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Exploring Genetic Targets Modulating Immune Responses in Metastasis of Leukemia through Computational Analysis

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ABSTRACT: Leukemia metastasis represents a complex phenomenon in oncology, posing substantial challenges in treatment due to its intricate interactions with the immune system. This paper undertakes a detailed computational investigation into the genetic targets involved in shaping immune responses during leukemia metastasis. Through an exhaustive literature review and gene identification process, we have identified 25 genes that emerge repeatedly in the context of leukemia progression. Subsequent gene coexpression analysis has shed light on the interconnectedness of these genes, highlighting JAK1, STAT3, CXCL10, FAS, and SIRPA as central players within a molecular network. Furthermore, employing KEGG pathway analysis has provided insights into the specific biological pathways associated with these genes, emphasizing the roles of JAK1 in Human T-cell leukemia virus 1 infection and STAT3 in Acute myeloid leukemia. Additionally, miRNA analysis has revealed potential regulatory mechanisms, with hsa-miR-7-5p identified as a putative regulator of JAK1 and STAT3. This interdisciplinary approach, integrating computational methodologies with molecular biology, offers novel insights into the intricate mechanisms underpinning leukemia metastasis, and holds promise for the development of targeted therapeutic interventions.

KEYWORDS: Leukemia metastasis, Computational analysis, Genetic targets, Immune responses, JAK1, STAT3.

I. INTRODUCTION

Understanding the complex dynamics of leukemia metastasis is crucial for developing effective treatment strategies to combat this devastating disease. Leukemia, a heterogeneous group of hematologic malignancies, exhibits diverse clinical behaviors, with metastasis representing a significant challenge in patient management. This introduction will delve into the intricate interplay between leukemia cells and the immune system, highlighting the need for computational analysis to decipher the molecular landscape of metastatic disease.

A. The Challenge of Leukemia Metastasis:

Leukemia metastasis poses a formidable challenge in clinical oncology, characterized by the dissemination of leukemia cells from the bone marrow to distant organs and tissues. Unlike solid tumors, which often exhibit localized growth, leukemia cells can infiltrate multiple tissues, making eradication difficult.

B. The Role of the Immune System:

The immune system plays a dual role in leukemia metastasis, serving as both a defense mechanism against tumor cells and a facilitator of metastatic spread. Immune cells interact with leukemia cells in the tumor microenvironment, influencing tumor progression, immune evasion, and treatment response.

C. Leveraging Computational Analysis:

Computational analysis offers a powerful approach to unraveling the complex biology of leukemia metastasis. By integrating large-scale genomic data, bioinformatics tools, and computational modeling, researchers can decipher the genetic determinants, signaling pathways, and regulatory networks driving metastatic disease.

II. AIMS OF THE STUDY

This study aims to utilize computational methodologies to dissect the molecular landscape of leukemia metastasis. Through comprehensive literature review, gene identification, coexpression analysis, pathway mapping, and miRNA profiling, we seek to identify key genetic targets and regulatory networks implicated in leukemia metastasis.

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A. Implications for Treatment:

Understanding the molecular mechanisms underlying leukemia metastasis holds profound implications for treatment development. By identifying druggable targets, biomarkers of metastatic disease, and potential therapeutic interventions, this research aims to improve outcomes for leukemia patients facing metastatic progression.

B. Significance of the Research:

The insights gained from this study have the potential to transform the treatment paradigm for leukemia metastasis. By elucidating the molecular drivers of metastatic disease, we can develop targeted therapies tailored to individual patients, ultimately improving survival rates and quality of life.

III. METHODOLOGY

An extensive literature review was conducted, encompassing 250 research papers focused on leukemia metastasis. These papers were sourced from reputable databases including PubMed and Web of Science. The aim was to identify genes frequently mentioned in the literature as being associated with leukemia metastasis. From this review, a comprehensive list of 25 genes emerged as potential candidates, representing a broad spectrum of genetic factors implicated in the metastatic process. Notable genes included IL27RA, SIRPA, PTPN11, PTEN, KRAS, NRAS, RAD51, ATRX, MYC, JAK1, IFNAR1, CXCL10, STAT3, CXCR3, IL9, BCL2, BAX, NOTCH1, GATA2, PHF20, COL1, FAS, ASXL1, ETV6, and TET2.

