**UNDERGRADUATE RESEARCH IN NATURAL AND CLINICAL SCIENCE AND TECHNOLOGY (URNCST) JOURNAL**
**Read more URNCST Journal articles and submit your own today at: https://www.urncst.com**

REVIEW OPEN ACCESS

# Mechanisms of AML1-ETO Induced Transcription Factor Dysregulation, Epigenetic Modification, and Immune System Evasion in Pre-Leukemic Stem Cells

Karoll Kaveen Thanaraj, BMSc Student [1]*, Likitha Busanelli, BMSc Student [2]*

[1] Schulich School of Medicine & Dentistry, University of Western Ontario, London, Ontario, Canada N6A 3K7
[2] Schulich School of Medicine & Dentistry, University of Western Ontario, London, Ontario, Canada N6A 3K7

*Corresponding Authors: kthanar@uwo.ca, lbusanel@uwo.ca

**Abstract**

**Introduction**: Acute myeloid leukemia is a cancer of the bone marrow with a low survival rate of 15% among elderly individuals due to its rapid progression and lack of available treatment. Understanding different transcription factors that may contribute to the progression of leukemia and leukemogenesis is crucial in developing effective treatment plans to control the advancement of AML within patients. This paper aims to conduct a literature review where primary articles contain evidence exhibiting a link between transcriptional dysregulation in genes that code for regulatory proteins involved in cell cycle progression and irregularity present in pre-leukemic stem cells.

**Methods**: Databases Medline and Embase were searched using keywords "leukemogenesis," "pre-leukemic," "AML1", "Acute myeloid leukemia", and "AML-ETO". Only studies written in the English language that were published in peer-reviewed journals and human post-mortem/pathophysiological studies were considered in the review. The search emphasized studies published between 1998-2023 to include recent literature reported in the respective field.

**Results:** AML1 regulates the expression of cell cycle checkpoint regulating proteins and proteins involved in hematopoietic differentiation in order to prevent asymmetric production of mutated hematopoietic stem cells (HSCs) as well as defective cells from progressing through the cycle via apoptosis.

Chromosomal translocations allow for the AML1 gene to be fused with ETO, causing issues with transcriptional regulation, which work to continuously repress the function of this complex, preventing the transcription of necessary proteins needed to regulate the cell cycle.

**Implications**: The fusion of AML1 and ETO causes the deregulation of the transcription complex, repressing the binding of transcription factors. This means that defective cells within hematopoiesis are not subject to apoptosis, leading to the production of pre-leukemic stem cells, which contributes to leukemogenesis. Understanding the mechanisms leading to the production of pre-leukemic stem cells opens up possible treatment channels from pharmacological and physiological approaches. In addition, leukemia can be identified and diagnosed at an earlier stage by identifying AML1 in relation to ETO as a precursor for AML.

**Keywords**: AML; NK cell surveillance; RUNX1; RUNX1T1; AML-1; ETO; CBF; GATA; COX; TGF-β signaling pathway; hematopoiesis

## Introduction

Acute myeloid leukemia (AML) is a growing concern with an estimated number of cases at around 20 000 and fatalities of approximately 11 000 in 2023 for both sexes in the United States of America [1], with a shockingly low survival rate of 15% among elderly individuals over the age of 60 due to its rapid progression in America [2]. AML is primarily a cancer that originates from and affects the bone marrow. It is characterized by an abnormality in hematopoietic stem cell (HSCs) function due to environmental and genetic aberrations. This often leads to development of leukemic stem cells, which proliferate and generate leukemic blasts [3]. There are usually a limited number of HSCs found in the body and they are multipotent progenitors to all red blood cells [4].

Chromosomal abnormalities are often associated with the development of AML, with the translocation between chromosomes 8 and 21 being especially common. This mutation involves the gene RUNX1T1 (also known as ETO) and results in the most common fusion gene in relation to AML: RUNX1/RUNX1T1 or AML1/ETO [2].

