuration, recruits partner TFs such as IRF8 to the newly accessible regulatory landscape, and promotes normal myelopoiesis. Blue cylinders represent nucleosomes, green ellipse shapes represent PU.1, and orange ellipse shapes represent TF (IRF8). (C) Pharmacological redistribution of PU.1 occupancy redirects the transcriptional output from pro-leukemic programs toward myeloid differentiation. In untreated leukemic cells (left), PU.1 preferentially occupies high-affinity canonical ETS motifs at leukemic regulatory elements, thereby sustaining transcriptional programs that promote cell survival and proliferation while leaving differentiation-associated enhancers inaccessible. Treatment with a TF redistributor compound (right) displaces PU.1 from canonical high-affinity sites, followed by its repositioning to low-affinity composite motifs. Green ellipse shapes represent PU.1; red coils represent nucleosomes. Part (C) of the figure is adapted from Taylor et al. [23].

The functional activity of PU.1 is influenced, in part, by its DNA-binding affinity, which contributes to the site occupancy and transcriptional output [60]. The binding strength correlates with

the genomic occupancy and contributes to the threshold required for TF-dependent transactivation [60]. Affinity-dependent binding has been shown to influence the transcriptional activation thresholds in reporter systems, including the colony-stimulating factor 1 receptor (CSF1R) promoter model [60]. However, the transcriptional output remains governed by the epigenetic landscape, specifically by whether target sites are constitutively accessible, stably repressed, or dynamically remodeled during development [51]. The inhibitory effect of closed chromatin on full-length PU.1 is quantitatively offset by high-affinity binding at near-optimal sites [51]. Under conditions of elevated protein abundance, PU.1 may function as a negative cooperative buffer that modulates the transcriptional activity [52]. Recent single-molecule imaging studies have demonstrated that the PU.1 activity is also governed by stochastic transcriptional bursting. Using multiplexed single-molecule RNA fluorescence *in situ* hybridization (smFISH), Wheat et al. showed that reversible transcriptional bursts of PU.1, together with GATA1 and GATA2, generate transcriptional heterogeneity while maintaining hematopoietic stem-cell plasticity and robustness [63]. These findings identify transcriptional burst kinetics as an additional biophysical layer regulating PU.1-dependent cell-fate determination.

Specific compounds, such as heterocyclic diamidines, have been shown to perturb PU.1–DNA interactions in defined experimental systems [64,65]. Studies by Munde et al. have demonstrated that targeting PU.1–DNA binding is a feasible therapeutic approach by utilizing synthetic heterocyclic diamidines [64]. The pharmacological restriction of PU.1 binding sites induces a genomic redistribution of PU.1 occupancy, thus leading to enhanced transcription at specific target loci and promoting myeloid differentiation in AML cell lines and primary patient samples (Figure 1C) [23].

The sequence context and cofactor occupancy likely influence the sensitivity of PU.1 binding sites to pharmacological redistribution, although the precise mechanisms remain to be fully defined [23].

Alterations in the PU.1 expression levels may drive redistribution of RUNX1 from RUNX/PU.1 composite elements to RUNX monomeric binding sites [66]. Such PU.1-dependent reprogramming of RUNX1 occupancy may represent a pro-oncogenic mechanism by enhancing the transcription of autophagy-associated genes [66].

LSD1 is a critical epigenetic regulator in AML that operates within the REST corepressor (CoREST) complex, which contains histone deacetylases 1 and 2 (HDAC1/2) [67,68]. Through coordinated histone H3 lysine 4 (H3K4) demethylation and histone deacetylation, these complexes promote chromatin compaction into a repressive heterochromatic state, thereby reducing accessibility and suppressing transcription [67]. In *KMT2A::MLLT3* fusion AML, pharmacological inhibition of LSD1 enhances chromatin accessibility [22]. LSD1 inhibition enhances chromatin accessibility and reactivates PU.1- and CEBPA-dependent enhancer programs [22,24,67]. Disruption of the LSD1-GFI1 interaction promotes histone acetylation and activates myeloid gene expression programs (e.g., IRF8), thus highlighting a critical antagonism between PU.1 and GFI1 in regulating differentiation [22].

Notch signaling has been reported to modulate PU.1 activity through transcriptional and protein–protein interaction mechanisms in specific contexts; however, its role in AML appears to be context-dependent [48]. Notably, aged yet otherwise healthy human HSCs exhibit a modest decline in PU.1 expression and a bias toward myeloid lineage differentiation [25]. These results elucidate the mechanistic contribution of PU.1 suppression to AML pathogenesis and further highlight PU.1 reactivation as a promising strategy for differentiation-based therapeutic interventions in human AML [26].

In summary, PU.1 functions as a pioneer TF whose DNA-binding affinity, chromatin remodeling activity, and cooperative interactions with IRF8 and CEBPA establish the accessible regulatory

landscape required for myeloid differentiation, and its suppression represents both a mechanistic driver and a potential therapeutic target in AML.