A. String Database:

STRING is a database of known and predicted protein-protein interactions. The interactions include direct (physical) and indirect (functional) associations; they stem from computational prediction, from knowledge transfer between organisms, and from interactions aggregated from other (primary) databases.

STRING (Search Tool for the Retrieval of Interacting Genes/Proteins) is a bioinformatics resource that provides information about protein-protein interactions, as well as protein-DNA and protein-RNA interactions.

String pathway analysis involves mapping the identified genes onto known pathways to understand their functional relationships and interactions within biological networks.

It helps in elucidating the molecular mechanisms underlying complex biological processes such as leukemia metastasis.

Identified 25 genes that were frequently utilized in the literature: IL27RA, SIRPA, PTPN11, PTEN, KRAS, NRAS, RAD51, ATRX, MYC, JAK1, IFNAR1, CXCL10, STAT3, CXCR3, IL9, BCL2, BAX, NOTCH1, GATA2, PHF20, COL1, FAS, ASXL1, ETV6,

B. M ultiple Proteins by Names/Identifiers:

List of Names: IL27RA, SIRPA, PTPN11, PTEN, KRAS, NRAS, RAD51, ATRX, MYC, JAK1, IFNAR1, CXCL10, STAT3, CXCR3, IL9, BCL2, BAX, NOTCH1, GATA2, PHF20, COL1, FAS, ASXL1, ETV6, TET2

Organisms: Homo sapiens

IL27RA - Interleukin-27 receptor subunit alpha; Receptor for IL27. Requires IL6ST/gp130 to mediate signal transduction in response to IL27. This signaling system acts through STAT3 and STAT1. Involved in the regulation of Th1-type immune responses. Also appears to be involved in innate defense mechanisms.

SIRPA - Tyrosine-protein phosphatase non-receptor type substrate 1; Immunoglobulin-like cell surface receptor for CD47. Acts as docking protein and induces translocation of PTPN6, PTPN11 and other binding partners from the cytosol to the plasma membrane. Supports adhesion of cerebellar neurons, neurite outgrowth and glial cell attachment. May play a key role in intracellular signaling during synaptogenesis and in synaptic function (By similarity). Involved in the negative regulation of receptor tyrosine kinase-coupled cellular responses induced by cell adhesion, growth factors or insulin.

PTPN11 - Tyrosine-protein phosphatase non-receptor type 11; Acts downstream of various receptor and cytoplasmic protein tyrosine kinases to participate in the signal transduction from the cell surface to the nucleus. Positively regulates MAPK signal transduction pathway. Dephosphorylates GAB1, ARHGAP35 and EGFR. Dephosphorylates ROCK2 at 'Tyr-722' resulting in stimulatation of its RhoA binding activity. Dephosphorylates CDC73.

PTEN - Phosphatase and tensin homolog; Tumor suppressor. Acts as a dual-specificity protein phosphatase, dephosphorylating tyrosine-, serine- and threonine- phosphorylated proteins. Also acts as a lipid phosphatase, removing the phosphate in the D3 position of the inositol ring from phosphatidylinositol 3,4,5-trisphosphate, phosphatidylinositol 3,4- diphosphate, phosphatidylinositol 3-phosphate and inositol 1,3,4,5- tetrakisphosphate with order of substrate preference in vitro PtdIns(3,4,5)P3 > PtdIns(3,4)P2 > PtdIns3P > Ins(1,3,4,5)P4.

KRAS - GTPase KRas, N-terminally processed; Ras proteins bind GDP/GTP and possess intrinsic GTPase activity. Plays an important role in the regulation of cell proliferation. Plays a role in promoting oncogenic events by inducing

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transcriptional silencing of tumor suppressor genes (TSGs) in colorectal cancer (CRC) cells in a ZNF304-dependent manner.

NRAS - GTPase NRas; Ras proteins bind GDP/GTP and possess intrinsic GTPase activity.

RAD51 - DNA repair protein RAD51 homolog 1; Plays an important role in homologous strand exchange, a key step in DNA repair through homologous recombination (HR). Binds to single and double-stranded DNA and exhibits DNA-dependent ATPase activity. Catalyzes the recognition of homology and strand exchange between homologous DNA partners to form a joint molecule between a processed DNA break and the repair template. Binds to single-stranded DNA in an ATP-dependent manner to form nucleoprotein filaments which are essential for the homology search and strand exchange.