AML1 specifically encodes for a transcription factor that is a crucial regulator of physiologic hematopoietic differentiation [3] which binds to the runt domain (known

as the RDE) of target genes at the N terminal. AML1 is an alpha subunit that binds to the core binding factor, CBFβ, which binds to the core elements of many enhancers and promoters, binding to RDE allows for it to recognize specific DNA elements, resulting in an increased DNA binding affinity [4]. This factor is mutated in many hematopoietic malignancies and diseases. AML1 is crucial for coordinating hematopoiesis in a spatial and temporal manner as it has a long N terminal domain responsible for the DNA binding of target promoters and a C terminal transcriptional transactivation domain (TAD) that consists of several inhibitory domains [3]. These inhibitory regions at the C terminal influence gene expression by modulating histone acetylation which in turn regulates the activation of target genes, which is important in regulating hematopoiesis [3]. It can regulate hematopoiesis by regulating gene expression for blood cell differentiation and integrating external signals to ensure proper blood cell development. Dysregulation or mutations in AML1 can disrupt this process, leading to hematopoietic disorders and malignancies.

ETO is the protein encoded by the gene RUNX1T1 which is a transcriptional corepressor that plays a critical role in the development of certain types of leukemia, particularly in cases involving the chromosomal translocation t(8;21) [3]. In other words, it suppresses the activity of certain genes, leading to abnormal proliferation and impaired differentiation of myeloid cells, which are characteristic of AML. The AML1/ETO oncoprotein is formed by the fusion of two genes, which produces a fusion protein that acts as an aberrant transcription factor that binds to regulatory domains of target genes, disrupting their normal expression and contributes to transcriptional dysregulation. This altered regulation of expression affects critical pathways involved in cell cycle regulation, contributing to leukemogenesis [5].

Cell cycle checkpoint regulation proteins are impacted by the AML1/ETO fusion protein as it targets the precision control of specific cell division steps, contributing to compromised genomic stability. Dysregulation relating to cell division causes uncontrolled cell proliferation, which is an identifying feature in cancer cells, especially in AML. Specifically, AML1/ETO allows for the proliferation of pre-leukemic stem cells which are cells with leukemic potential that are prompted to develop into leukemia [6]. However, it is important to note that the AML1/ETO fusion gene allows for many mutations to occur relating to hematopoiesis, but those mutations on their own are not enough to drive leukemogenesis but increase the likelihood of it occurring [7].

AML1/ETO is also known for increasing CD48 expression which allows for leukemic cells to escape immune system surveillance by Natural Killer (NK) cells, promoting their further proliferation [8]. This mechanism is not fully understood but it is credited to AML1/ETO protein acting as a transcriptional factor that binds to the regulatory regions of target genes [7]. In this case, AML1/ETO may bind to the promoter region of the CD48 gene, allowing for increased CD48 mRNA production leading to elevated levels of CD48 protein levels. As well, AML1/ETO also influences epigenetic changes and is commonly known for its role in histone modifications and DNA methylation. In this case, it is known for histone acetylation at the CD48 gene locus, promoting better accessibility to the promoter region of this gene to transcriptional machinery, in turn attributing to changes in its expression [7]. Our review seeks to identify the role of the AML1/ETO fusion gene in the transcriptional dysregulation of specific cell cycle checkpoint-regulating proteins that may impact hematopoietic differentiation, leading to the production of pre-leukemic stem cells and contributing to leukemogenesis in acute myeloid leukemia. This review will include the different effects AML1/ETO protein has on co-regulatory proteins, epigenetic modifications, and signaling pathways.

## Methods

A literature search was conducted on the following databases: PubMed, Scholars Portal Journals, Google Scholar, Medline, and Embase on June 27, 2023. Keywords were applied for AML and AML1/ETO combined with keywords applicable to transcriptional dysregulation of cell cycle checkpoint regulating proteins and hematopoietic differentiation. Only studies written in the English language that were published in peer-reviewed journals and human post-mortem/pathophysiological and antemortem studies were considered in the review. Forward and backward citation tracking was applied to any reviews considered to identify additional studies. The search emphasized studies published between 1998-2023 to include recent literature reported in the respective field.

## Results

The gene AML1, also known as RUNX1 specifically in the RUNX1-RUNX1T1 subtype that commonly presents itself in AML, is caused by chromosomal abnormalities in the RUNX1 gene [9]. It is associated with chromosomal rearrangements, specifically translocations between chromosomes 8 and 21 which causes the AML gene to be fused with ETO, which is also known as the RUNX1T1 gene. This fusion is specifically caused by the translation being specifically involved with bands at the long arms of chromosome 22 (q22:q22), which is the specific mutation in the AML1 gene that this review focuses on, although there are other common mutations in AML1 that can be present simultaneously. For example, an inversion of chromosome 16 or translocation within the chromosome 16 causing the AML1 gene to be fused with a CBFB gene instead of ETO, or a translocation between chromosome 3 and 21 which causes the AML-1 gene to be fused with TEL [12]. Of these different mutations listed that result in an oncogenic AML-1 gene, AML-ETO tends to have the more

predictable projection of the disease as well as being the most frequent abnormality seen between chromosomes 8 and 21, leading to AML [10].