## 3. IRF8

IRF8 is a tightly regulated TF essential for hematopoietic lineage determination, and disruption of its activity impairs normal hematopoiesis and promotes leukemogenesis [27]. Structurally, IRF8 contains an N-terminal DNA-binding domain (DBD) and a C-terminal IRF association domain (IAD), which facilitates heterodimerization with partner TFs [28]. Structural modeling indicated that the N87 residue of IRF8 lies within hydrogen-bonding distance of the DNA-binding interface, thus implying an important contribution to DNA recognition and binding stability [69]. The +41-kb *Irf8* enhancer regulates the activity of the cis-linked +32-kb enhancer by enhancing chromatin accessibility and TF binding, independent of transcription of the associated long non-coding RNA (lncRNA) *Gm39266* [70]. Functionally, IRF8 operates as a versatile regulator by forming heterodimeric complexes with members of the ETS and IRF families [29]. It enables binding to specific DNA elements, including IFN-stimulated response elements (ISRE), ETS/IRF response elements (EIRE), ETS/IRF composite elements (EICE), and IRF/ETS composite elements (IECE), to regulate the expression of lineage-specific differentiation genes [29]. These complexes can act as both transcriptional activators and repressors, depending on the specific binding partner and chromatin context [29]. In particular, IRF8 interacts with essential TFs such as PU.1 and CEBPA to exert dual regulatory control over myeloid differentiation, thereby promoting monocyte/macrophage gene programs while constraining granulocyte differentiation [30].

At the chromatin level, IRF8 genomic occupancy is strongly associated with transcriptionally active regions. Chromatin profiling reveals that IRF8-occupied promoter regions are enriched for the active histone mark H3K4 trimethylation (H3K4me3) and RNA polymerase II, whereas distal IRF8-bound sites preferentially display the enhancer-associated mark H3K4 monomethylation (H3K4me1) [11]. In contrast, these loci show low levels of the repressive modification H3K27 trimethylation (H3K27me3), thus indicating that IRF8 binding predominantly occurs within transcriptionally active and accessible chromatin contexts, consistent with a role as a context-dependent regulator rather than a pioneer TF [11]. Although chromatin-level cooperation between IRF8 and PU.1 was previously unclear, recent findings by Pingul et al. have demonstrated that IRF8 collaborates with PU.1 to sustain PU.1/myeloid ecotropic viral integration site 1 (MEIS1)-driven transcriptional programs in AML [31]. Quantitative chromatin occupancy analyses further demonstrated that IRF8 stabilizes PU.1 binding at leukemia-specific enhancers through cooperative protein–protein interactions. Acute IRF8 depletion rapidly reduced PU.1 occupancy while active chromatin marks remained largely unaffected, highlighting TF occupancy dynamics as an important biophysical mechanism underlying IRF8-dependent gene regulation in AML [31].

Beyond its role in differentiation, IRF8 functions as a regulator of apoptosis and a classical tumor-suppressor in AML, thereby maintaining physiological myelopoiesis while preventing leukemogenesis [71–73]. The IRF8–STAT5 (signal transducer and activator of transcription 5) axis plays a pivotal role in hematologic malignancies, in which STAT5-mediated repression of IRF8 is associated with disease progression and poor prognosis [74]. Supporting its clinical relevance, an analysis of adult AML cohorts treated under Southwest Oncology Group (SWOG) protocols identified both wild-type and splice-variant IRF8 transcripts as independent adverse prognostic biomarkers for

relapse-free survival [27].

Notably, despite its tumor-suppressor function, emerging evidence indicates that certain AML subsets exhibit a functional dependency on IRF8 for leukemic maintenance, thereby reflecting a context-dependent rewiring of lineage transcriptional programs [17,31]. IRF8 and Myocyte Enhancer Factor 2D (MEF2D) establish a positive-feedback transcriptional loop that maintains the oncogenic state in AML, likely through hijacking a normal myeloid regulatory program [17]. The rapid suppression of IRF8 and MYC proto-oncogene (MYC) following zinc finger MYND domain-containing protein 8 (ZMYND8) loss further identifies ZMYND8 as a key regulator of IRF–MEF2–MYC transcriptional networks in AML and potentially other hematologic malignancies [17]. Although reduced PU.1 and IRF8 expression promotes preleukemic transformation, subsets of AML remain dependent on these factors for survival, thus highlighting their context-dependent roles in leukemogenesis [31]. IRF8 exerts either repressive or activating effects depending on the DNA motif, chromatin context, and associated cofactors. In general, ISRE-associated binding has been linked to repressive functions, whereas IECE occupancy is more commonly associated with transcriptional activation [75]. Their dual functions may arise from the combined influence of the cellular context, mutational background, and dosage-sensitive nature of myeloid TF activity.

Collectively, IRF8 functions as a context-dependent regulator of myeloid identity whose cooperative binding with composite ETS factors, such as PU.1, at composite regulatory elements reinforces lineage-specific transcriptional programs. In AML, this regulatory circuitry is frequently co-opted to support leukemic self-renewal rather than terminal differentiation, thus underscoring the critical dependence of the myeloid transcriptional network on specific partner interactions.

