UMSHA Press

AJMB
Avicenna Journal of Medical Biochemistry

Avicenna J Med Biochem. 2025;13(1):51-59. doi:10.34172/ajmb.2627

http://ajmb.umsha.ac.ir

Review Article

Targeting Signal Transducer and Activator of Transcription 3 in Acute Myeloid Leukemia: From Oncogenic Mechanisms and Genetic Variants to Therapeutic Inhibition

Miaad Banay Golrizi[1], Mohammad Hossein Shams[2,3], Nima Nezami[4], Hassan Rafieemehr[5*]

[1]Department of Molecular Virology, Farzan Molecular and Pathobiology Laboratory, Hamadan, Iran
[2]Department of Biochemistry, School of Medicine, Iran University of Medical Sciences, Tehran, Iran
[3]Student Research Committee, Iran University of Medical Sciences, Tehran, Iran
[4]Student Research Committee, Hamadan University of Medical Sciences, Hamadan, Iran
[5]Department of Medical Laboratory Sciences, School of Alied Medical Sciences, Hamadan University of Medical Sciences, Hamadan, Iran

Article history:
Received: July 25, 2025
Revised: September 8, 2025
Accepted: September 21, 2025
ePublished: October 31, 2025

***Corresponding author:**
Hassan Rafieemehr,
Email: ha.rafee@umsha.ac.ir

Abstract

Acute myeloid leukemia (AML) is a hematologic malignancy that is characterized by impaired proliferation and differentiation of hematopoietic stem cells, often leading to poor prognosis. Identifying new therapeutic targets is crucial for improving treatment outcomes. Signal transducer and activator of transcription 3 (STAT3) is a critical oncogene that is implicated in AML. In addition, it is a transcription factor that is activated via phosphorylation by members of the Janus kinase protein family and regulates the expression of several genes involved in oncogenic pathways. This research reviewed studies evaluating the role of STAT3 in AML. This review study investigated over 50 relevant articles focusing on STAT3-related genetic alterations, including mutations (e.g., STAT3-RARα fusion) and single-nucleotide polymorphisms, such as rs1905339 (A>G), rs9909659 (G/A), and rs17886724 (T/C). It also evaluated current experimental and clinical research on STAT3-targeted therapies, including compounds such as trametinib, artesunate, OPB-51602, napabucasin, atovaquone, ortho-topolin, and W1046. STAT3 genomic variations were linked to AML prognosis and disease progression. According to preclinical and clinical studies, inhibiting the expression of STAT3 could impair the survival of AML blasts and improve the prognosis of patients. However, there is currently no approved, effective STAT3-targeting therapy available for AML patients. Overall, STAT3 dysfunction plays a pivotal role in the progression of AML. Nonetheless, further investigations into STAT3-targeted therapies may lead to the development of effective compounds, offering improved prognosis and treatment strategies for AML patients.

Keywords: Acute myeloid leukemia, STAT3, Pathogenesis, Mutation, Polymorphism, Clinical effects

Please cite this article as follows: Banay Golrizi M, Shams MH, Nezami N, Rafieemehr H. Targeting signal transducer and activator of transcription 3 in acute myeloid leukemia: from oncogenic mechanisms and genetic variants to therapeutic inhibition. Avicenna J Med Biochem. 2025;13(1):51-59. doi:10.34172/ajmb.2627

Background

Leukemias are a group of multifactorial disorders caused by the uncontrolled proliferation of bone marrow hematopoietic lineages, which occur after the accumulation of mutations and chromosomal abnormalities. In addition, acute myeloid leukemia (AML) is a common hematological malignancy that is featured by impaired proliferation and differentiation of myeloid progenitor cells or hematopoietic stem cells and the accumulation of immature blasts in the bone marrow and peripheral blood (1). According to the World Health Organization standards, the diagnosis of AML is based on cytogenetic, morphological, and immunological changes and molecular characteristics. Despite the high prevalence of this malignancy in old age (65–70 years old), many cases of pediatric AML have been reported as well. Chromosome abnormalities are observed in 50–60% of AML cases, and these abnormalities are the basis of different challenges, such as resistance to treatment, recurrence, and reduced prognosis of patients (1-3). AML is usually characterized by rapid progression and genetic heterogeneity with a poor prognosis and therapy resistance (4). It is associated with an overall 5-year survival rate equal to 25%. Although these cases and chemotherapy challenges (e.g., bone marrow niche or serum trace element alterations) are considered obstacles to the treatment of the disease, the identification of important and common molecular markers in the process

of pathogenesis and development of the disease to target therapy (5-8) will yield promising results.

Molecular markers are biomarkers that appear due to differences in the expression and function of genes compared to normal cells. Due to their presence in signaling pathways and other cellular mechanisms, these markers are highly essential in the progression of malignancies, so that drug compounds, such as Fedratinib (a strong inhibitor of the Janus kinase/signal transducer and activator of transcription [JAK/STAT] signaling pathway), have led to a favorable prognosis in 78% of AML cases (6). This vital signaling pathway (JAK-STAT signal transmission pathway) includes many molecular markers of different diseases. STAT proteins, important members of this key pathway, play an essential role in various biological functions, including cell proliferation and survival, angiogenesis, apoptosis, and inflammation. Accordingly, aberrant STAT activation has been widely reported in some human diseases, especially immunodeficiency, inflammation, cancers, and other proliferative disorders (9). The function of STAT proteins is generally influenced by their association with JAK family proteins, which are receptor-associated tyrosine kinases. These enzymes include JAK1, JAK2, JAK3, and TYK2 in mammals (10). When cytokines or growth factors bind to cell membrane receptors, these enzymes phosphorylate and activate a wide range of STAT family proteins, such as STAT1, STAT2, STAT3, STAT4, STAT5a, STAT5b, and STAT6. The family has a common molecular topology that is organized in a special way (10). It is noteworthy that the STAT protein family must be dimerized to regulate gene transcription and be transported to the nucleus after activation (2). STAT3 is a member of this family that acts as an oncogene in a wide range of solid tumors, including breast, prostate, lung, pancreatic, colorectal, and hematological malignancies. In addition, several studies demonstrated a significant increase in the expression of STAT3 in AML samples compared to the control group (about 44%–76% of the initial samples of AML patients have shown increased activation of STAT3 and STAT5a/b phosphorylation). Further, previous research reported patients with abnormal phosphorylation in the STAT3 protein found in AML samples. Its extent is related to interleukin (IL)-6 signaling (11). Likewise, Shagerdi Esmaeli et al confirmed the role of homeobox transcript antisense intergenic ribonucleic acid (a long non-coding RNA) in AML proliferation by increasing the expression of STAT3 (12). The STAT3 protein has an important role in processes such as tumor progression, metastasis, and angiogenesis. Its antagonists considerably affect pathogenesis inhibition. Considering that this protein is malignant, existing studies indicate that the inhibition of STAT3 expression is a treatment for some malignancies (e.g., lung, colorectal, prostate, and leukemia). The upcoming review article examines the difference in the expression, genetic variations, ontology, and targeted therapy of STAT3 in AML in order to better understand this leukemia's pathogenesis and help future studies expand its targeted therapy.