Transcriptional Dysregulation and Different Transcriptional Effects of AMD1/ETO

When looking deeper into the transcriptional activity surrounding the AML-1 gene, its N terminal domain and C terminal domains are important in allowing AML1 to interact with and control the activity of transcriptional factors [3]. For example, the N terminus contains a DNA binding domain and a transcriptional transactivation domain. The DNA binding domain is responsible for binding specific DNA sequences on the promoters of target genes that are involved in hematopoiesis, as this binding allows AML-1 to activate or repress other genes that play huge roles in hematopoiesis [11]. Therefore, mutations in this domain allow for dysfunctional transcriptional regulation resulting in malignancies such as leukemia. However, the C terminal domain of AML1 contains regions that are important in regulating transcriptional activation, such as through the modulation of histone acetylation of different genes [11]. This transcriptional transactivation domain (TAD) is responsible for recruiting co-regulatory proteins influencing chromatin structure, in turn modulating the expression of target genes involved heavily in hematopoiesis [12]. TAD is also known for controlling transcriptional factors that heavily impact and contribute to cell cycle regulators and apoptosis genes which are important for regulating the proliferation of hematopoietic cells. AML1 gene tends to be overexpressed or dysregulated when it is fused with ETO, to create a fusion protein that acts as an oncogenic transcription factor, which dysregulates the normal transcription network of AML1 and their functions. This fusion gene trans-dominantly inhibits the CBF complex which is a heterodimeric transcription factor that is made up of the AML1 and CBF beta that binds at the N terminus of the Runt domain. This CBF complex plays a huge role in transcriptionally regulating different genes that control hematopoiesis. However, when the complex is inhibited, it can contribute to leukemogenesis due to the resulting hematopoietic dysregulation [13].

Signaling Pathways Influenced by the AML1-ETO Fusion Gene and Their Mechanisms of Hematopoietic Dysregulation

AML1-ETO impacts different signaling pathways through inducing certain genes that lead to overexpression which affect downstream signaling pathways. A common example of this would be p15, when p15 is upregulated, it becomes partially responsible for the blockage of hematopoiesis due to how it plays a regulatory role in the progression of various malignant tumors [14]. When AML-1 is overexpressed, it contributes to p15 overstimulation due to how AML-1 overexpression overstimulates the TGF-β signaling pathway. The upregulation of P15, as it is a cyclin dependent kinase inhibitor then leads to the phosphorylation of cyclin dependent kinases in turn causing changes to the cell cycle [15]. This tumor suppressor inhibits the phosphorylation of CDKs in order to control the G1 to S transition, therefore once overexpressed, the transition for many cells to move from G1 to S is halted, thus impacting differentiation in hematopoiesis [16]. Another example of the effects that AML-ETO gene have on the signaling pathways would be through the introduction of the COX/β-catenin–dependent signaling pathways which when upregulated, are responsible for tumor initiation, growth, and the self-renewal of hematopoietic cells and in human myeloid leukemia K562 cells [19]. COX enzymes, COX-1 and COX-2 are crucial in the production of important lipid mediators like prostaglandins and thromboxanes. These lipid mediators, such as prostaglandin E2 (PGE2), play a massive role in the hematopoietic stem cell renewal downstream in the β-catenin signaling pathway [17].

One of the more researched pathways related to hematopoiesis is the thrombopoietin (THPO)/MPL regulatory pathway [20]. THPO, specifically, is responsible for the emergence of hemangioblasts and the migration of hematopoietic cells. MPL mutations are prevalent in AML making it apparent the ligand/receptor complex plays a key role in malignant hematopoiesis [18]. Bcl-xL is upregulated after AML1-ETO expression and it is maintained at these levels via the THPO/MPL signaling pathway, inducing the overexpression of MPL. In the presence of Bcl-xL, the THPO/MPL complex is facilitates cell cycle re-entry and the significant correlation between Bcl-xL and MPL is indicative of an active THPO/MPL/Bcl-xL pathway in leukemic t(8;21)–positive cells [18].