## 4. CEBPA

CEBPA is a single-exon gene on chromosome 19q13.1 that encodes a 358-amino acid protein of approximately 42 kDa belonging to the CCAAT/enhancer-binding protein (CEBP) family [33]. At its core, CEBPA functions as a molecular switch that plays a key role in regulating the balance between cellular proliferation and terminal differentiation [34]. It achieves this by simultaneously activating lineage-specific target genes, including CCAAT/enhancer-binding protein epsilon (*CEBPE*) and microRNA-34a (*miR-34a*), and suppressing cell cycle progression through direct interactions with Cyclin-dependent kinase 2/3 (CDK2/3) and retinoblastoma protein (pRb) [35,36]. In granulopoiesis, this antiproliferative function is reinforced by cooperative engagement with transcriptional co-regulators, including CREB-binding protein/p300 (CBP/p300), c-Jun, TIP60, and MYC-associated factor X (Max) [34], thus illustrating that CEBPA does not act alone but as part of a larger transcriptional assembly, whose composition determines its output.

The physical integrity of this assembly critically depends on the basic leucine zipper (bZIP) domain, which mediates both DNA binding and obligate dimerization. Missense mutations non-randomly cluster within the basic region of the bZIP domain, with conserved residues R300 and R297, which make direct contact with DNA, being disproportionately affected [37]. CEBPA DNA recognition is governed by a set of basic region residues, with Arg289 serving as a critical determinant of stable DNA binding and sequence specificity [76]. Val296 contributes to target-site selectivity, and its mutation has been reported to broaden DNA-binding preferences toward alternative motifs, including CRE-like sequences [76]. In-frame insertions/deletions (InDels) and frameshift-inducing mutations are distributed across the broader bZIP domain, and the specific location of each mutation

influences its functional consequences [37]. Specific CEBPA mutants, particularly those affecting the bZIP domain, have been shown to impair chromatin accessibility at distal regulatory elements [53]. This finding is mechanistically important because it demonstrates that CEBPA mutations do not simply abolish CEBPA activity in isolation but physically remodel the chromatin landscape available to partner TFs. Isoform switching further disrupts this process at the protein level. The truncated p30 isoform lacks the N-terminal transactivation domain present in full-length p42, and this structural difference has measurable biophysical consequences. In AML, recurrent CEBPA mutations selectively abolish the full-length p42 isoform while preserving p30, thus suggesting that the loss of p42-mediated differentiation programs is a major contributor to leukemogenesis [77]. Although p30 retains sufficient transcriptional activity to regulate most target genes, a subset of differentiation-critical loci remains highly dependent on p42, thus supporting a model in which impaired differentiation rather than complete loss of CEBPA function drives malignant transformation [77]. Consistent with this model, p42 and p30 bind similar genomic regions and regulate overlapping transcriptional networks; p42 uniquely activates key targets such as Early growth response 1 (*EGR1)* and tribbles pseudokinase 1 (*TRIB1)* [77]. These genes regulate myeloid differentiation, growth arrest, and ERK1/2-dependent feedback signaling and are selectively diminished in CEBPA-mutant AML [77]. Recent work further demonstrated that, despite a largely overlapping chromatin occupancy, the leukemia-associated p30 isoform exhibits defective enhancer activation and impaired AP-1–dependent transcriptional programs, thus resulting in attenuated inflammatory responses and increased tolerance to inflammatory stress [13]. These findings indicate that CEBPA isoforms differ not only in transcriptional output but also in their ability to coordinate cooperative enhancer activation with partner TFs.

The DEK-CEBPA interaction adds another layer of regulation that is sensitive to post-translational modifications. DEK associates with CEBPA in a S21-dependent manner, and this interaction is required for normal myeloid gene expression and granulocytic differentiation [34,36]. Oncogenic signaling that disrupts this phosphorylation-dependent axis can uncouple proliferation from differentiation, a mechanistic route for leukemogenesis that operates upstream of the transcriptional output [34]. Notably, mutations within the CEBPA mono-allelic N-terminal TAD mutation ($CEBPA^{smTAD}$) region show a significantly higher co-occurrence with DNA methylation regulators such as DNA methyltransferase 3 alpha (DNMT3A), Tet methylcytosine dioxygenase 2 (TET2), isocitrate dehydrogenase 1 (IDH1), and IDH2 [38]. This pattern is absent in bZIP domain mutants, thus suggesting that the TAD and bZIP domains engage the epigenetic machinery through distinct and separable physical interfaces [38].

Beyond its interactions within the myeloid TF network, CEBPA also intersects with epigenetic machinery by directly binding to the N-terminus of DNMT3A, thus blocking its access to DNA and inhibiting its methyltransferase activity [54]. This positions CEBPA as a regulator of DNA methylation patterning rather than merely a transcriptional activator. Consistent with this broader regulatory role, mutant CEBPA co-localizes with RUNX1 and activator protein 1 (AP-1) at composite CEBPA/AP-1 regulatory element sites identified within CEBPA N/C-specific DNase-hypersensitive regions [18]. In contrast, sites specific to t(8;21) AML and healthy blasts show enrichment of the canonical AP-1 motif [18]. This co-occupancy pattern suggests that mutant CEBPA actively reshapes the cooperative binding landscape at shared regulatory loci, with consequences that extend to RUNX1- and AP-1-driven transcriptional programs.