Basic Function and Activity of Signal Transducer and Activator of Transcription 3 Pathways and the Survival or Apoptosis of Blast Cells

The STAT protein forms part of a crucial intracellular pathway that interacts with external signaling molecules, including cytokines (e.g., IL-6, IL-27, IL-31, and IL-22), platelet-derived growth factor, leukemia inhibitory factor, and cardiotrophin-like cytokine factor 1. Moreover, their receptors interact and lead to the regulation of gene transcription. STAT family proteins have several amino acids between 750 and 850. Furthermore, STAT3 has 770 amino acids, and its coding gene is located at position 17q21. All STAT proteins act similarly and perform many vital functions in the cell. One of their most distinctive features is the Src homology 2 (SH2) domain, located at the protein's C end (13). The SH2 domain (Figure 1) is required for several steps in STAT signaling because it recognizes and binds phosphotyrosine motifs, allowing for the combination of extracellular chemicals with the cell membrane receptor responsible for signal transduction (2). In addition, activating the JAK protein facilitates recognition and binding (2). During JAK-STAT signaling, the binding of the extracellular ligand leads to its conformational change, and this structural change is the basis for the binding of the JAK family intracellular kinases. After binding to the receptor, JAK leads to the binding of STAT3 to this receptor region through the phosphorylation of its intracellular domain. After STAT3 binds to the receptor, JAK phosphorylates its SH2 domain from tyrosine 705 (Y705). The STAT3 homodimer or STAT3-STAT1 heterodimer is formed as a result of this phosphorylation. The resulting dimer will act as a transcription factor by crossing the nuclear membrane and binding to the TTCN3GAA sequence (Figure 1). Additionally, STAT3 regulates the expression of important genes in cell cycle growth (progression), genes encoding cell cycle checkpoint proteins, and apoptosis. This protein will also decrease the expression of genes encoding cell cycle checkpoint proteins (e.g., P53, P21, and P27) but will

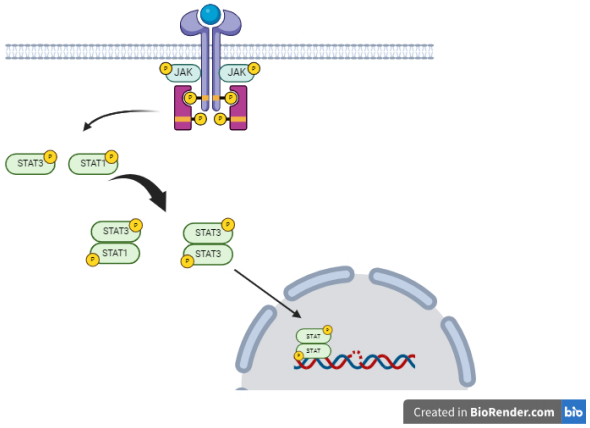

Figure 1. The JAK-STAT Signaling Pathway. *Note.* JAK: Janus kinase; STAT3: Signal transducer and activator of transcription 3

increase the expression of genes involved in cell growth (e.g., cyclins D1, D2, D3, A, and B, Cdc25A, and Cdc2). On the other hand, STAT3 leads to a decrease in the expression of genes involved in apoptosis (e.g., -Xl, IAPs, and Mcl-1). In addition, according to available studies, this protein will lead to the expression of SLC1A5 by the *MYC* gene. It also plays a significant role in oxidative phosphorylation and is effective in the pathogenesis of leukemic cells. Based on the studies, the β isoform, unlike α, acts as an anti-tumor agent in such a way that the expression ratio of STAT3 β/α is related to the increase in the overall survival of patients (14-16). Therefore, to achieve the appropriate treatment, the α isoform of this protein should be antagonistic.

Activation Cycle of Signal Transducer and Activator of Transcription 3

During signal transduction, a STAT protein becomes tyrosine-phosphorylated by a member of the JAK family. Tyrosine-phosphorylated STAT proteins then dimerize through their SH2 domains. The STAT3 dimer subsequently translocates into the nucleus, where it acts as a transcription factor. The activation of the STAT3 pathway is a transient process that is terminated by several negative regulators. These regulators may inhibit the pathway or directly inactivate phosphorylated STAT3. In tumor cells, however, such regulators are often inactive or unable to effectively suppress the pathway. The negative regulators of STAT3 comprise several groups of proteins with diverse mechanisms of action (17).

The protein inhibitor of activated STAT (PIAS) family consists of genes sharing approximately 40% sequence homology. All PIAS genes encode proteins containing a conserved zinc finger domain in their central region. These proteins negatively regulate STAT3 and various signaling pathways by blocking deoxyribonucleic acid (DNA) binding, activating co-repressors, and facilitating SUMOylation. Furthermore, PIAS proteins can bind to STAT3 dimers and mediate their inactivation. Notably, PIAS3 primarily binds to STAT3 and is undetectable in various malignancies (18-20).

The suppressor of cytokine signaling family includes eight SH2 domain-containing proteins that act as negative regulators of the JAK/STAT pathway. Hypermethylation and inactivation of suppressor of cytokine signaling 1 have been reported in AML; its activation suppresses leukemia cell growth (21,22).

Protein tyrosine phosphatases are another group of STAT3 inhibitors. This family comprises several phosphatases that dephosphorylate phospho-tyrosine residues in their substrates. Considering that tyrosine phosphorylation is the key activation mechanism of STAT3, protein tyrosine phosphatases serve as essential negative regulators of this pathway (20).

Activity of Signal Transducer and Activator of Transcription 3 Signaling Pathways and Survival or Apoptosis of Blast Cells

Some studies have identified the STAT3 protein as a significant oncogene responsible for 70% of malignancies. This issue is important in regulating the expression of many genes encoding anti-apoptotic and growth factors by this transcription factor (23,24). Reducing apoptosis and increasing the survival of leukemic blasts are of interest; in such a way, inhibiting the expression of this protein using small interfering RNA will lead to the stimulation of apoptosis in AML blasts (10,25). It will increase the survival and proliferation of leukemic blasts. However, the exact mechanism of this process in AML is unknown due to the lack of sufficient understanding of STAT3 targets. However, the association of this protein with patients' poor prognosis has been proven. In some studies, deletion mutation and lack of the *STAT3* gene product have led to the increased differentiation of hematopoietic stem cells into cells such as macrophages and neutrophils, indicating the important role of the protein in maintaining the fundamentality of bone marrow cells. Moreover, several studies demonstrated increased STAT3 phosphorylation in several malignancies. Conversely, most of these changes inhibit tumorigenesis and processes promoting malignancy. Although most STAT3 phosphorylations are anti-tumor, Y705 phosphorylation (abundant in AML) will lead to the increased stemness of cells (26).