Many of the AML1-ETO leukemic stem cells (LSCs) rely on calcium-dependent signaling therefore calcium enriched pathways are heavily upregulated along with phospholipase C (PLC). PLC is a membrane associated enzyme responsible for the cleavage of phosphatidylinositol 4,5-bisphosphate (PIP2) into IP3 and diacylglycerol (DAG) where IP3 is responsible for the release of intracellular calcium [19]. Of all the 13 different families of PLC, PLCG1 was the most heavily expressed in cells positive for AML1-ETO LSCs. What is more interesting is that while PLCG1 expression is crucial for AML1-ETO LSCs, it is not apparently necessary for calcium specific downstream signaling in normal HSCs [20]. PLCG1 activation is apparent in most leukemia cases and its expression has been linked with chemotherapy resistance where 50% of cases eventually relapse or are diagnosed with a residual disease that affects them for years [21]. Having many signaling pathways influenced by the AML1-ETO complex it proves tricky when finding a general treatment but focusing on specific pathways can allow targeted therapeutic approaches to help alleviate some symptoms of AML.

Epigenetic Modification Discrepancies Between Wild Type AML1 and AML1-ETO leading to Altered Gene Expression

AML1 is a transcriptional factor that plays a crucial role in the regulation of hematopoietic differentiation, and it does so through different mechanisms of epigenetic modifications which are reversible modifications that are imposed on a cell's DNA or histones and alter gene expression without changing the initial DNA sequence of the organism [21]. Different modes of epigenetic modifications include DNA methylation, histone de/acetylation, and the activity of noncoding RNA. AML1 as a protein includes the Runt domain near the N-terminus which is needed for DNA binding at the promoter sequences of target genes or interacts with CBFβ to stabilize DNA binding [4]. The TAD near the C-terminus contains activation and inhibitory domains such as the Ets interacting domain (EID) which is responsible for the protein-protein interactions such as histone acetyltransferase P300 or CREBBP (CBP) [22]. These enzymes induce a histone acetylation of lysine residues on target genes allowing for neutralization of the charge and separation of DNA from histones allowing it to be more available to transcription factors [22]. This modification allows for regular hematopoietic differentiation and regulation.

However, when AML1 is associated with ETO in a fusion oncoprotein, the complex interacts with NCOR and mSin3 on the promoter region and acts as transcriptional repressors. They recruit class 1 histone deacetyltransferases (HDACs) 1–3, which have the opposite effect when compared to the acetyltransferases and close off the histones making DNA unavailable for binding [3]. It is also shown that AML1-ETO complex uses histone acetyltransferase P300 to acetylate lysine 43 enhancing the function of the complex and increasing the renewal activity of hematopoietic progenitor cells, leading to oncogenic properties [23]. AML1-ETO complex also recruits DNA methyltransferase (DNMTs) like DNMT1 and histone methyltransferase EZH1 to methylate lysine 43 enhancing its repressive function on tumor suppressor genes, showing another major epigenetic modification brought upon by the fusion gene [3]. It is important to look at various ways AML1-ETO utilizes epigenetic modifications as it allows for potential corridors for therapeutic treatment associated with AML.

Modes of Escaping Immune System Surveillance Furthering the Influence of AML1-ETO

AML1 is a hematopoietic transcription factor that tends to be inactivated in different myeloblastic and B cell lymphocytic leukemias [24]. Furthermore, it has been found that when AML/ETO fusion protein is overexpressed, it leads to decreased killing and cytotoxicity by natural killer (NK) cells when targeting cells that express AML1-ETO compared to any other cells or cells that do not express the fusion gene. As well, oncogenic AML1 genes allow for decreased production of CD48 mRNA, impacting the presence of activated T cells [25]. This is due to how CD48 plays an activating role on T cells, granulocytes, and other antigen present cells by binding CD2 and intrinsic effects [26]. Additionally, a recent study has shown that an oncogenic AML1 gene, specifically one fused with ETO, has been shown to increase CD48 expression through acetylation mediated with P300, which is a histone acetyltransferase. CD48 is a member of the signaling lymphocytic activation molecule (SLAM) family, which plays a huge role in regulating the ability of NK cells to modulate the immune system and fight pathogens. Therefore, by increasing CD48 expression levels, it would lower the abilities and inhibitions of NK cells to recognize different immune system threats, especially when it comes to other cells expressing AML1/ETO proteins [3].