Taken together, CEBPA functions as a biophysical hub integrating DNA binding, obligate

dimerization, cofactor recruitment, and epigenetic regulation into a molecular switch controlling granulocytic differentiation, and its mutational disruption reshapes the cooperative binding landscape shared with partner TFs across the myeloid network.

## 5. RUNX1

The *RUNX1* gene encodes the α-subunit of the core-binding factor (CBF), a TF broadly expressed in hematopoietic cells that plays a critical role in the initiation and maintenance of definitive hematopoiesis [39].

At the molecular level, the functional dependency on the CBF complex is underscored by the observation that, even in *RUNX1* translocation-driven leukemias, cells retain a survival dependency on the remaining wild-type *RUNX1* allele [40]. This indicates that a partial loss of complex function is leukemogenic, whereas complete abrogation may be incompatible with cell survival [40]. Quantitative biophysical analyses further demonstrated that an enhanced RUNX1–DNA binding affinity is a critical determinant of leukemogenesis. Using bio-layer interferometry together with genome-wide chromatin occupancy analyses, Zhen et al. showed that leukemogenic CBFβ–SMMHC enhances RUNX1 binding affinity to its target DNA and increases RUNX1 chromatin occupancy, thus identifying RUNX1–DNA interaction as a key biophysical mechanism driving leukemogenesis [78].

The functional disruption of *RUNX1* in AML arises through multiple mutational mechanisms.

RUNX1 mutations occur in approximately 10% of AML cases, with higher frequencies observed in older patient populations [54]. The prevalence of RUNX1 mutations increases with age, affecting approximately 5–10% of patients younger than 60 years and 10–20% of those older than 60 years [41]. RUNX1 point mutations are largely mutually exclusive with recurrent cytogenetic abnormalities in AML [54]. Despite ongoing debate regarding the prevalence and impact of germline *RUNX1* mutations in AML, the analyzed patient group showed no evidence of germline involvement, likely reflecting the highly variable age of onset characteristic of familial platelet disorder (FPD) [79]. Critically, somatic *RUNX1* mutations frequently co-occur with mutations in genes encoding epigenetic regulators, *additional sex combs-like 1 (ASXL1)*, *IDH2*, *KMT2A*, and *enhancer of zeste homolog 2* (*EZH2),* all of which directly modify chromatin states [54,80]. The age-dependent stratification of these co-mutations shows that *ASXL1* predominates in older patients and RAS mutations predominate in younger individuals [80]. This pattern suggests that distinct molecular mechanisms of chromatin and signaling dysregulation converge on *RUNX1*-mutated AML via distinct biological pathways [80].

The locus Runx1 Regulatory Element 21 (R1RE21) harbors AML-associated single nucleotide polymorphisms (SNPs) and serves as the breakpoint region in t(8; 21) translocations involving *RUNX1* and Eight-Twenty-One (*ETO)*, where a long non-coding RNA promotes chromatin relaxation [81]. This relaxed chromatin state increases the susceptibility of myeloid cells to double-strand breaks, thereby facilitating chromosomal translocations [81]. The physical consequence of this translocation on chromatin organization is further evidenced by the finding that, although *RUNX1-ETO* exhibits a broadly similar binding profile across model systems, in vitro-generated cells markedly differ from t(8; 21) AML patient cells [55]. This distinction is reflected in their open chromatin landscapes and associated TF motif patterns [55]. Biophysical analyses using differential scanning fluorimetry (DSF) and microscale thermophoresis (MST) showed that the small molecule 7.44 destabilizes nervy homology region 2 domain (NHR2) tetramers and promotes dimer formation, thus revealing a mechanism by which it disrupts the oligomerization-dependent oncogenic activity of *RUNX1::RUNX1*

partner transcriptional co-repressor 1 (*RUNX1T1*) in t(8;21) AML [82]. Biophysical analyses identified molecule 7.44 as a promising lead compound for optimization, thus supporting the development of more potent inhibitors targeting *RUNX1::RUNX1T1* oncogenic activity in t(8; 21) AML [82].

Its promoter and enhancer chromatin interactions also govern the regulation of RUNX1 transcriptional activity. Short hairpin RNA-mediated Bromodomain-containing protein 4 (*BRD4)* knockdown suppresses *RUNX1* expression and its downstream transcriptional targets, inducing cell death in *RUNX1*-mutant-expressing AML cells [56]. Correspondingly, bromodomain and extra-terminal domain (BET) protein inhibition reduced BRD4 occupancy at the *RUNX1* promoter and Runx1 enhancer 1 (eR1), thus resulting in decreased *RUNX1* transcriptional activity, the inhibition of colony growth, induction of differentiation and apoptosis, and reduced viability of primary AML progenitor cells expressing mutant RUNX1 [56]. Additionally, loss-of-function mutations in Max-gene-associated (*MGA)*, a dual-specific TF, have been identified in patients and may functionally cooperate with the *RUNX1::RUNX1T1* oncoprotein [83].