Structure of Signal Transducer and Activator of Transcription 3

The STAT3 polypeptide consists of 770 amino acids and six conserved domains, including the N-terminal domain, coiled-coil domain, DNA-binding domain, linker domain, SH2 domain, and C-terminal domain (Figure 2). These domains have significant roles in STAT3 functions. The N-terminal domain mediates the binding of STAT3 or other proteins, leading to its dimerization, tetramerization, or formation of heterodimerized complexes. These binding activities mediate DNA binding, localization, and transcription regulatory effects of STAT3 (17). In addition, processes such as receptor binding, phosphorylation, DNA binding, and dimerization are mediated by the coiled-coil domain (27). The tyrosine residue, which is mentioned as the phosphorylation target of JAK, is part of the C-terminal domain (also referred to as the trans-

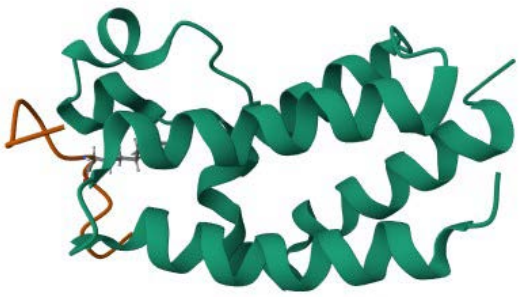

Figure 2. The Three-Dimensional Structure of STAT3. *Note*. STAT3: Signal transducer and activator of transcription 3. *Source*. The PDBe--KB Data Bank (https://www.ebi.ac.uk/pdbe/pdbe-kb/)

activation domain) (28).

Transcriptional Targets of Signal Transducer and Activator of Transcription 3

In the current study, the TFlink database (https://tflink.net/) and available literature were used to identify the transcriptional targets of STAT3. The previously identified transcriptional targets of STAT3 are depicted in Figure 3 (29).

Genetic Changes of Signal Transducer and Activator of Transcription 3 and Their Effect on Acute Myeloid Leukemia

Considering the important role of the STAT3 protein in different cellular processes, the strong impact of genetic variants of this protein on the pathogenesis of AML is not far from expected. Generally, mutations and polymorphisms are the most essential changes in genetic sequences. Mutations include any genetic changes in gene sequences that affect people's phenotype. On the other hand, polymorphisms are alterations without an obvious impact on the phenotype and have a high frequency in the human population (30).

Mutations

Signal Transducer and Activator of Transcription 3-Retinoic Acid Receptor Alpha Fusion

Mutations are one of the most fundamental causes of many malignancies and include various types (e.g., point mutations, deletions, insertions, or fusions). The gene fusion between RARA and PML is one of the vital types of gene fusions in AML. This mutation has an effective role in the occurrence and progression of the pathogenesis of the AML M3 subgroup. There are also cases of this type of leukemia with t(15;17)(q22;q12) chromosomal translocation (31,32). According to the study by Yao et al, the *STAT3-RARA* gene fusion is one of the gene fusions observed in some M3 AML patients without commonly expressed mutations. In this study, researchers investigated the mentioned fusion using a whole-genome sequencing technique in 2 patients with acute promyeloid leukemia. The intended fusion leads to the connection of the functional domains of both genes at the protein level and increases the rate of homodimerization and excessive activation of proteins. According to studies, samples containing this fusion are sensitive to all-trans retinoic acid (33).

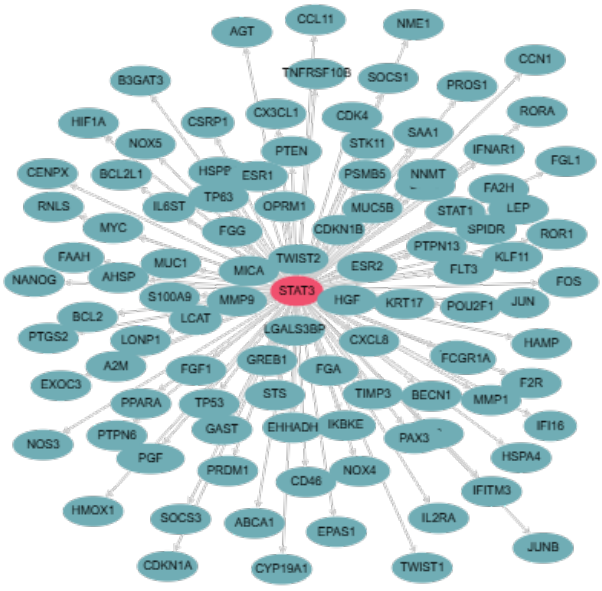

Figure 3. Genes Targeted by STAT3. *Note*. STAT3: Signal transducer and activator of transcription 3. *Source*. The TFlink database (https://tflink.net/)

Polymorphisms

Polymorphisms are a large group of human genomic variations that have a frequency of more than 1% in the human population. Unlike mutations, they do not have an obvious and direct effect on people's traits. The importance of these changes and their investigation in the field of oncology is related to their impact on people's susceptibility to various diseases, individual differences in response to multiple treatments, and differences in the immunological responses of individuals in multiple diseases (30). Considering the important role of STATs in the pathogenesis of various cancers, it is suggested that researchers evaluate the effect of polymorphisms in these genes on the prognosis and pathogenesis of cancers. For example, Xu et al indicated that the rs1905339 (A > G) polymorphism in STAT3 will lead to an increased risk of breast cancer (34). They investigated the relationship between single-nucleotide polymorphisms in the *STAT3* gene (including rs9909659G/A and rs17886724T/C) and the prognosis of patients with AML and found that the TC/CC genotype of rs17886724 has a higher frequency than the T/T genotype in the group with poor prognosis. In addition, Chen et al. and Zhong et al reported that the GG genotype of rs9909659 significantly reduces patients' recovery rate (35,36). However, regarding nucleotides in genes related to the immune system, Liu et al failed to prove the relationship between STAT3 polymorphism and the prognosis of AML patients (37).