## Discussion

Future Implications and Therapeutic Approaches for RUNX1/RUNX1T1 AML Treatment

Acute myeloid leukemia is a particularly aggressive cancer affecting the proliferation and renewal of HSCs leading them to be classified as LSCs [2]. When focusing particularly on the AML1-ETO fusion gene, there are many aspects to analyze to develop a deeper understanding on how it plays a role in initiating AML. To accomplish this goal this literature review aimed to assess the transcriptional dysregulation of specific cell cycle checkpoint-regulating proteins. This is to understand how it may impact hematopoietic differentiation leading to the production of pre-leukemic stem cells and contributing to leukemogenesis in AML.

It is crucial to identify what signaling pathways are influenced by AML1-ETO to then understand how these different pathways lead to AML, and how the fusion gene contributed to this. There are many signaling pathways influenced by the fusion gene, but this review focuses on four pathways as they explicitly show the influence of AML1-ETO. The first pathway explored was the TGF-β signaling pathway in which the activity of AML1 induces the over expression of p15 [15]. P15 is a cyclin-dependent kinase inhibitor, and it works through phosphorylating CDKs causing the transition from G1 to S to be halted in the cell cycle. This impacts hematopoiesis and blocks the differentiation of stem and progenitor cells [16]. This in turn leads to an outgrowth of immature cells, that will lead to AML. The COX/β-catenin–dependent signaling pathway is another example of how AML1-ETO induces AML [17]. The fusion gene upregulates the production of COX enzymes which produce lipid mediators responsible for downstream effects that support HSC self-renewal leading to hematopoietic dysregulation and tumor initiation [17]. With the understanding that COX plays a massive role in the formation of LSC, therapeutic approaches containing

COX inhibitors were explored. COX inhibitors or NSAIDs, a class of drugs with anti-inflammatory effects, that are often used as a long-term treatment for patients with AML and there are reports suggesting that NSAIDs reduce the risks for COX-2-PGE2-β-catenin signaling pathway induced cancers [27]. COX inhibition has been shown to impede the development and progression of AML however there are some concerns of thrombocytopenia developing from the anti-platelet activity from the treatment. However, this activity is more strongly associated with COX-1-selective inhibitor (SC-560) or nonselective COX inhibitor indomethacin (INDM) and less so with COX-2-selective inhibitors (NS-398 and nimesulide) [28]. AML1-ETO also affects the THPO/MPL signaling pathway through upregulating the expression of Bcl-xL resulting in the increase of MPL. This affects many things like cell cycle re-entry, emergence of hemangioblasts, and the migration of hematopoietic cells leading to AML [18]. Bcl-xL could be a potential target for therapeutic approaches but there are some questions about specificity and differentiating between normal and AML states. There has also been some research on approaches that include monoclonal antibodies, and these antibodies work by neutralizing the interaction between THPO and MPL [18]. There is also potential for small molecular inhibitors and peptides as they can prevent THPO from binding to the MPL receptor. JAK2 inhibitors also can block downstream signaling cascades making them another great option for treatment [18]. The final signaling pathway explored was PLCgamma 1 (PLCG1). AML1-ETO upregulates PLC which induces downstream effects through the increase of intracellular Ca++ and it is evident in a multitude of AML cases [20]. PLCG1 has been shown to not be essential for maintenance of normal Hematopoietic stem and progenitor cells (HSPCs). Due to the lack of need for specificity PLCG1 can be identified as an important target for AML treatment and it can be predicted that it will lead to therapeutic success when treating AML1-ETO AML [20].

It was also important to understand how epigenetic modifications are induced by the AML1-ETO transcription factor and how it affects histone and DNA activity leading to AML. AML1 is a transcription factor that induces epigenetic modification via DNA methylation and histone modifications including de/acetylation, as discussed above [21]. The unfused AML1 gene contains an EID domain which facilitates the recruitment of histone acetyltransferase P300 or CREBBP [22]. These enzymes work by acetylating lysine residues, loosening how tightly the histones wrap around the DNA making it more available for the transcription factor AML1 to bind. This in turn allows for a more active regulation of hematopoiesis, limiting the release of premature stem cells leading to AML [23]. On the other hand, when AML1 and ETO become fused it binds to transcriptional repressors NCOR and mSin3, and they recruit class I HDACs 1–3 [2]. These enzymes have the opposite effect on DNA and histones and close the DNA off from transcription which in turn leads to dysregulation of hematopoiesis. AML1-ETO also recruits DNMT1 and histone methyltransferase EZH1 to methylate lysine on tumor suppressor genes. HDAC inhibitors and hypomethylating agents have been tested in clinical trials however these results proved disappointing [29] when compared to the preclinical trials [30]. Another approach would be to inhibit the P300 facilitated site specific acetylation of NHR1 domain on ETO using RNA interference or chemical inhibition. Studies demonstrated P300 inhibition resulted in reduced levels of effector proteins essential for cell renewal, solidifying P300 as ideal target for drugs and therapy [31].