A gene set enrichment analysis (GSEA) of Kyoto Encyclopedia of Genes and Genomes (KEGG) pathways indicated that *RUNX1* mutations are associated with perturbations in adherens junctions, WNT, MAPK, JAK-STAT signaling, and cell adhesion molecules, thus reflecting the broad downstream transcriptional consequences of *RUNX1* dysregulation [42]. The co-occurrence of *RUNX1* mutations with *DNMT3A* or *IDH1* mutations further compounds molecular dysfunction [84]. Patients harboring *RUNX1*-mutant/*DNMT3A*-mutant or *RUNX1*-mutant/*IDH1*-mutant combinations exhibit lower complete remission rates compared to their respective wild-type counterparts [84]. In the pediatric context, *FLT3*-ITD frequently co-occurs with *RUNX1* mutations in AML, although this combination does not significantly alter the prognosis beyond the known adverse effects of *FLT3*-ITD alone [79]. Cancer-associated RUNX1 missense mutations (R80C, R142K, D171N, R174Q, P176H, and R177Q) are predicted to impair DNA binding and may, in some instances, alter drug-binding properties [85].

Therapeutically, compounds that directly inhibit the RUNX-*CBFB* transcriptional complex demonstrate significant activity in MLL fusion leukemia and are anticipated to offer a favorable therapeutic window relative to normal HSCs [86]. This suggests that transcriptional complex disruption represents a promising molecular targeting strategy in AML [86].

Overall, RUNX1 is a dosage-sensitive scaffolding factor within the core-binding factor complex whose mutational inactivation destabilizes cooperative transcriptional networks and promotes epigenetic dysregulation through co-occurring mutations. This renders leukemic cells dependent on alternative oncogenic programs that are increasingly amenable to targeted pharmacological intervention.

## 6. GFI1

GFI1 is a transcriptional repressor whose DNA-binding specificity is conferred by six C2H2-type zinc-finger motifs located at its C-terminus, which collectively recognize the consensus sequence TAAATCAC(A/T)GC [43]. The repressive activity is mediated by a conserved 20-amino acid N-terminal motif known as the SNAG domain [44]. The SNAG domain serves as the primary recruitment interface for LSD1 and its associated corepressors, overlaps with a nuclear localization signal, and functions independently of its position or orientation within the protein [44]. The functional importance of this domain is demonstrated by a single amino acid substitution of proline at position 2

with alanine (P2A), which markedly reduces the repressive activity without disrupting nuclear localization [44]. This suggests that the structural integrity of this domain is critical for its repressive function [44]. Beyond myeloid regulation, GFI1 participates in T-cell lymphomagenesis, B and T cell activation, and dendritic cell maturation, thus reflecting the breadth of its regulatory reach across hematopoietic lineages [45].

The repressive function of GFI1 is executed through its assembly within the LSD1-CoREST-HDAC1/2 complex [57]. In addition to the LSD1–CoREST complex, GFI1 associates with the nucleosome remodeling and deacetylase (NuRD) complex through interactions with chromodomain helicase DNA-binding protein 4 (CHD4) and other NuRD components. Genome-wide chromatin occupancy analyses demonstrated that GFI1/CHD4 complexes preferentially localize to transcriptionally active and bivalent regulatory elements, where they dynamically regulate chromatin accessibility and nucleosome remodeling during myeloid differentiation [87]. GFI1 engages LSD1 through the SNAG domain [58], and together with HDAC1/2, drives coordinated H3K4 demethylation and histone deacetylation that compacts chromatin at enhancer regions into a transcriptionally repressive state [67,68]. Consistent with its chromatin association with GFI1 and LSD1, high-mobility group protein 20B (HMG20B) binding sites are highly enriched for the GFI1 consensus motif, particularly at the strongest peaks confirmed by Multiple EM for Motif Elicitation-ChIP (MEME-ChIP) [88]. HMG20B co-localizes with GFI1 and LSD1 on chromatin and supports GFI1-dependent transcriptional repression by stabilizing LSD1 through its coiled-coil domain at target sites [88]. Notably, the SNAG domain is not strictly required for GFI1 interactions with the corepressors euchromatic histone lysine methyltransferase 2 (EHMT2) and HDAC1, revealing that regions outside the SNAG domain also contribute to repressive complex assembly [89]. This multi-domain engagement suggests that these TFs cooperate to mediate gene repression, potentially with distinct functional characteristics [89]. GFI1-mediated repression may still extend further, with emerging evidence implicating phase separation and enhanced RNA polymerase II promoter pausing as additional physical mechanisms, though these remain to be fully characterized [88].

A closely related but distinct paralogue, growth factor independent 1B (GFI1B), was identified in humans through a sequence homology-based screening approach, thereby utilizing the zinc finger coding sequences of both chicken and mouse GFI1 as probes under low-stringency hybridization conditions [59]. Despite only 39% protein similarity in their intermediate domains, Gfi1 and Gfi1b exhibit over 89% sequence identity within their SNAG and zinc finger domains [89]. GFI1B interacts at the protein level with key hematopoietic TFs, namely stem cell leukemia factor (SCL), E2A immunoglobulin enhancer-binding factor (E2A), and GATA binding protein 1 (GATA1) [89]. Additionally, it associates with multiple corepressor complexes, including RUNX1T1, core-binding factor subunit alpha-2 translocation partner 3 (CBFA2T3), LSD1, histone deacetylases (HDACs), and EHMT2 [89]. Notably, GFI1B expression remains high in megakaryocyte-erythroid progenitors (MEPs) and megakaryocyte precursors (MKPs), and is sustained throughout the terminal differentiation of both the megakaryocytic and erythroid lineages [59].