Signal Transducer and Activator of Transcription 3 as a Therapeutic Target in Acute Myeloid Leukemia

STAT proteins have a dual function in the cell, acting as a messenger between the cell surface and the nucleus while being directly involved in transcriptional regulation. Considering the important upstream role of STAT3 in metabolism, cell division, proliferation, and inhibition of myeloid differentiation, its inhibition can be regarded as a suitable treatment strategy for AML patients, as many studies have been conducted in this regard (Table 1) (5). For example, Minus et al inhibited STAT3 in AML xenograft cells using naphthalene sulfonamide and hybrid sulfonamide-rhodium (38). Likewise, Amaya et al used SF25 as an effective antagonist of the DNA binding domain in STAT3 (15). They also concluded that the inhibition of this protein leads to a decrease in oxygen

Table 1. Recently Formulated Anti-STAT3 Agents

Agent Name	Compound	Targeting Mechanism	Effect	AML Subclass/Cell Line	Research
AZD9150	Antisense oligonucleotides	Reducing the gene expression by targeting the gene sequence	This agent will increase hematopoietic differentiation in AML.	Some AML and MDS cell lines include NB4, MOLM14, MDS-L, MV411, KG1, MOLM13, KT1, and CMK	Shastri et al (42)
Trametinib	Small molecules	Enhancing the STAT3 level in combination with all-trans retinoic acid	Increasing STAT3 is necessary for the differentiation of the HL60 cell line.	HL60 cell line	Lu et al (50)
Artesunate	Small molecules	Reducing STAT3 expression	It increases apoptosis by activating caspase 3 and 8.	THP-1 cell line (acute monocytic leukemia cell line)	Tan et al (51)
3aa	Small molecules from naphthalene sulfonamide inhibitors	Inhibiting the STAT3 phosphorylation through G-CSF	It increases apoptosis.	Kasumi-1 human AML cells	Minus et al (38)
Curcumin-Thalidomide combination	Small molecules	Inhibiting the STAT3 expression	It increases apoptosis.	U937 and KG-1 cell lines	Mohammadi Kian et al (39)
OPB-51602	Small molecules	Inhibiting the STAT3 phosphorylation	It clarifies the effectiveness of OPB-51602.	A clinical trial on patients with AML M4, M2, and M6	Ogura et al (40)
Napabucasin	Small molecules	Inducing DNA damage	It inhibits the STAT3 pathway.	THP-1, U937, OCI-AML3, and Molm-13 cell lines	Bi et al (41)
STAT3 decoy oligodeoxynucleotide	Oligonucleotides	Attaching to DNA-binding domain of STAT3	It inhibits STAT3 transcriptional activity.	M1, M4, M5, AML-MLD, and AML-NOS	Zhang et al (43)
Atovaquone	Naphthoquinone-Based small molecule	Decreasing STAT3 activation	It reduces cell survival and proliferation.	THP-1, MV4-11, MOLM3, NB4, Kasumi, HL60, KGL, and HEL	Lee et al, Xiang et al, and Minus et al (38,44, 45)
Ortho-Topolin	A cytokine secreted from m Populus × robusta leaves	Inhibiting the STAT3 phosphorylation	It increases apoptosis.	HL-60 cell line	Wang et al (48)
W1046	Small molecule	Decreasing STAT3 activation	It reduces V-domain Ig suppressor of T cell activation gene expression.	MOLM13 and MV4	Mo et al (49)

Note. AML: Acute myeloid leukemia; MDS: Myelodysplastic syndrome; STAT3: Signal transducer and activator of transcription 3; Ig: Immunoglobulin.

consumption rate in the sample. In such a way, inhibiting this protein specifically leads to the death of leukemic stem cells without affecting the life of hematopoietic stem cells. Likewise, Mohammadi Kian et al confirmed the negative effect of the thalidomide-curcumin combination on the survival and proliferation of KG-1 and U937 cell lines by reducing STAT3 expression (39). Similarly, Ogura et al, in their phase I clinical trial, utilized oral OPB-51602 to inhibit STAT3 in patients with hematologic malignancies with a history of relapse or resistance to treatment with a "3 + 3" intensification design. Although they found no clear therapeutic effect, a stable condition emerged in 2 patients with AML (40). In their in vitro and in vivo study, Bi et al inhibited AML cell lines in the laboratory and animal models using BBI608 and indicated that this compound inhibits the STAT3 signaling pathway (41). In their study, Shastri et al, in addition to reporting the negative effect of increased expression of STAT3 in blood malignancy sufferers, succeeded in stimulating the differentiation and inhibiting the pathogenesis of AML cell lines and other malignancies using the STAT3 antisense oligonucleotide inhibitor (AZD9150) (42). Zhang et al also used small interfering RNA binding to the CpG island, which affected STAT3 expression (CpG-STAT3dODN) in limiting AML cell lines. Based on their results, CpG-STAT3dODN can be a suitable candidate for inhibiting the function of STAT3 in AML and other blood malignancies (43). According to existing studies, naphthoquinone and its derivatives also have inhibitory and negative effects on AML cells (44). One of the important targets of these compounds is STAT3. For example, Xiang et al concluded that atovaquone can prevent the phosphorylation and activation of STAT3 by acting as an inhibitor (45). Similarly, Delebinski et al evaluated the effect of ViscumTT (mistletoe plant extract) on AML cells. During this study, they noticed the negative impact of this compound on AML cells (46). According to the results of research by Kleinsimon et al, Viscum TT acts as an inhibitor of STAT3 phosphorylation, so that this function may lead to the limiting effect of the mentioned drug on AML blasts (47). Cytokine secreted from Populus x robusta (ortho-tooling riboside) can also be investigated as a suitable therapeutic agent in AML cells due to the stimulation of myeloid differentiation by reducing the amount of phosphorylated STAT3 (48). Mo et al observed a significant increase in the expression of the V-domain immunoglobulin suppressor of T cell activation (VISTA) and the correlation of the expression of this protein with

the expression of STAT3 in AML samples; this is because of the hyperactivation of STAT3 due to VISTA activity. These researchers succeeded in increasing T-lymphocyte-mediated cell death in AML by inhibiting VISTA with the help of anti-VISTA mAb. In this study, W1046 was also utilized as a strong inhibitor of STAT3 (49).

Signal Transducer and Activator of Transcription 3 Interactions

The interaction of STAT3 with other proteins is also important because of the effect of the interacting protein on STAT3. According to the data available in the STRING (https://string-db.org/) and GeneMANIA (https://genemania.org/) databases, some important proteins (Figures 4 and 5) interact with STAT3. These interactions can be essential in AML. These proteins include CREBBP (CREB binding protein), CDKN1A (cyclin-dependent kinase inhibitor 1A), CCR1, 2, and 5 (C-C motif chemokine receptor 1, 2, and 5), SRC (SRC proto-oncogene, non-receptor tyrosine kinase), BHLHE40 (basic helix-loop-helix family member e40), EP300 (E1A binding protein p300), PRKCD (protein kinase C delta), NMI (N-myc and STAT interactor), and EGFR (epidermal growth factor receptor) (51-62).