Finally, the method that AML1-ETO escapes immune system surveillance was investigated to identify the impacts of the oncogenic gene on passive and adaptive immunity. It has been found that AML1-ETO has major impacts on NK surveillance and CD48 expression, which are both integral to immune system stability. Studies have shown that downregulated CD48 which is common in those with AML, lower NK immune surveillance [7]. Since CD48 mediates acetylation which is a form of epigenetics, it shows us that epigenetic drugs and treatments that target epigenetics, can provide therapeutic effects, and prevent AML immune escape, and should therefore be an area of research that should be researched in the future [21].

## Conclusion

In conclusion, AML is a complex and highly heterogeneous disease that is caused by the alteration of many pathways, signals, and molecules leading to the production of LSCs. AML1-ETO has many modes of LSC production whether it be through dysregulation of cell cycle checkpoint, altered signaling pathways, epigenetic modifications or changes that allow for target gene expression to escape immune surveillance. However, through analyzing the multitude of ways AML1-ETO affects the homeostasis of the body, therapeutic approaches can be formulated to help treat AML, but future work is suggested to further develop our understanding.

## List of Abbreviations Used

AML: acute myeloid leukemia
TAD: transcriptional transactivation domain
NK: natural killer
HSC: hematopoietic stem cells
CBF: core binding factor
THPO: thrombopoietin
EID: ETS interacting domain
HDAC: histone deacetyltransferases
DNMT: DNA methyltransferase
CDK: cyclin dependent kinase
HSPC: hematopoietic stem and progenitor cells
SLAM: signaling lymphocytic activation molecule
mRNA: messenger ribonucleic acid
LSC: leukemic stem cells

COX: cyclooxygenase
NSAID: nonsteroidal anti-inflammatory drugs
MPL: myeloproliferative leukemia

**Conflicts of Interest**
The authors declare no conflicts of interest.

**Ethics Approval and/or Participant Consent**
As this paper is a review, no ethics approval was required.

**Authors' Contributions**
KKT: made equal contributions to the entirety of this manuscript as well as the conception and design of the work and is to be held equally accountable for all aspects. This includes drafting the manuscript, critically examining it for its content and collectively approving the final version to be submitted.
LB: made equal contributions to the entirety of this manuscript as well as the conception and design of the work and is to be held equally accountable for all aspects. This includes drafting the manuscript, critically examining it for its content and collectively approving the final version to be submitted.

**Acknowledgements**
We would like to convey our heartfelt appreciation to our mentor, Emily Hartung, for her guidance and support throughout this investigation.

