BHARATI INTERNATIONAL JOURNAL OF MULTIDISCIPLINARY RESEARCH & DEVELOPMENT (BIJMRD)

(Open Access Peer-Reviewed International Journal)

DOI Link :: https://doi.org/10.70798/Bijmrd/02080022

Available Online: www.bijmrd.com|BIJMRD Volume: 2| Issue: 8| September 2024| e-ISSN: 2584-1890

Regulation of Different Transcription Factors in Acute Myeloid Leukemia (AML): Molecular Insights

Tanusree Naskar

PhD Research Scholar (JRF), Culcutta University, Mail Id: tanusreenaskar16922@gmail.com

Abstract:

Acute myeloid leukemia (AML) is a heterogeneous hematologic malignancy characterized by clonal expansion of myeloid progenitor cells, impaired differentiation, and aberrant proliferation. Transcription factors play a pivotal role in governing hematopoietic lineage commitment, differentiation, and survival, and their dysregulation is central to AML pathogenesis. Key transcription factors implicated in AML include PU.1, C/EBPα, RUNX1, GATA2, and AML1-ETO fusion proteins, each orchestrating distinct but interconnected signaling networks. Alterations in transcription factor expression or activity, often via mutations, epigenetic modifications, or signaling pathway deregulation, contribute to leukemogenesis, chemoresistance, and poor prognosis. This review highlights current knowledge on the regulation of transcription factors in AML, including upstream modulators, downstream targets, and cross-talk with oncogenic pathways. Additionally, it discusses experimental insights from AML cell lines, patient-derived xenografts, and clinical samples, with a focus on translational approaches targeting transcription factor networks. Understanding the molecular regulation of transcription factors in AML offers opportunities for novel therapeutic interventions, including small molecule inhibitors, epigenetic modulators, and targeted combination therapies.

Keywords: *AML, Transcription factors, PU.1, C/EBPα, RUNX1, GATA2, AML1-ETO, Epigenetic Regulation, Therapeutic Targets.*

Introduction

Acute myeloid leukemia (AML) is a clonal disorder of hematopoietic progenitors characterized by a block in differentiation and excessive proliferation of myeloid blasts (Döhner et al., 2015). Despite advancements in chemotherapy, targeted therapies, and hematopoietic stem cell transplantation, AML remains associated with high relapse rates and poor survival outcomes, particularly in elderly patients or those with high-risk cytogenetic abnormalities (Estey & Döhner, 2006).

Transcription factors (TFs) are proteins that regulate gene expression by binding to specific DNA sequences in promoters or enhancers. In hematopoietic, TFs coordinate lineage specification, maturation, and survival of myeloid progenitors. Dysregulation of TFs—through mutations, chromosomal rearrangements, altered expression, or post-translational modifications—disrupts normal hematopoietic, contributing to AML pathogenesis (Zhang et al., 2020). Understanding the regulation of TFs in AML is critical to decipher leukemogenesis and identify therapeutic vulnerabilities.

Objectives: This review highlights current knowledge on the regulation of transcription factors in AML, including upstream modulators, downstream targets, and cross-talk with oncogenic pathways. Additionally, it discusses experimental insights from AML cell lines, patient-derived xenografts, and clinical samples, with a focus on translational approaches targeting transcription factor networks.

Key Transcription Factors in Acute Myeloid Leukemia (AML)

Transcription factors (TFs) constitute the central regulatory machinery governing hematopoiesis, orchestrating the balance between self-renewal, proliferation, differentiation, and apoptosis. In acute myeloid leukemia (AML), disruption of these tightly controlled transcriptional programs leads to leukemic transformation, characterized by the accumulation of immature myeloid blasts, impaired differentiation, and enhanced survival. The dysregulation of key TFs not only drives leukemogenesis but also contributes to disease heterogeneity, therapeutic resistance, and adverse clinical outcomes.

Among the most critical TFs implicated in AML is PU.1 (SPI1), a member of the ETS family, which plays a fundamental role in both myeloid and lymphoid lineage commitment. PU.1 regulates a wide array of genes involved in hematopoietic differentiation, immune function, and apoptosis. In AML, reduced expression or functional inhibition of PU.1—often mediated by oncogenic drivers such as FLT3-ITD or the AML1-ETO fusion protein—results in a blockade of differentiation and uncontrolled cellular proliferation (Rosenbauer & Tenen, 2007). Its activity is intricately controlled through epigenetic mechanisms, including promoter methylation and histone modifications, as well as post-translational modifications such as phosphorylation and ubiquitination. Furthermore, PU.1 interacts with other TFs like C/EBPα and RUNX1 to establish lineage-specific transcriptional networks (Laslo et al., 2006).