GFI1/GFI1B participate in auto-repressive circuits and are modulated by key hematopoietic TFs, including RUNX1, GATA1/2, and PU.1 [59]. Moreover, the dose-dependency of GFI1 function is biologically meaningful: complete loss of GFI1 disrupts lymphoid and myeloid differentiation, whereas partial reduction paradoxically enhances progenitor and mature cell generation [46]. This suggests that GFI1 operates within a concentration-sensitive regulatory window rather than as a simple binary switch.

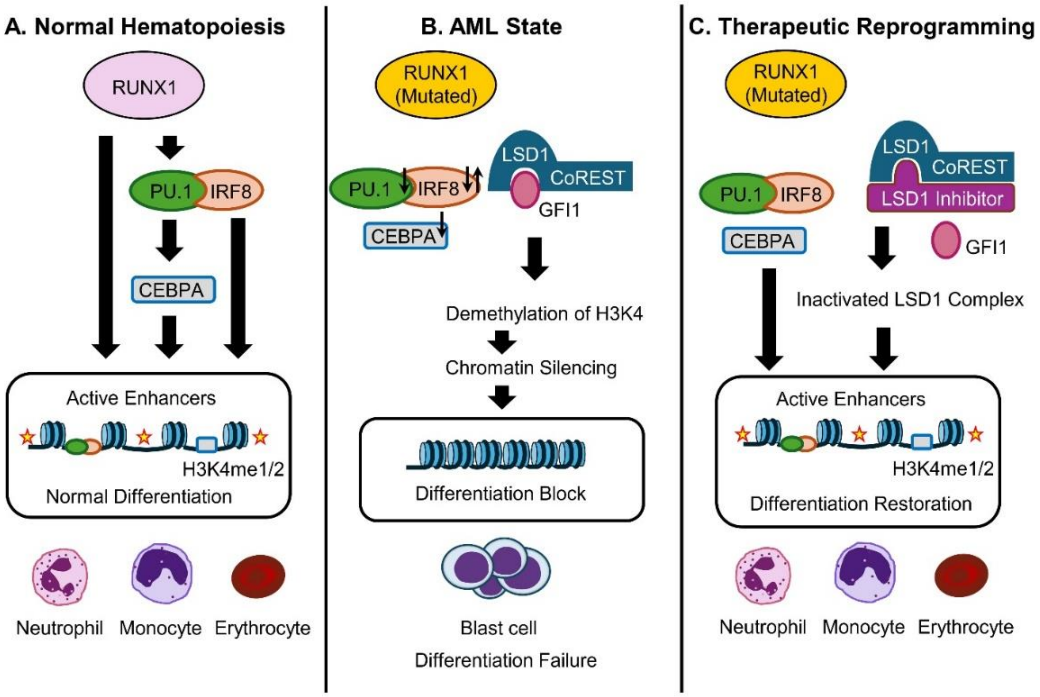


**Figure 2.** TF network disruption and therapeutic reprogramming in AML. (A) Normal hematopoiesis. Lineage TFs (PU.1, IRF8, CEBPA, RUNX1) maintain active H3K4me1/2-marked enhancers, enabling open chromatin and normal differentiation. (B) AML state. The LSD1–CoREST complex, recruited by GFI1, removes methyl groups from H3K4me1/2, thereby silencing lineage enhancers. This suppresses PU.1, IRF8, and CEBPA, thus causing chromatin compaction, differentiation arrest, and blast accumulation. Mutant RUNX1 reinforces this repression. (C) Therapeutic reprogramming. LSD1 inhibition restores H3K4me1/2, reactivates enhancers, re-expresses PU.1/IRF8/CEBPA, and induces differentiation. Stars denote active enhancer marks, teal cylinders represent nucleosomes, and the red flat-headed arrow indicates LSD1–CoREST–GFI1-mediated repression of lineage-specific enhancer activity (via H3K4me1/2 demethylation), thus resulting in reduced expression of PU.1, IRF8, and CEBPA.

Figure 2 illustrates the disruption of TF networks in AML and their therapeutic reprogramming, with a particular focus on targeting LSD1. Pharmacological disruption of the GFI1–LSD1 interface has been informative, both as a mechanistic tool and as a therapeutic strategy. Inhibition of LSD1, either by small molecules or genetic approaches, disrupts the GFI1/GFI1B–CoREST–HDAC1/2 repressive complex, thus leading to enhancer derepression, reactivation of TFs such as PU.1, CEBPA, and IRF8, and suppression of c-MYC signaling [57]. This reprogramming upregulates differentiation-associated genes such as *CD11b*, *CD86*, *LY96*, and *LYZ*, and induces cell cycle inhibitors *p21* and *p27*, thus promoting morphological differentiation of AML cells [57]. Treatment with OG86 in THP1 AML cells similarly disrupts endogenous GFI1-LSD1 association, as confirmed by immunoprecipitation [68], thus providing direct pharmacological evidence that this protein–protein interaction is a tractable therapeutic target. The complexity of this interface is further illustrated by the

observation that SP-2509-mediated disruption of GFI1-LSD1 binding and SNAG domain mutations produce opposing effects on *NOTCH3* surface expression [58]. This divergence suggests that LSD1 may compete with an unidentified co-activator for SNAG domain occupancy in an Ikaros Family Zinc Finger 1 (IKAROS)-dependent manner [58]. Separately, LSD1 knockout elevates H3K27 acetylation and BRD4 occupancy at the GFI1 locus itself, thereby increasing GFI1 expression [57]. Yet paradoxically, in the absence of the intact LSD1-CoREST-HDAC1/2 complex, elevated GFI1 is insufficient to maintain repression of differentiation programs [57].