CREBBP is a ubiquitously expressed protein that is involved in the co-expression of transcription factors and chromatin remodeling. This protein plays a vital role in embryonic development, growth control, and hematopoiesis. It also contributes to the pathogenesis of AML. For instance, Assem et al mentioned the dysregulation of CREBBP in de novo AML (63,64). On the other hand, CREBBP has a paralog called EP300. This histone acetyltransferase participates in various cellular processes. CREBBP/EP300 maintains hematopoiesis; thus, the malfunction of this complex acts as a leukemogenic factor in some AML cases (65).

CDKN1A (p21) is another protein that interacts with STAT3. This protein is a master regulator of phagocytosis in acute leukemia. Macrophages inhibit SIRPα receptors by secreting p21. SIRPα are phagocytosis inhibitors in leukemic cells. Hence, p21 positively regulates phagocytosis in leukemic cells (66).

Hu et al evaluated the effect of Src inhibitors on the blasts of AML. They found that Src mediates the cytoprotective accumulation of myeloid cell leukemia sequence 1 and induces transcription via STAT3 in leukemic cells. Therefore, Src inhibitors potentiate the activity of myeloid cell leukemia sequence 1 antagonists (67).

Conclusion

Due to its important role in cell proliferation and survival, STAT3 is a key factor in the pathogenesis of AML. This transcription factor is a member of the STAT family. Moreover, STAT3 is tyrosine-phosphorylated by a kinase family called "JAK" during various signaling pathways. Phosphorylated STATs dimerize and regulate the expression of various genes. Due to the functions of STAT3, its hyperactivation, variation, and inhibition affect cell survival and patient prognosis in AML. For instance, the dysfunction of STAT3 regulators, leading

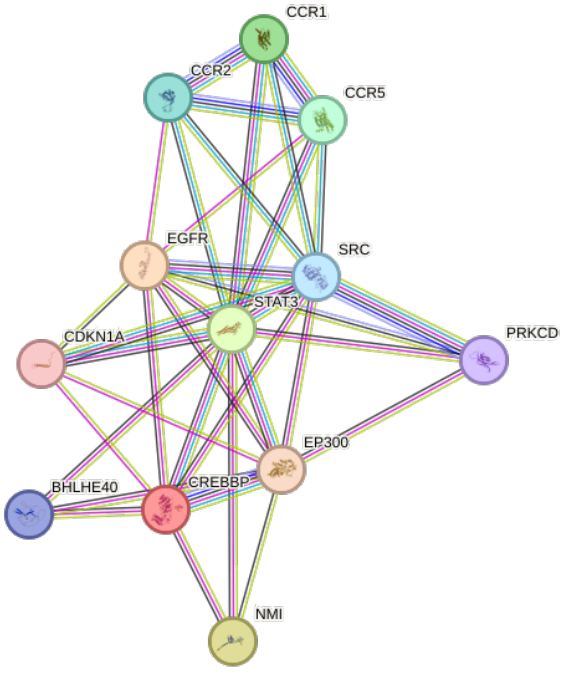

Figure 4. The Protein-Protein Interaction Network of the Mentioned Genes Associated With STAT3
Note. STAT3: Signal transducer and activator of transcription 3. *Source*. The STRING database (https://string-db.org/)

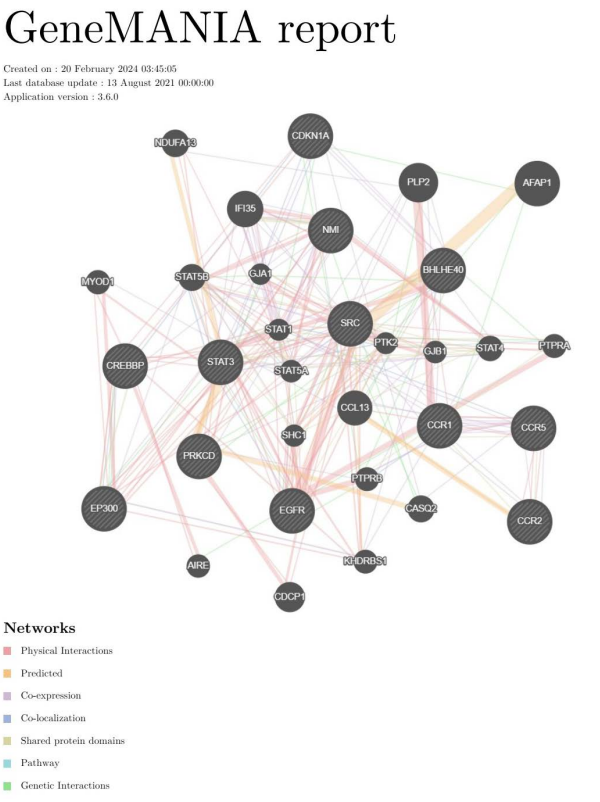

Figure 5. Functionally Associated and Interacted Genes for the Mentioned Gene List. *Source*. The GeneMANIA database (52) (https://genemania.org/)

to its hyperactivation, has been proven in malignancies. In addition, various anticancer agents act as inhibitors of STAT3. Despite its important roles, the underlying mechanism in the leukemogenic effect of STAT3 is not completely clear. Accordingly, future studies should focus on this important marker as a pathogenesis factor and a therapeutic target in AML.

Acknowledgments

We sincerely thank all colleagues and staff at Hamadan University of Medical Sciences for their valuable support, guidance, and contributions to this study. We also acknowledge the technical and administrative assistance provided by the university, which was essential for the completion of this research.

Authors' Contribution

Conceptualization: Miaad Banay Golrizi, Hassan Rafieemehr.
Data curation: Hassan Rafieemehr.
Formal analysis: Mohammad Hossein Shams.
Funding acquisition: Hassan Rafieemehr.
Investigation: Miaad Banay Golrizi, Mohammad Hossein Shams, Nima Nezami.
Methodology: Miaad Banay Golrizi, Hassan Rafieemehr.
Project administration: Hassan Rafieemehr.
Resources: Hassan Rafieemehr.
Software: Mohammad Hossein Shams, Nima Nezami.
Supervision: Hassan Rafieemehr.
Validation: Hassan Rafieemehr, Mohammad Hossein Shams.
Visualization: Mohammad Hossein Shams, Miaad Banay Golrizi.
Writing–original draft: Mohammad Hossein Shams, Miaad Banay Golrizi.
Writing–review & editing: Mohammad Hossein Shams, Miaad Banay Golrizi, Hassan Rafieemehr.