Another pivotal regulator is C/EBPα (CCAAT/enhancer-binding protein alpha), which is essential for granulocytic differentiation. Mutations in the *CEBPA* gene, observed in approximately 10–15% of AML cases, often lead to the production of truncated or dysfunctional protein isoforms that act in a dominant-negative manner, thereby inhibiting normal differentiation processes (Pabst & Mueller, 2007). These mutations may affect either the N-terminal region—leading to altered transcriptional activation—or the C-terminal domain, impairing DNA-binding capacity. C/EBPα also cooperates with PU.1 to regulate myeloid gene expression, and its function is modulated by epigenetic factors such as DNA methylation and histone acetylation, further underscoring its central role in AML pathogenesis.

RUNX1 (AML1) is another indispensable transcription factor involved in definitive hematopoiesis. Chromosomal translocations affecting RUNX1, particularly t(8;21)(q22;q22), generate the AML1-ETO fusion protein, which acts as a transcriptional repressor by recruiting co-repressors and histone deacetylases, thereby silencing genes required for differentiation (Pabst et al., 2001). RUNX1 activity is also influenced by multiple intracellular signaling pathways, including MAPK, PI3K/AKT, and GSK3, which regulate its phosphorylation status, DNA-binding affinity, and protein stability. Disruption of RUNX1-mediated transcriptional control is a hallmark of several AML subtypes.

GATA2 plays a crucial role in maintaining hematopoietic stem cell (HSC) quiescence and self-renewal. In AML, aberrant expression or mutation of GATA2 enhances leukemic stem cell survival and contributes to resistance against chemotherapy (Hsu et al., 2011). Its regulatory mechanisms involve promoter methylation, protein–protein interactions with TFs such as PU.1 and RUNX1, and modulation by oncogenic signaling pathways like FLT3-ITD and JAK2. These pathways influence GATA2 activity through phosphorylation and other post-translational modifications, thereby altering transcriptional outputs.

In addition to these key regulators, several other TFs significantly contribute to AML progression. c-MYC is a potent oncogenic TF that drives cellular proliferation, metabolic reprogramming, and apoptosis, and is frequently overexpressed in aggressive AML subtypes. NF-κB plays a central role in regulating cell survival

and inflammatory responses, and its constitutive activation is associated with chemoresistance and disease persistence. Furthermore, HOXA9 and MEIS1 are key regulators of leukemic stem cell maintenance and are often co-expressed in AML cases with poor prognosis, reinforcing self-renewal and blocking differentiation (Huang et al., 2008).

Collectively, these transcription factors form a highly interconnected regulatory network, where alterations in one component can propagate through the system, amplifying leukemogenic signals. The complexity and redundancy of this network highlight the challenges in targeting AML therapeutically, while also offering multiple potential intervention points for precision medicine approaches.

Upstream Regulation of Transcription Factors in AML

The activity of transcription factors in AML is not autonomous but is governed by a sophisticated network of upstream regulatory mechanisms that integrate extracellular signals, intracellular pathways, and epigenetic modifications. These regulatory layers collectively determine the transcriptional landscape of leukemic cells and influence disease progression and treatment response.

Signaling pathways play a central role in modulating TF function. The PI3K/AKT pathway is a key regulator of cell survival and proliferation, influencing the nuclear localization and transcriptional activity of TFs such as PU.1 and C/EBPα (Martelli et al., 2010). Similarly, the MAPK/ERK pathway regulates phosphorylation events that affect TF stability, DNA-binding affinity, and transcriptional output. The JAK/STAT signaling cascade transduces signals from cytokines and growth factors to the nucleus, thereby modulating TF-mediated gene expression programs critical for hematopoietic differentiation (Rosenbauer & Tenen, 2007). Additionally, the Wnt/β-catenin pathway plays a crucial role in maintaining leukemic stem cell self-renewal and promoting resistance to differentiation signals, further contributing to disease persistence.

Epigenetic regulation constitutes another crucial layer of TF control. DNA methyltransferases (DNMTs) mediate promoter methylation, leading to transcriptional silencing of key TF genes. Histone-modifying enzymes—including histone deacetylases (HDACs), histone acetyltransferases (HATs), and polycomb group proteins such as EZH2—alter chromatin structure and accessibility, thereby influencing TF binding to target gene promoters (Rosenbauer & Tenen, 2007). For example, hypermethylation of PU.1 or C/EBPα promoters results in decreased expression and impaired differentiation, a hallmark of AML.