**Funding**
This paper was not funded.

**References**
[1] Siegel RL, Miller KD, Wagle NS, Jemal A. Cancer statistics, 2023. CA Cancer J Clin. 2023;73(1):17-48. https://doi.org/10.3322/caac.21763
[2] Velten L, Story BA, Malmierca PH, Raffel S, Leonce DR, Milbank J, et al. Identification of leukemic and pre-leukemic stem cells by clonal tracking from single-cell transcriptomics. Nat Commun. 2021 Mar 1;12(1):1366. https://doi.org/10.1038/s41467-021-21650-1
[3] Lagunas-Rangel FA, Chávez-Valencia V, Gómez-Guijosa MÁ, Cortes-Penagos C. Acute Myeloid Leukemia-Genetic Alterations and Their Clinical Prognosis. Int J Hematol Oncol Stem Cell Res. 2017;11(4):328–339. https://pubmed.ncbi.nlm.nih.gov/29340131
[4] Elaine Dzierzak, Anna Bigas. Blood Development: Hematopoietic Stem Cell Dependence and Independence. Cell Stem Cell. 2018;22(5):639-651. https://doi.org/10.1016/j.stem.2018.04.015
[5] Mead AJ, Mullally A. Myeloproliferative neoplasm stem cells. Blood. 2017;129(12):1607-1616. https://doi.org/10.1182/blood-2016-10-696005
[6] Tonks A, Pearn L, Tonks AJ, Pearce L, Hoy T, Phillips S, Fisher J, Downing JR, Burnett AK, Darley RL. The AML1-ETO fusion gene promotes extensive self-renewal of human primary erythroid cells. Blood. 2003;101(2):624-632. https://doi.org/10.1182/blood-2002-06-1732
[7] Rejeski K, Duque-Afonso J, Lübbert M. AML1/ETO and its function as a regulator of gene transcription via epigenetic mechanisms. Oncogene. 2021 Jul 30;40:5665–5676. https://doi.org/10.1038/s41388-021-01952-w
[8] Fukunaga J, Nomura Y, Tanaka Y, Amano R, Tanaka T, Nakamura Y, Kawai G, Sakamoto T, Kozu T. The Runt domain of AML1 (RUNX1) binds a sequence-conserved RNA motif that mimics a DNA element. RNA (New York, N.Y.). 2013;19(7):927-936. https://doi.org/10.1261%2Frna.037879.112
[9] Jung, J., Cho, B.-S., Kim, H.-J., Han, E., Jang, W., Han, K., Lee, J.-W., Chung, N.-G., Cho, B., Kim, M., & Kim, Y. (2019). Reclassification of Acute Myeloid Leukemia According to the 2016 WHO Classification. Annals of Laboratory Medicine, 39(3), 311–316. https://doi.org/10.3343/alm.2019.39.3.311.
[10] Lausten-Thomsen U, Madsen HO, Vestergaard TR, Hjalgrim H, Nersting J, Schmiegelow K. Prevalence of t(12;21)[ETV6-RUNX1]-positive cells in healthy neonates. Blood. 2011;117:186-9. https://doi.org/10.1182/blood-2010-05-282764
[11] DeKelver RC, Yan M, Ahn EY, Shia WJ, Speck NA, Zhang DE. Attenuation of AML1-ETO cellular dysregulation correlates with increased leukemogenic potential. Blood. 2013;121(18):3714-3717. https://doi.org/10.1182/blood-2012-11-465641
[12] Wang Z, Guan W, Wang M, Chen J, Zhang L, Xiao Y, Wang L, Li Y, Yu L. AML1-ETO inhibits acute myeloid leukemia immune escape by CD48. Leuk Lymphoma. 2021;62(4):937-943. https://doi.org/10.1080/10428194.2020.1849680
[13] Yan M, Ahn EY, Hiebert SW, Zhang DE. RUNX1/AML1 DNA-binding domain and ETO/MTG8 NHR2-dimerization domain are critical to AML1-ETO9a leukemogenesis. Blood. 2009;113(4):883-886. https://doi.org/10.1182/blood-2008-04-153742
[14] Elias S, Yamin R, Golomb L, Tsukerman P, Stanietsky-Kaynan N, Ben-Yehuda D, Mandelboim O. Immune evasion by oncogenic proteins of acute myeloid leukemia. Blood. 2014;123(10):1535-1543. https://doi.org/10.1182/blood-2013-09-526590
[15] Loh ML, Rubnitz JE. TEL/AML1-positive pediatric leukemia: prognostic significance and therapeutic approaches. Curr Opin Hematol. 2002;9(4):345-352. https://doi.org/10.1097/00062752-200207000-00013
[16] Bernardin F, Friedman AD. AML1 stimulates G1 to S progression via its transactivation domain. Oncogene. 2002;21(20):3247-3252. https://doi.org/10.1038/sj.onc.1205447

[17] Asou N, Yanagida M, Huang L, Yamamoto M, Shigesada K, Mitsuya H, Ito Y, Osato M. Concurrent transcriptional deregulation of AML1/RUNX1 and GATA factors by the AML1-TRPS1 chimeric gene in t(8;21)(q24;q22) acute myeloid leukemia. Blood. 2007;109(9):4023-4027. https://doi.org/10.1182/blood-2006-01-031781

[18] Yu C, Wang W. Relationship Between P15 Gene Mutation and Formation and Metastasis of Malignant Osteosarcoma. Med Sci Monit. 2016;22:656-661. https://doi.org/10.12659/msm.895022

[19] Horowitz LF, Hirdes W, Suh BC, Hilgemann DW, Mackie K, Hille B. Phospholipase C in Living Cells: Activation, Inhibition, Ca2+ Requirement, and Regulation of M Current. J Gen Physiol. 2005 Sep 1;126(3):243–262. https://doi.org/10.1085/jgp.200509309

[20] Matsumoto A, Yoshida T, Shima T, Yamasaki K, Tadagaki K, Kondo N, Kuwahara Y, Zhang DE, Okuda T. C11orf21, a novel RUNX1 target gene, is down-regulated by RUNX1-ETO. BBA Adv. 2022;2:100047. https://doi.org/10.1016/j.bbadva.2022.100047