Competing Interests

The authors declare no conflict of interests. Figures were created with BioRender software (https://biorender.com/).

Ethical Approval

This article contains no studies performed by the authors with human participants or animals.

Funding

The present study was supported by Hamadan University of Medical Sciences. The authors would like to express their gratitude to the Research and Technology Deputy of Hamadan University of Medical Sciences for their supports.

Informed Consent

Informed consent was not required since no human participants or animals were included in this study.

References

1. Maleki Behzad M, Abbasi M, Oliaei I, Ghorbani Gholiabad S, Rafieemehr H. Effects of lifestyle and environmental factors on the risk of acute myeloid leukemia: result of a hospital-based case-control study. J Res Health Sci. 2021;21(3):e00525. doi: 10.34172/jrhs.2021.58.
2. De Kouchkovsky I, Abdul-Hay M. 'Acute myeloid leukemia: a comprehensive review and 2016 update'. Blood Cancer J. 2016;6(7):e441. doi: 10.1038/bcj.2016.50.
3. Ippolito MR, Martis V, Martin S, Tijhuis AE, Hong C, Wardenaar R, et al. Gene copy-number changes and chromosomal instability induced by aneuploidy confer resistance to chemotherapy. Dev Cell. 2021;56(17):2440-54.e6. doi: 10.1016/j.devcel.2021.07.006.
4. Motahari F, Karampourian A, Rafieemehr H. Different mechanisms of cancer drug resistance: a brief review. Avicenna J Care Health Oper Room. 2023;1(2):68-72. doi: 10.34172/ajchor.5.
5. Moser B, Edtmayer S, Witalisz-Siepracka A, Stoiber D. The ups and downs of STAT inhibition in acute myeloid leukemia. Biomedicines. 2021;9(8):1051. doi: 10.3390/biomedicines9081051.
6. Babu G, Chaudhuri P, Rajappa M, Biswas M, Sansar B, Rajegowda C, et al. JAK-STAT inhibitor as a potential therapeutic opportunity in AML patients resistant to cytarabine and epigenetic therapy. Cancer Biol Ther. 2021;22(1):66-78. doi: 10.1080/15384047.2020.1831371.
7. Rafieemehr H, Farmany A, Ghorbani S, Jafari M, Maleki Behzad M. Serum trace element levels in cancer patients undergoing chemotherapy: a before-after analysis. Biol Trace Elem Res. 2024;202(10):4367-74. doi: 10.1007/s12011-023-04025-z.
8. Rafieemehr H, Maleki Behzad M, Azandeh S, Farshchi N, Ghasemi Dehcheshmeh M, Saki N. Chemo/radiotherapy-induced bone marrow niche alterations. Cancer Invest. 2021;39(2):180-94. doi: 10.1080/07357907.2020.1855353.
9. Hu X, Li J, Fu M, Zhao X, Wang W. The JAK/STAT signaling pathway: from bench to clinic. Signal Transduct Target Ther. 2021;6(1):402. doi: 10.1038/s41392-021-00791-1.
10. Shi Y, Zhang Z, Qu X, Zhu X, Zhao L, Wei R, et al. Roles of STAT3 in leukemia (review). Int J Oncol. 2018;53(1):7-20. doi: 10.3892/ijo.2018.4386.
11. Kramer MH, Zhang Q, Sprung R, Day RB, Erdmann-Gilmore P, Li Y, et al. Proteomic and phosphoproteomic landscapes of acute myeloid leukemia. Blood. 2022;140(13):1533-48. doi: 10.1182/blood.2022016033.
12. Shagerdi Esmaeli N, Asadi S, Bashash D, Salari S, Hamidpour M. Involvement value of FLT-3, c-Myc, STAT3, p27, and HOTAIR gene expression in acute myeloid leukemia patients: a molecular perspective to a novel leukemogenesis mechanism. Int J Hematol Oncol Stem Cell Res. 2023;17(3):145-55. doi: 10.18502/ijhoscr.v17i3.13304.
13. Stark GR, Darnell JE Jr. The JAK-STAT pathway at twenty. Immunity. 2012;36(4):503-14. doi: 10.1016/j.immuni.2012.03.013.
14. Hou D, Wang B, You R, Wang X, Liu J, Zhan W, et al. Stromal cells promote chemoresistance of acute myeloid leukemia cells via activation of the IL-6/STAT3/OXPHOS axis. Ann Transl Med. 2020;8(21):1346. doi: 10.21037/atm-20-3191.
15. Amaya ML, Inguva A, Pei S, Jones C, Krug A, Ye H, et al. The STAT3-MYC axis promotes survival of leukemia stem cells by regulating SLC1A5 and oxidative phosphorylation. Blood. 2022;139(4):584-96. doi: 10.1182/blood.2021013201.
16. Aigner P, Mizutani T, Horvath J, Eder T, Heber S, Lind K, et al. STAT3β is a tumor suppressor in acute myeloid leukemia. Blood Adv. 2019;3(13):1989-2002. doi: 10.1182/bloodadvances.2018026385.
17. Wang HQ, Man QW, Huo FY, Gao X, Lin H, Li SR, et al. STAT3 pathway in cancers: past, present, and future. MedComm (2020). 2022;3(2):e124. doi: 10.1002/mco2.124.
18. Chung CD, Liao J, Liu B, Rao X, Jay P, Berta P, et al. Specific inhibition of STAT3 signal transduction by PIAS3. Science. 1997;278(5344):1803-5. doi: 10.1126/science.278.5344.1803.
19. Zhang Q, Raghunath PN, Xue L, Majewski M, Carpentieri DF, Odum N, et al. Multilevel dysregulation of STAT3 activation in anaplastic lymphoma kinase-positive T/null-cell lymphoma. J Immunol. 2002;168(1):466-74. doi: 10.4049/jimmunol.168.1.466.
20. Wu M, Song D, Li H, Yang Y, Ma X, Deng S, et al. Negative