Post-transcriptional regulation by microRNAs (miRNAs) adds another layer of complexity. miRNAs such as miR-155, miR-29, and miR-34 regulate TF expression by binding to their mRNAs and inhibiting translation or promoting degradation. These interactions fine-tune the expression of critical TFs like PU.1 and C/EBPα, thereby influencing cellular processes such as proliferation, apoptosis, and differentiation (Huang et al., 2008). Dysregulation of miRNA networks disrupts this balance, contributing to leukemic transformation and resistance to therapy.

Chromosomal rearrangements represent a major genetic mechanism disrupting TF function in AML. Fusion proteins such as AML1-ETO (from t(8;21)) and PML-RARA (from t(15;17)) alter transcriptional regulation by recruiting co-repressors and chromatin-modifying complexes, leading to sustained repression of genes required for differentiation (Pabst et al., 2001). These aberrations not only modify gene expression patterns but also establish stable epigenetic states that perpetuate the leukemic phenotype.

Downstream Targets and Functional Consequences

The dysregulation of transcription factors (TFs) in acute myeloid leukemia (AML) triggers a cascade of downstream molecular events that profoundly alter cellular homeostasis. These effects extend across multiple biological processes, including differentiation, proliferation, apoptosis, and stem cell maintenance, ultimately driving leukemic transformation and disease progression.

One of the most defining features of AML is the blockade of cellular differentiation, which arises primarily from the repression or functional inactivation of key TFs such as PU.1, C/EBPα, and RUNX1. These factors normally regulate genes essential for granulocytic and monocytic maturation. Their suppression disrupts lineage-specific transcriptional programs, preventing the transition of hematopoietic progenitors into mature blood cells. As a result, immature myeloid blasts accumulate in the bone marrow and peripheral blood, contributing to hematopoietic failure and the characteristic clinical manifestations of AML (Rosenbauer & Tenen, 2007). This differentiation arrest is not merely a passive consequence but an actively maintained state reinforced by oncogenic signaling and epigenetic repression.

In parallel, uncontrolled cellular proliferation is driven by the activation of oncogenic transcriptional programs. TFs such as c-MYC and E2F1, along with downstream cyclins and cyclin-dependent kinases, promote continuous cell cycle progression and expansion of leukemic clones. c-MYC, in particular, orchestrates a broad transcriptional network that enhances ribosomal biogenesis, metabolic activity, and DNA replication, thereby sustaining rapid cell division. This hyperproliferative state is a hallmark of aggressive AML subtypes and contributes to disease burden and progression (Huang et al., 2008).

Another critical consequence of TF dysregulation is the evasion of apoptosis, which allows leukemic cells to survive despite genomic instability and external stressors such as chemotherapy. This survival advantage is mediated through the upregulation of anti-apoptotic proteins, particularly members of the Bcl-2 family, and the concurrent suppression of pro-apoptotic signaling pathways, including death receptor-mediated mechanisms. Altered TF activity reshapes the expression of these apoptotic regulators, tipping the balance toward cell survival and contributing to treatment resistance (Ling et al., 2017).

Equally important is the maintenance of stemness and self-renewal capacity, largely governed by TFs such as MEIS1, HOXA9, and GATA2. These factors sustain the leukemic stem cell (LSC) population, which possesses the unique ability to initiate, propagate, and re-establish the disease even after apparent remission. LSCs are inherently resistant to conventional therapies, and their persistence is a major cause of relapse in AML patients. By preserving stem-like transcriptional programs and inhibiting differentiation, these TFs create a reservoir of therapy-resistant cells that perpetuate the disease (Hsu et al., 2011).

Collectively, the dysregulation of transcription factors leads to a comprehensive rewiring of gene expression networks, integrating signals that simultaneously promote proliferation, inhibit differentiation, enhance survival, and sustain stemness. This multifaceted disruption underscores the complexity of AML pathogenesis and highlights the importance of targeting TF-driven pathways to achieve durable therapeutic responses.

Experimental Models for Studying Transcription Factor Regulation

Understanding the intricate regulation of transcription factors in AML requires robust and versatile experimental systems. A wide range of in vitro and molecular approaches has been developed to investigate TF function, regulatory mechanisms, and their contribution to leukemogenesis.

In vitro AML cell lines serve as foundational models for studying TF dynamics. Cell lines such as HL-60, KG1α, NB4, and MOLM-13 are extensively utilized due to their well-characterized genetic profiles and their ability to recapitulate key aspects of AML biology. For instance, HL-60 cells are widely used to study differentiation processes, while NB4 cells provide a model for acute promyelocytic leukemia and response to differentiation-inducing agents. These systems enable controlled experimental manipulation and reproducible analysis of TF activity (Ling et al., 2017; Suangtamai & Tanyong, 2016).