ATRX - Transcriptional regulator ATRX; Involved in transcriptional regulation and chromatin remodeling. Facilitates DNA replication in multiple cellular environments and is required for efficient replication of a subset of genomic loci. Binds to DNA tandem repeat sequences in both telomeres and euchromatin and in vitro binds DNA quadruplex structures. May help stabilizing G-rich regions into regular chromatin structures by remodeling G4 DNA and incorporating H3.3-containing nucleosomes.

MYC - Myc proto-oncogene protein; Transcription factor that binds DNA in a non-specific manner, yet also specifically recognizes the core sequence 5'-CAC[GA]TG-3'. Activates the transcription of growth-related genes. Binds to the VEGFA promoter, promoting VEGFA production and subsequent sprouting angiogenesis. Regulator of somatic reprogramming, controls self-renewal of embryonic stem cells. Functions with TAF6L to activate target gene expression through RNA polymerase II pause release (By similarity).

JAK1 - Tyrosine-protein kinase JAK1; Tyrosine kinase of the non-receptor type, involved in the IFN-alpha/beta/gamma signal pathway. Kinase partner for the interleukin (IL)-2 receptor as well as interleukin (IL)-10 receptor.

IFNAR1 - Interferon alpha/beta receptor 1; Component of the receptor for type I interferons, including interferons alpha, IFNB1 and IFNW1. Functions in general as heterodimer with IFNAR2. Type I interferon binding activates the JAK-STAT signaling cascade, and triggers tyrosine phosphorylation of a number of proteins including JAKs, TYK2, STAT proteins and the IFNR alpha- and beta-subunits themselves. Can form an active IFNB1 receptor by itself and activate a signaling cascade that does not involve activation of the JAK-STAT pathway (By similarity).

CXCL10 - C-X-C motif chemokine 10; Pro-inflammatory cytokine that is involved in a wide variety of processes such as chemotaxis, differentiation, and activation of peripheral immune cells, regulation of cell growth, apoptosis and modulation of angiostatic effects. Plays thereby an important role during viral infections by stimulating the activation and migration of immune cells to the infected sites (By similarity).

STAT3 - Signal transducer and activator of transcription 3; Signal transducer and transcription activator that mediates cellular responses to interleukins, KITLG/SCF, LEP and other growth factors. Once activated, recruits coactivators, such as NCOA1 or MED1, to the promoter region of the target gene. May mediate cellular responses to activated FGFR1, FGFR2, FGFR3 and FGFR4. Binds to the interleukin-6 (IL-6)-responsive elements identified in the promoters of various acute-phase protein genes.

CXCR3 - C-X-C chemokine receptor type 3; [Isoform 1]: Receptor for the C-X-C chemokine CXCL9, CXCL10 and CXCL11 and mediates the proliferation, survival and angiogenic activity of human mesangial cells (HMC) through a heterotrimeric G- protein signaling pathway. Binds to CCL21. Probably promotes cell chemotaxis response. [Isoform 3]: Mediates the activity of CXCL11.

IL9 - Interleukin-9; Supports IL-2 independent and IL-4 independent growth of helper T-cells; Belongs to the IL-7/IL-9 family.

BCL2 - Apoptosis regulator Bcl-2; Suppresses apoptosis in a variety of cell systems including factor-dependent lymphohematopoietic and neural cells. Regulates cell death by controlling the mitochondrial membrane permeability. Appears to function in a feedback loop system with caspases. Inhibits caspase activity either by preventing the release of cytochrome c from the mitochondria and/or by binding to the apoptosis-activating factor (APAF-1). May attenuate inflammation by impairing NLRP1-inflammasome activation, hence CASP1 activation and IL1B release.

BAX - Apoptosis regulator BAX; Plays a role in the mitochondrial apoptotic process. Under normal conditions, BAX is largely cytosolic via constant retrotranslocation from mitochondria to the cytosol mediated by BCL2L1/Bcl-xL, which avoids accumulation of toxic BAX levels at the mitochondrial outer membrane (MOM). Under stress conditions, undergoes a conformation change that causes translocation to the mitochondrion membrane, leading to the release of cytochrome c that then triggers apoptosis. Promotes activation of CASP3, and thereby apoptosis.