The GFI1-36N variant (rs34631763) substitutes serine with asparagine at position 36, within the linker region between the SNAG domain and zinc-finger motifs, a segment predicted to mediate protein–protein interactions [12]. This substitution may disturb partner factor engagement, which is a plausible structural basis for the functional association between this variant and AML risk.

Altogether, GFI1 functions as a key transcriptional repressor within the myeloid regulatory network, thereby exerting concentration-sensitive, domain-dependent control over chromatin accessibility at differentiation-associated enhancers through the LSD1-CoREST-HDAC1/2 complex. Pharmacological uncoupling of GFI1 from this complex represents a mechanistically validated strategy to restore differentiation in AML.

## 7. Molecular profiles and pharmacological targeting of TFs

### *7.1. PU.1*

High-affinity PU.1 motifs are not always bound in vivo, implying that chromatin accessibility limits binding at some sites [49]. PU.1 binding is typically associated with local DNA demethylation rather than being dictated by DNA methylation, which is consistent with a role for PU.1 in recruiting demethylation machinery [49]. PU.1 promotes chromatin opening and is essential to maintain accessibility at numerous target sites [51]. While it collaborates with RUNX1 to facilitate chromatin remodeling and gene activation, PU.1 binding itself does not depend on RUNX1 [51]. PU.1 inhibition selectively compromises the survival and self-renewal capacity of $PU.1^{lo}$ -induced AML cells, thus supporting the therapeutic relevance of targeting PU.1-dependent regulatory circuits [90]. Conversely, pharmacological redistribution of PU.1 can redirect transcriptional programs toward differentiation, thus revealing a novel approach to manipulate leukemic cell fate [23].

### *7.2. IRF8*

IRF8 is a 426-amino-acid TF containing a DBD and an IAD [71]. While the DBD recognizes promoter DNA motifs, the IAD recruits partner TFs that confer high-affinity, sequence-specific DNA binding, thus enabling precise regulation of target gene expression [71]. IRF8 can activate gene expression by recruiting CBP/p300 to target promoters, leading to H3K27 acetylation, chromatin relaxation, and enhanced transcriptional accessibility [91]. Liss et al. (2021) identified IRF8 as a promising biomarker and potential therapeutic target in a subset of AML cases [11]. The transcriptional activity of IRF8 is context-dependent: binding to ISRE elements usually mediates repression, whereas occupancy of EICE or IECE motifs promotes gene activation, thus reflecting the influence of both cis-regulatory sequences and interacting partners [75].

### *7.3. CEBPA*

CEBPA is composed of two principal functional regions: TADs, which mediate interactions with the transcriptional machinery and regulatory cofactors; and bZIP, which facilitates sequence-specific DNA binding [92]. CEBPA binding drives 3D genome reorganization by establishing long-range chromatin interactions that facilitate the activation of myeloid transcriptional programs [93]. Deletion of CEBPA binding sites disrupts these interactions, thus highlighting a direct role for CEBPA in chromatin architecture remodeling during lineage commitment [93]. Kovecses et al. (2025) elucidated that delivery of the CEBPA-51 small activating RNA into AML cell lines markedly increases CEBPA expression [94]. Notably, this RNA activation–mediated upregulation enhances the responsiveness of AML cells to FLT3 inhibition, thus indicating a potential combinatorial therapeutic strategy [94].

### *7.4. RUNX1*

RUNX1-ETO interferes with RUNX1 activity by competing for shared DNA-binding sites, thereby repressing motif-dependent RUNX1 target genes [95]. However, genes regulated by RUNX1 through motif-independent mechanisms appear resistant to RUNX1-ETO-mediated inhibition, thus highlighting the context-dependent disruption of RUNX1 transcriptional programs [95]. An assay for transposase-accessible chromatin using sequencing (ATAC-seq) profiling revealed an open chromatin configuration at the RUNX1 eR1 enhancer, which is consistent with its regulatory activity [56]. T-cell receptor (TCR)-engineered T cells targeting RUNX1 frameshift mutation-derived neoantigens efficiently eliminated RUNX1-mutant AML cells and LSCs in preclinical models, thus supporting TCR-based immunotherapy as a promising treatment strategy for RUNX1-mutated AML [96].