Advances in genetic engineering technologies have significantly enhanced the ability to interrogate TF function. Techniques such as shRNA-mediated knockdown allow selective suppression of gene expression, while CRISPR/Cas9 genome editing enables precise gene disruption or modification. Lentiviral

overexpression systems further facilitate the study of TF gain-of-function effects. Together, these approaches provide powerful tools to dissect the roles of individual TFs in regulating proliferation, differentiation, apoptosis, and leukemic transformation.

At the chromatin level, high-throughput sequencing technologies have revolutionized the study of transcriptional regulation. Chromatin immunoprecipitation followed by sequencing (ChIP-seq) allows genome-wide mapping of TF binding sites, revealing direct target genes and regulatory circuits. Assay for transposase-accessible chromatin using sequencing (ATAC-seq) provides insights into chromatin accessibility and epigenetic landscapes, highlighting regions of active transcriptional regulation. These techniques are essential for constructing comprehensive TF regulatory networks and understanding how they are altered in AML.

Reporter assays, particularly luciferase-based systems, are widely used to assess promoter activity and transcriptional responses under different experimental conditions. These assays enable real-time monitoring of TF-mediated gene regulation and are valuable for studying the effects of mutations, signaling pathways, and pharmacological agents on transcriptional activity.

In addition, pharmacological approaches offer important insights into TF regulation and therapeutic targeting. Small molecule inhibitors targeting signaling pathways (e.g., PI3K/AKT, MAPK), epigenetic modifiers such as histone deacetylase (HDAC) inhibitors, and miRNA-based therapeutics allow researchers to modulate TF activity indirectly. These interventions help elucidate upstream regulatory mechanisms and identify potential strategies for restoring normal transcriptional control in leukemic cells (Martelli et al., 2010).

Overall, the integration of cellular models, genetic tools, chromatin profiling techniques, and pharmacological interventions provides a comprehensive framework for studying transcription factor regulation in AML. These experimental platforms not only deepen our understanding of disease mechanisms but also pave the way for the development of targeted therapies aimed at reprogramming aberrant transcriptional networks, restoring differentiation, and overcoming chemoresistance.

Therapeutic Implications of Transcription Factor Regulation in AML

The complex regulatory landscape of transcription factors (TFs) in acute myeloid leukemia (AML) presents a fertile ground for the development of innovative and targeted therapeutic strategies. Since TF dysregulation lies at the core of leukemogenesis—driving differentiation arrest, uncontrolled proliferation, resistance to apoptosis, and persistence of leukemic stem cells—therapeutic interventions aimed at restoring or modulating TF activity hold significant promise. Rather than targeting isolated pathways, TF-centered therapies offer a systems-level approach capable of reprogramming aberrant gene expression networks and reinstating normal hematopoietic function.

Direct Transcription Factor Targeting: One of the most promising therapeutic avenues involves the direct targeting of transcription factors or their associated complexes. Although TFs have traditionally been considered “undruggable” due to their structural characteristics, recent advances in molecular pharmacology have enabled the development of small molecules, peptide inhibitors, and synthetic DNA decoys that can interfere with TF-DNA binding or disrupt critical protein–protein interactions.

For instance, targeting the AML1-ETO fusion protein, generated by the t(8;21) translocation, has shown considerable therapeutic potential. AML1-ETO functions as a transcriptional repressor by recruiting co-repressors and histone deacetylases (HDACs), thereby silencing genes essential for differentiation. Disrupting these repressive complexes can relieve transcriptional inhibition, reactivate RUNX1 target genes, and restore differentiation pathways (Pabst et al., 2001).

Similarly, strategies aimed at enhancing the activity of tumor-suppressive TFs such as PU.1 and C/EBPα are gaining attention. Pharmacological agents or gene therapy approaches that restore their expression or function can overcome differentiation blockade, promote maturation of leukemic blasts, and suppress proliferation (Rosenbauer & Tenen, 2007). These approaches shift the therapeutic paradigm from cytotoxicity to cellular reprogramming.

Epigenetic Therapy: Epigenetic dysregulation is a major mechanism underlying TF silencing in AML, making epigenetic therapy a highly effective and clinically validated strategy. Agents targeting DNA methylation and histone modifications can reverse transcriptional repression and restore normal gene expression patterns.