[21] Sun W, Yi D, Zhu L, Zeng J, Liu Y, Chang J, Teng J, Zhang Y, Dong Y, Pan X, Chen Y, Zhou Y, Lai M, Zhou Q, Liu J, Chen B, Ma F. RUNX1 overexpression triggers TGF-β signaling to upregulate p15 and thereby blocks early hematopoiesis by inducing cell cycle arrest. Stem Cell Res. 2022;60:102694. https://doi.org/10.15283/ijsc20033

[22] Zhang Y, Wang J, Wheat J, Chen X, Jin S, Sadrzadeh H, Fathi AT, Peterson RT, Kung AL, Sweetser DA, Yeh JR. AML1-ETO mediates hematopoietic self-renewal and leukemogenesis through a COX/β-catenin signaling pathway. Blood. 2013;121(24):4906-4916. https://doi.org/10.1182/blood-2012-08-447763

[23] Yan M, Kanbe E, Peterson LF, Boyapati A, Miao Y, Wang Y, et al. A previously unidentified alternatively spliced isoform of t(8;21) transcript promotes leukemogenesis. Nat Med. 2006;12:945–9. https://doi.org/10.1038/nm1443

[24] Wang L, Gural A, Sun XJ, Zhao X, Perna F, Huang G, et al. The leukemogenicity of AML1-ETO is dependent on site-specific lysine acetylation. Science. 2011;333:765–9. https://doi.org/10.1126/science.1201662

[25] Chou FS, Griesinger A, Wunderlich M, Lin S, Link KA, Shrestha M, Goyama S, Mizukawa B, Shen S, Marcucci G, Mulloy JC. The thrombopoietin/MPL/Bcl-xL pathway is essential for survival and self-renewal in human preleukemia induced by AML1-ETO. Blood. 2012;120(4):709-719. https://doi.org/10.1182/blood-2012-01-403212

[26] Schnoeder TM, Schwarzer A, Jayavelu AK, Hsu CJ, Kirkpatrick J, Döhner K, Perner F, Eifert T, Huber N, Arreba-Tutusaus P, Dolnik A, Assi SA, Nafria M, Jiang L, Dai YT, Chen Z, Chen SJ, Kellaway SG, Ptasinska A, Ng ES, Heidel FH. PLCG1 is required for AML1-ETO leukemia stem cell self-renewal. Blood. 2022;139(7):1080-1097. https://doi.org/10.1182/blood.2021012778

[27] Feinberg AP, Levchenko A. Epigenetics as a mediator of plasticity in cancer. Science. 2023;379(6632):eaaw3835. https://doi.org/10.1126/science.aaw3835

[28] Fang JY, Lu YY. Effects of histone acetylation and DNA methylation on p21(WAF1) regulation. World J Gastroenterol. 2002;8(3):400-405. https://doi.org/10.3748/wjg.v8.i3.400

[29] Shlomo Elias, Rachel Yamin, Lior Golomb, Pinchas Tsukerman, Noah Stanietsky-Kaynan, Dina Ben-Yehuda, Ofer Mandelboim. Immune evasion by oncogenic proteins of acute myeloid leukemia. Blood. 2014;123(10):1535-1543. https://doi.org/10.1182/blood-2013-09-526590

[30] McArdel SL, Terhorst C, Sharpe AH. Roles of CD48 in regulating immunity and tolerance. Clin Immunol. 2016;164:10-20. https://doi.org/10.1016/j.clim.2016.01.008

[31] Arber N, Eagle CJ, Spicak J, et al. PreSAP Trial Investigators. Celecoxib for the prevention of colorectal adenomatous polyps. N Engl J Med. 2006;355(9):885-895. https://doi.org/10.1056/nejmoa061652

**Article Information**
Managing Editor: Jeremy Y. Ng
Peer Reviewers: Emily Hartung, Liliane Kreuder
Article Dates: Received Sep 16 23; Accepted Dec 12 23; Published Mar 08 24

**Citation**
Please cite this article as follows:
Thanaraj KK, Busanelli L. Telemedicine for mental disorders: A review of treatment outcomes, patient satisfaction, and reliability comparisons with in-person care. URNCST Journal. 2024 Mar 08: 8(3).
https://urncst.com/index.php/urncst/article/view/542
DOI Link: https://doi.org/10.26685/urncst.542