NOTCH1 - Neurogenic locus notch homolog protein 1; Functions as a receptor for membrane-bound ligands Jagged-1 (JAG1), Jagged-2 (JAG2) and Delta-1 (DLL1) to regulate cell-fate determination. Upon ligand activation through the released notch intracellular domain (NICD) it forms a transcriptional activator complex with RBPJ/RBPSUH and activates genes of the enhancer of split locus. Affects the implementation of differentiation, proliferation and apoptotic

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programs. Involved in angiogenesis; negatively regulates endothelial cell proliferation and migration and angiogenic sprouting.

GATA2 - Endothelial transcription factor GATA-2; Transcriptional activator which regulates endothelin-1 gene expression in endothelial cells. Binds to the consensus sequence 5'- AGATAG-3'.

PHF20 - PHD finger protein 20; Methyllysine-binding protein, component of the MOF histone acetyltransferase protein complex. Not required for maintaining the global histone H4 'Lys-16' acetylation (H4K16ac) levels or locus specific histone acetylation, but instead works downstream in transcriptional regulation of MOF target genes (By similarity). As part of the NSL complex it may be involved in acetylation of nucleosomal histone H4 on several lysine residues. Contributes to methyllysine- dependent p53/TP53 stabilization and up-regulation after DNA damage.

COL14A1 - Collagen alpha-1(XIV) chain; Plays an adhesive role by integrating collagen bundles. It is probably associated with the surface of interstitial collagen fibrils via COL1. The COL2 domain may then serve as a rigid arm which sticks out from the fibril and protrudes the large N-terminal globular domain into the extracellular space, where it might interact with other matrix molecules or cell surface receptors (By similarity).

FAS - Tumor necrosis factor receptor superfamily member 6; Receptor for TNFSF6/FASLG. The adapter molecule FADD recruits caspase-8 to the activated receptor. The resulting death-inducing signaling complex (DISC) performs caspase-8 proteolytic activation which initiates the subsequent cascade of caspases (aspartate-specific cysteine proteases) mediating apoptosis. FAS-mediated apoptosis may have a role in the induction of peripheral tolerance, in the antigen-stimulated suicide of mature T-cells, or both. The secreted isoforms 2 to 6 block apoptosis (in vitro).

ASXL1 - Polycomb group protein ASXL1; Probable Polycomb group (PcG) protein involved in transcriptional regulation mediated by ligand-bound nuclear hormone receptors, such as retinoic acid receptors (RARs) and peroxisome proliferator-activated receptor gamma (PPARG). Acts as coactivator of RARA and RXRA through association with NCOA1. Acts as corepressor for PPARG and suppresses its adipocyte differentiation-inducing activity (By similarity).

ETV6 - Transcription factor ETV6; Transcriptional repressor; binds to the DNA sequence 5'- CCGGAAGT-3'. Plays a role in hematopoiesis and malignant transformation; Belongs to the ETS family.

TET2 - Methylcytosine dioxygenase TET2; Dioxygenase that catalyzes the conversion of the modified genomic base 5-methylcytosine (5mC) into 5-hydroxymethylcytosine (5hmC) and plays a key role in active DNA demethylation. Has a preference for 5-hydroxymethylcytosine in CpG motifs. Also mediates subsequent conversion of 5hmC into 5-formylcytosine (5fC), and conversion of 5fC to 5-carboxylcytosine (5caC). Conversion of 5mC into 5hmC, 5fC and 5caC probably constitutes the first step in cytosine demethylation.

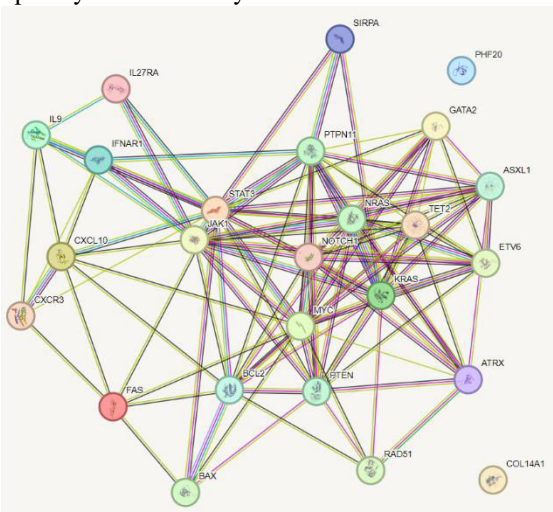

Fig.1 String Data Base

C. K-means clustering

K-means clustering is a type of unsupervised learning method, which is used when we don't have labeled data as in our case, we have unlabeled data (means, without defined categories or groups). The goal of this algorithm is to find groups in the data, whereas the no. of groups is represented by the variable K. KMEANS accepts a parameter to specify the number of clusters that you want to obtain.