DNA methyltransferase (DNMT) inhibitors, such as azacitidine and decitabine, function by demethylating promoter regions of key TF genes, thereby reactivating their transcription. For example, demethylation of the PU.1 promoter restores its expression and promotes myeloid differentiation.

In parallel, histone deacetylase (HDAC) inhibitors enhance histone acetylation, leading to a more open chromatin structure and increased accessibility of TFs to their target genes. This can restore the activity of TFs such as C/EBPα and RUNX1, facilitating the reactivation of differentiation-associated transcriptional programs (Rosenbauer & Tenen, 2007).

Epigenetic therapies not only target TF expression directly but also reshape the broader chromatin landscape, thereby amplifying their therapeutic impact across multiple gene networks.

Targeting Upstream Signaling Pathways: Given that TF activity is tightly regulated by intracellular signaling cascades, targeting upstream pathways represents an effective indirect strategy to modulate transcriptional programs. Key oncogenic pathways such as FLT3, PI3K/AKT, and MAPK/ERK are frequently dysregulated in AML and play a crucial role in suppressing differentiation-promoting TFs while enhancing survival signals.

Inhibition of these pathways can restore TF function and sensitize leukemic cells to apoptosis. For example, FLT3 inhibitors have been shown to relieve the suppression of PU.1, thereby promoting differentiation and reducing leukemic cell survival (Martelli et al., 2010; Huang et al., 2008). Similarly, targeting PI3K/AKT signaling can modulate TF localization and activity, leading to reduced proliferation and enhanced therapeutic responsiveness.

This approach highlights the interconnected nature of signaling and transcriptional regulation, where modulation at one level can have far-reaching downstream effects.

Combination and Differentiation-Based Therapies: A growing body of evidence supports the use of combination therapies that integrate TF modulation with conventional treatment modalities. These strategies are particularly effective because they simultaneously target multiple aspects of leukemic biology.

For instance, combining TF reactivation strategies with standard chemotherapeutic agents such as cytarabine enhances cytotoxic efficacy while promoting differentiation. The use of all-trans retinoic acid (ATRA) in acute promyelocytic leukemia (APL) serves as a classic example of differentiation therapy, where modulation of transcriptional regulation leads to the maturation of leukemic cells.

Reactivation of PU.1 or C/EBPα in combination with chemotherapy or epigenetic drugs has been shown to induce both differentiation and apoptosis, thereby reducing tumor burden and lowering relapse rates (Rosenbauer & Tenen, 2007; Huang et al., 2008). Similarly, targeting fusion proteins like AML1-ETO or PML-RARA alongside epigenetic modulators can restore normal transcriptional programs and overcome differentiation blocks.

Such multi-targeted approaches are particularly valuable in high-risk or chemoresistant AML, where monotherapies often fail.

Preclinical and Translational Evidence: Substantial preclinical and translational research supports the therapeutic potential of targeting transcription factor networks in AML. Studies using AML cell lines such as HL-60, NB4, and MOLM-13 have demonstrated that restoration of TFs like PU.1 and C/EBPα induces granulocytic differentiation, cell cycle arrest, and apoptosis.

Similarly, inhibition of AML1-ETO-mediated repression restores RUNX1 target gene expression, leading to reduced proliferation and enhanced differentiation (Rosenbauer & Tenen, 2007; Huang et al., 2008). Animal models further corroborate these findings, showing decreased leukemic burden and prolonged survival following TF-targeted interventions.

These findings underscore that TF-based therapies are not merely conceptual but represent actionable and clinically relevant strategies. They hold particular promise for patients with refractory or relapsed AML, where conventional treatments are often inadequate.

Conclusion

Transcription factors are central to the pathogenesis of AML, orchestrating gene networks that regulate proliferation, differentiation, apoptosis, and stemness. Their dysregulation through mutations, epigenetic modifications, and signaling crosstalk drives leukemogenesis and chemoresistance. AML cell lines and patient-derived models provide critical platforms to study TF regulation and identify therapeutic targets. Targeting transcription factor networks, either directly or through upstream modulators and epigenetic therapies, holds promise for precision treatment strategies aimed at overcoming differentiation blocks, inducing apoptosis, and eradicating leukemic stem cells. Integrating mechanistic insights into clinical strategies will be key to improving outcomes in AML patients.

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Citation: **Naskar. T.,** (2024) "Regulation of Different Transcription Factors in Acute Myeloid Leukemia (AML): Molecular Insights", *Bharati International Journal of Multidisciplinary Research & Development (BIJMRD)*, Vol-2, Issue-8, September-2024.