regulators of STAT3 signaling pathway in cancers. Cancer Manag Res. 2019;11:4957-69. doi: 10.2147/cmar.S206175.
21. Kim MH, Kim MS, Kim W, Kang MA, Cacalano NA, Kang SB, et al. Suppressor of cytokine signaling (SOCS) genes are silenced by DNA hypermethylation and histone deacetylation and regulate response to radiotherapy in cervical cancer cells. PLoS One. 2015;10(4):e0123133. doi: 10.1371/journal.pone.0123133.
22. Watanabe D, Ezoe S, Fujimoto M, Kimura A, Saito Y, Nagai H, et al. Suppressor of cytokine signalling-1 gene silencing in acute myeloid leukaemia and human haematopoietic cell lines. Br J Haematol. 2004;126(5):726-35. doi: 10.1111/j.1365-2141.2004.05107.x.
23. Tolomeo M, Cascio A. The multifaced role of STAT3 in cancer and its implication for anticancer therapy. Int J Mol Sci. 2021;22(2):603. doi: 10.3390/ijms22020603.
24. Zeinalzadeh E, Valerievich Yumashev A, Rahman HS, Marofi F, Shomali N, Samadi Kafil H, et al. The role of Janus kinase/STAT3 pathway in hematologic malignancies with an emphasis on epigenetics. Front Genet. 2021;12:703883. doi: 10.3389/fgene.2021.703883.
25. Cook AM, Li L, Ho Y, Lin A, Li L, Stein A, et al. Role of altered growth factor receptor-mediated JAK2 signaling in growth and maintenance of human acute myeloid leukemia stem cells. Blood. 2014;123(18):2826-37. doi: 10.1182/blood-2013-05-505735.
26. Bruserud Ø, Nepstad I, Hauge M, Hatfield KJ, Reikvam H. STAT3 as a possible therapeutic target in human malignancies: lessons from acute myeloid leukemia. Expert Rev Hematol. 2015;8(1):29-41. doi: 10.1586/17474086.2015.971005.
27. Zhang T, Kee WH, Seow KT, Fung W, Cao X. The coiled-coil domain of STAT3 is essential for its SH2 domain-mediated receptor binding and subsequent activation induced by epidermal growth factor and interleukin-6. Mol Cell Biol. 2000;20(19):7132-9. doi: 10.1128/mcb.20.19.7132-7139.2000.
28. Haan S, Hemmann U, Hassiepen U, Schaper F, Schneider-Mergener J, Wollmer A, et al. Characterization and binding specificity of the monomeric STAT3-SH2 domain. J Biol Chem. 1999;274(3):1342-8. doi: 10.1074/jbc.274.3.1342.
29. Liska O, Bohár B, Hidas A, Korcsmáros T, Papp B, Fazekas D, et al. TFLink: an integrated gateway to access transcription factor-target gene interactions for multiple species. Database (Oxford). 2022;2022:baac083. doi: 10.1093/database/baac083.
30. Turnpenny PD, Ellard S, Cleaver R. Emery's Elements of Medical Genetics E-Book. Elsevier Health Sciences; 2020.
31. Chen Z, Brand NJ, Chen A, Chen SJ, Tong JH, Wang ZY, et al. Fusion between a novel Krüppel-like zinc finger gene and the retinoic acid receptor-alpha locus due to a variant t(11;17) translocation associated with acute promyelocytic leukaemia. EMBO J. 1993;12(3):1161-7. doi: 10.1002/j.1460-2075.1993.tb05757.x.
32. de Thé H, Chen Z. Acute promyelocytic leukaemia: novel insights into the mechanisms of cure. Nat Rev Cancer. 2010;10(11):775-83. doi: 10.1038/nrc2943.
33. Yao L, Wen L, Wang N, Liu T, Xu Y, Ruan C, et al. Identification of novel recurrent STAT3-RARA fusions in acute promyelocytic leukemia lacking t(15;17)(q22;q12)/PML-RARA. Blood. 2018;131(8):935-9. doi: 10.1182/blood-2017-09-807370.
34. Xu P, Wang X, Xu Y, Chen B, Ouyang J. The rs9909659G/A polymorphisms of the STAT3 gene provide prognostic information in acute myeloid leukemia. Transl Cancer Res. 2016;5(4):448-57. doi: 10.21037/tcr.2016.07.01.
35. Chen BA, Zhong YJ, Feng JF, Cheng L, Li Y, Qian J, et al. The activator of transcription 3 (STAT3) gene polymorphisms are associated with treatment outcomes in acute myeloid leukemia. Blood. 2010;116(21):4858. doi: 10.1182/blood.V116.21.4858.4858.
36. Zhong Y, Feng J, Chen B, Cheng L, Li Y, Qian J, et al. Signal transducer and activator of transcription 3 (STAT3) gene polymorphisms are associated with treatment outcomes in acute myeloid leukemia. Int J Lab Hematol. 2012;34(4):383-9. doi: 10.1111/j.1751-553X.2012.01406.x.
37. Liu Q, Hua M, Yan S, Zhang C, Wang R, Yang X, et al. Immunorelated gene polymorphisms associated with acute myeloid leukemia. Clin Exp Immunol. 2020;201(3):266-78. doi: 10.1111/cei.13446.
38. Minus MB, Wang H, Munoz JO, Stevens AM, Mangubat-Medina AE, Krueger MJ, et al. Targeting STAT3 anti-apoptosis pathways with organic and hybrid organic-inorganic inhibitors. Org Biomol Chem. 2020;18(17):3288-96. doi: 10.1039/c9ob02682g.
39. Mohammadi Kian M, Salemi M, Bahadoran M, Haghi A, Dashti N, Mohammadi S, et al. Curcumin combined with thalidomide reduces expression of STAT3 and Bcl-xL, leading to apoptosis in acute myeloid leukemia cell lines. Drug Des Devel Ther. 2020;14:185-94. doi: 10.2147/dddt.S228610.
40. Ogura M, Uchida T, Terui Y, Hayakawa F, Kobayashi Y, Taniwaki M, et al. Phase I study of OPB-51602, an oral inhibitor of signal transducer and activator of transcription 3, in patients with relapsed/refractory hematological malignancies. Cancer Sci. 2015;106(7):896-901. doi: 10.1111/cas.12683.
41. Bi S, Chen K, Feng L, Fu G, Yang Q, Deng M, et al. Napabucasin (BBI608) eliminate AML cells in vitro and in vivo via inhibition of STAT3 pathway and induction of DNA damage. Eur J Pharmacol. 2019;855:252-61. doi: 10.1016/j.ejphar.2019.05.020.
42. Shastri A, Choudhary G, Teixeira M, Gordon-Mitchell S, Ramachandra N, Bernard L, et al. Antisense STAT3 inhibitor decreases viability of myelodysplastic and leukemic stem cells. J Clin Invest. 2018;128(12):5479-88. doi: 10.1172/jci120156.
43. Zhang Q, Hossain DM, Duttagupta P, Moreira D, Zhao X, Won H, et al. Serum-resistant CpG-STAT3 decoy for targeting survival and immune checkpoint signaling in acute myeloid leukemia. Blood. 2016;127(13):1687-700. doi: 10.1182/blood-2015-08-665604.
44. Lee MH, Lapidus RG, Ferraris D, Emadi A. Analysis of the mechanisms of action of naphthoquinone-based anti-acute myeloid leukemia chemotherapeutics. Molecules. 2019;24(17):3121. doi: 10.3390/molecules24173121.
45. Xiang M, Kim H, Ho VT, Walker SR, Bar-Natan M, Anahtar M, et al. Gene expression-based discovery of atovaquone as a STAT3 inhibitor and anticancer agent. Blood. 2016;128(14):1845-53. doi: 10.1182/blood-2015-07-660506.
46. Delebinski CI, Twardziok M, Kleinsimon S, Hoff F, Mulsow K, Rolff J, et al. A natural combination extract of *Viscum album* L. containing both triterpene acids and lectins is highly effective against AML in vivo. PLoS One. 2015;10(8):e0133892. doi: 10.1371/journal.pone.0133892.
47. Kleinsimon S, Longmuss E, Rolff J, Jäger S, Eggert A, Delebinski C, et al. GADD45A and CDKN1A are involved in apoptosis and cell cycle modulatory effects of viscumTT with further inactivation of the STAT3 pathway. Sci Rep. 2018;8(1):5750. doi: 10.1038/s41598-018-24075-x.
48. Wang L, Cheng J, Lin F, Liu S, Pan H, Li M, et al. Ortho-topolin riboside induced differentiation through inhibition of STAT3 signaling in acute myeloid leukemia HL-60 cells. Turk J Haematol. 2019;36(3):162-8. doi: 10.4274/tjh.galenos.2019.2019.0020.
49. Mo J, Deng L, Peng K, Ouyang S, Ding W, Lou L, et al. Targeting STAT3-VISTA axis to suppress tumor aggression and burden in acute myeloid leukemia. J Hematol Oncol. 2023;16(1):15. doi: 10.1186/s13045-023-01410-y.
50. Lu H, Li ZY, Ding M, Liang C, Weng XQ, Sheng Y, et al. Trametinib enhances ATRA-induced differentiation in