### *7.5. GFI1*

GFI1 is both a transcriptional target and an interacting partner of AML1/ETO, binding the ETO Nervy homology region 2 (NHR2) domain that is required for AML induction, thus implicating GFI1 in AML1/ETO-mediated leukemogenesis [12]. Chromodomain helicase DNA-binding protein 4 (CHD4)-bound regions are characterized by a more repressive chromatin environment, whereas sites co-occupied by GFI1 and CHD4 exhibit intermediate histone modification patterns, indicating that GFI1 modulates nucleosome remodeling and deacetylase (NuRD)-dependent chromatin remodeling [87]. Small-molecule inhibition of LSD1 promotes terminal differentiation of leukemic cells by disrupting the interaction between GFI1/GFI1B and the CoREST chromatin-remodeling complex [97]. This mechanism highlights the therapeutic potential of targeting GFI1-dependent epigenetic regulation in AML.

## 8. Interconnected transcriptional network of myeloid TFs in AML

These TFs work together as a connected myeloid transcriptional network, rather than acting alone. PU.1 acts as a pioneer TF that increases chromatin accessibility and, together with CEBPA and IRF8, controls gene expression during myeloid differentiation [30,50]. Changes in PU.1 levels can shift TF binding, thereby moving RUNX1 from RUNX/PU.1 composite sites to RUNX-only sites [66]. This shift alters transcriptional programs linked to leukemogenesis [66]. As a result, RUNX1 activity is

closely tied to PU.1-dependent chromatin and transcriptional regulation [66].

IRF8 helps regulate gene expression by forming complexes with ETS-family TFs, such as PU.1, at EICE and IECE elements to control genes involved in cell differentiation [29]. By interacting with PU.1 and CEBPA, IRF8 supports monocyte and macrophage differentiation while limiting granulocytic differentiation [30]. This shows the strong cooperation among these myeloid TFs.

In contrast, GFI1 acts as a transcriptional repressor by bringing together the LSD1–CoREST–HDAC1/2 complex, which compacts chromatin and reduces gene expression [67,68]. GFI1 and GFI1B are also part of larger hematopoietic regulatory networks through their interactions with RUNX1, PU.1, and other key TFs [59]. Blocking the GFI1–LSD1 complex, either with drugs or genetic changes, leads to enhancer activation, more open chromatin, and reactivation of transcriptional programs controlled by PU.1, CEBPA, and IRF8 [22,24,57,67]. In AML cells, blocking LSD1 disrupts GFI1's repression, turns on myeloid differentiation genes such as IRF8 and supports transcriptional programs linked to differentiation [22,57]. Recent single-molecule analyses further indicate that this TF network is dynamically regulated at the level of transcriptional kinetics. Following cytarabine exposure, AML cells rapidly increase the transcriptional burst frequency of PU.1, RUNX1, and CEBPA, thereby generating adaptive transcriptional states that promote chemotherapy resistance [98].

Collectively, these findings indicate that PU.1, IRF8, CEBPA, RUNX1, and GFI1 participate in an interconnected transcriptional network that regulates myeloid differentiation. PU.1, IRF8, CEBPA, and RUNX1 cooperate to establish and maintain lineage-specific gene expression programs, whereas GFI1–LSD1-mediated repression antagonizes these differentiation-associated pathways.

## 9. Conclusions

The tumor-suppressive functions of PU.1, IRF8, CEBPA, RUNX1, and GFI1 derive from their participation in an integrated biophysical network. This network is characterized by DNA-binding affinity, cooperative complex assembly, chromatin accessibility, and dynamic protein–protein interactions, which together maintain the transcriptional programs required for normal myeloid differentiation. Disruption of this network, rather than the loss of any individual factor, establishes the conditions necessary for leukemic transformation. Several critical biophysical questions regarding this network remain unresolved. Quantitative parameters, including binding affinities, molecular residence times, and stoichiometric thresholds that regulate TF competition and cooperativity at shared enhancers, are not well defined in primary leukemic cells. The contribution of biomolecular condensates and phase separation to TF concentration at active regulatory elements introduces additional complexity that has only been superficially investigated in myeloid cells. Whether leukemia-associated mutations influence the phase behavior of these factors remains a significant open question. From a therapeutic standpoint, the biophysical framework outlined here offers substantial translational potential. Pharmacological targeting of the PU.1–DNA interface, the GFI1-LSD1 protein–protein interaction, and the regulation of RUNX1 demonstrates that TF networks, previously considered undruggable, are now increasingly amenable to structure-guided intervention. Achieving therapeutic selectivity will depend on precise mapping of molecular interfaces that are preferentially active in leukemic compared to normal hematopoietic cells.

A rigorous biophysical understanding of myeloid TF function is central to advance the study of AML. As structural biology, single-cell genomics, and quantitative biophysics converge, mechanistic insights into this disease will expand, thus facilitating the development of more precise therapeutic

strategies.

## Use of generative-AI tools declaration

Artificial Intelligence (AI) tools were used solely for language editing and proofreading. No AI tools were used for the generation of scientific content or figure preparation.

## Acknowledgments

The authors thank Kumiko Fukushima (Kumamoto University) for administrative and secretarial support during the preparation of this manuscript.

## Conflict of interest

The authors declare no conflict of interest.

## Author contributions

Writing–original draft: A.K.M.A., H.G.; Writing–review & editing: M.T., H.G.; Conceptualization: H.G.

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