Cluster 1:

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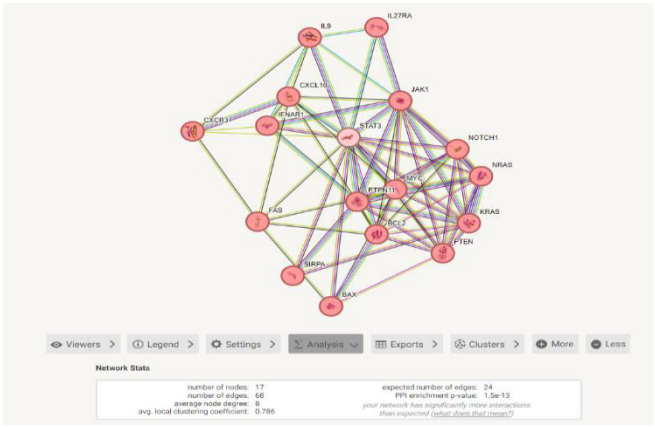

Fig.2 K-means cluster 1 in string database

Cluster 2:

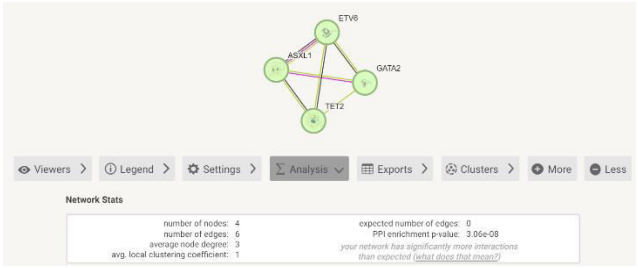

Fig.3 K-means cluster 2 in string database

Cluster 3:

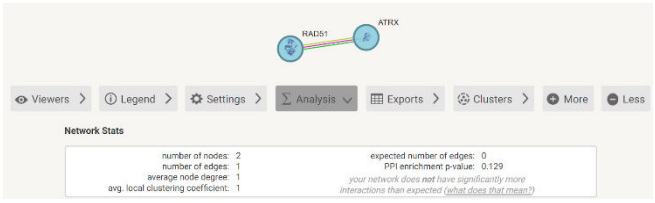

Fig.4 K-means cluster 3 in string database

Sortlisted Gene from Cluster 1:

BAX, BCL2, CXCL10, CXCR3, FAS, IFNAR1, IL27RA, IL9, JAK1, KRAS, MYC, NOTCH1, NRAS, PTEN, PTPN11, SIRPA, STAT3

D. Gene Coexpression

Proteins whose genes are observed to be correlated in expression, across a large number of experiments.