AML cells. Leuk Lymphoma. 2021;62(14):3361-72. doi: 10.1080/10428194.2021.1961231.
51. Tan M, Rong Y, Su Q, Chen Y. Artesunate induces apoptosis via inhibition of STAT3 in THP-1 cells. Leuk Res. 2017;62:98-103. doi: 10.1016/j.leukres.2017.09.022.
52. Wang R, Cherukuri P, Luo J. Activation of STAT3 sequence-specific DNA binding and transcription by p300/CREB-binding protein-mediated acetylation. J Biol Chem. 2005;280(12):11528-34. doi: 10.1074/jbc.M413930200.
53. Coqueret O, Gascan H. Functional interaction of STAT3 transcription factor with the cell cycle inhibitor p21WAF1/CIP1/SDI1. J Biol Chem. 2000;275(25):18794-800. doi: 10.1074/jbc.M001601200.
54. Shahrara S, Amin MA, Woods JM, Haines GK, Koch AE. Chemokine receptor expression and in vivo signaling pathways in the joints of rats with adjuvant-induced arthritis. Arthritis Rheum. 2003;48(12):3568-83. doi: 10.1002/art.11344.
55. Tsai YT, Su YH, Fang SS, Huang TN, Qiu Y, Jou YS, et al. Etk, a Btk family tyrosine kinase, mediates cellular transformation by linking Src to STAT3 activation. Mol Cell Biol. 2000;20(6):2043-54. doi: 10.1128/mcb.20.6.2043-2054.2000.
56. Ivanova AV, Ivanov SV, Zhang X, Ivanov VN, Timofeeva OA, Lerman MI. STRA13 interacts with STAT3 and modulates transcription of STAT3-dependent targets. J Mol Biol. 2004;340(4):641-53. doi: 10.1016/j.jmb.2004.05.025.
57. Yuan ZL, Guan YJ, Chatterjee D, Chin YE. STAT3 dimerization regulated by reversible acetylation of a single lysine residue. Science. 2005;307(5707):269-73. doi: 10.1126/science.1105166.
58. Jain N, Zhang T, Kee WH, Li W, Cao X. Protein kinase C delta associates with and phosphorylates STAT3 in an interleukin-6-dependent manner. J Biol Chem. 1999;274(34):24392-400. doi: 10.1074/jbc.274.34.24392.
59. Zhu M, John S, Berg M, Leonard WJ. Functional association of Nmi with STAT5 and STAT1 in IL-2- and IFNgamma-mediated signaling. Cell. 1999;96(1):121-30. doi: 10.1016/s0092-8674(00)80965-4.
60. Shao H, Cheng HY, Cook RG, Tweardy DJ. Identification and characterization of signal transducer and activator of transcription 3 recruitment sites within the epidermal growth factor receptor. Cancer Res. 2003;63(14):3923-30.
61. Lufei C, Ma J, Huang G, Zhang T, Novotny-Diermayr V, Ong CT, et al. GRIM-19, a death-regulatory gene product, suppresses STAT3 activity via functional interaction. EMBO J. 2003;22(6):1325-35. doi: 10.1093/emboj/cdg135.
62. Lo HW, Hsu SC, Ali-Seyed M, Gunduz M, Xia W, Wei Y, et al. Nuclear interaction of EGFR and STAT3 in the activation of the iNOS/NO pathway. Cancer Cell. 2005;7(6):575-89. doi: 10.1016/j.ccr.2005.05.007.
63. Assem M, El Leithy AA, Hassan NM, Al-Karmalawy AA, Abozaid M, Allam RM, et al. A significant correlation exists between CREBBP and CEBPA gene expression in de novo adult acute myeloid leukemia. Sci Rep. 2025;15(1):12473. doi: 10.1038/s41598-025-93024-2.
64. GeneCards. CREBBP Gene Card Page [Internet]. Available from: https://www.genecards.org/cgi-bin/carddisp.pl?gene=CREBBP. Accessed October 2025.
65. Chen YJ, Zhao Y, Yao MY, Wang YF, Ma M, Yu CC, et al. Concurrent inhibition of p300/CBP and FLT3 enhances cytotoxicity and overcomes resistance in acute myeloid leukemia. Acta Pharmacol Sin. 2025;46(5):1390-403. doi: 10.1038/s41401-025-01479-w.
66. Allouch A, Voisin L, Zhang Y, Raza SQ, Lecluse Y, Calvo J, et al. CDKN1A is a target for phagocytosis-mediated cellular immunotherapy in acute leukemia. Nat Commun. 2022;13(1):6739. doi: 10.1038/s41467-022-34548-3.
67. Hu X, Li L, Nkwocha J, Kmieciak M, Shang S, Cowart LA, et al. Src inhibition potentiates MCL-1 antagonist activity in acute myeloid leukemia. Signal Transduct Target Ther. 2025;10(1):50. doi: 10.1038/s41392-025-02125-x.