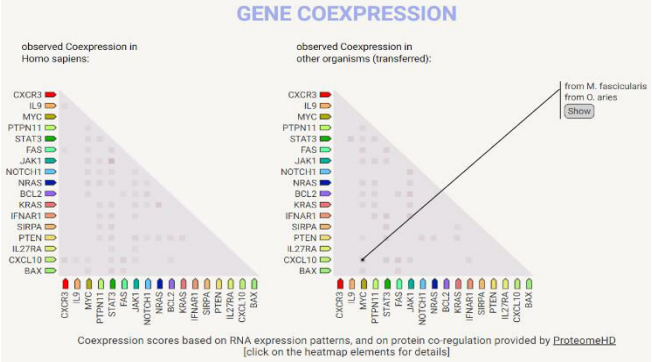

Fig.5 Gene Coexpression in string database

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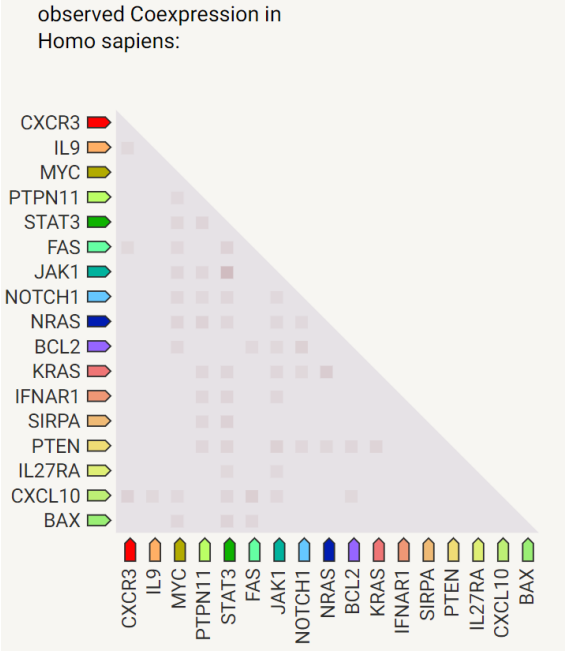

Fig.6 Homo sapiens gene coexpression in string database

TABLE I. GENE COEXPRESSION SCORE

Gene	Coexpression Score
JAK1	0.184
STAT3	0.184
CXCL10	0.144
FAS	0.144
SIRPA	0.116

1. STAT3 & JAK1 (0.184):

STAT3, a signal transducer and activator of transcription 3, mediates cellular responses to various growth factors and interleukins. It recruits coactivators to target gene promoters and is activated by multiple cytokines. JAK1, a tyrosine-protein kinase, is involved in the IFN-alpha/beta/gamma signal pathway and serves as a kinase partner for several interleukin receptors.

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2. JAK1 & STAT3 (0.184):

JAK1, a non-receptor tyrosine kinase, partners with interleukin receptors in signal transduction pathways. It plays a crucial role in cytokine signaling. STAT3, on the other hand, acts as a transcription activator in response to various cytokines and growth factors. This co-expression suggests a functional relationship in mediating cellular responses.

3. FAS & CXCL10 (0.144):

FAS, a tumor necrosis factor receptor, is involved in apoptosis induction and immune regulation. CXCL10, a pro-inflammatory cytokine, plays a role in immune cell activation and chemotaxis. This co-expression may indicate a link between apoptotic pathways and immune responses.

4. CXCL10 & FAS (0.144):

CXCL10, a chemokine involved in immune cell activation and migration, shows co-expression with FAS, a receptor involved in apoptosis induction and immune regulation. This suggests a potential crosstalk between immune activation and apoptosis pathways.

5. STAT3 & SIRPA (0.116):

STAT3, a key transcription activator, mediates cellular responses to various stimuli including growth factors and cytokines. SIRPA, a cell surface receptor, plays a role in cell adhesion and intracellular signaling. The co-expression between these genes suggests a potential regulatory relationship in cellular signaling pathways.

E. KEGG Pathway

For the "Human T-cell leukemia virus 1 infection" pathway (hsa05166), JAK1's role is prominent. In this pathway, HTLV-1, a retrovirus implicated in T-cell leukemia, infects human T-cells and integrates its proviral DNA into the host genome. JAK1 is involved in signaling cascades triggered by HTLV-1 infection, particularly through the activation of cytokine receptors. The activation of JAK1 can lead to the phosphorylation and activation of downstream effectors, including STAT proteins such as STAT3. This activation contributes to the transcriptional regulation of genes involved in cell proliferation, survival, and viral replication, ultimately promoting the progression of T-cell leukemia associated with HTLV-1 infection.

For the "Acute myeloid leukemia" pathway (map05221), STAT3's involvement is crucial. In this pathway, dysregulation of STAT3 signaling is implicated in the pathogenesis of acute myeloid leukemia (AML). Mutations or aberrant activation of upstream signaling molecules, such as receptor tyrosine kinases or cytokine receptors, can lead to the constitutive activation of STAT3. Activated STAT3 translocates to the nucleus, where it regulates the expression of genes involved in leukemic cell proliferation, survival, and differentiation. Additionally, STAT3 activation in the bone marrow microenvironment may contribute to the leukemic niche, promoting leukemic cell survival and chemoresistance. Therefore, targeting STAT3 signaling represents a potential therapeutic strategy for the treatment of AML by inhibiting leukemic cell growth and enhancing sensitivity to chemotherapy.

JAK1 is highlighted in the pathway associated with HTLV-1 infection, whereas STAT3 is emphasized in the pathway related to acute myeloid leukemia. Both molecules play critical roles in the signaling cascades underlying the pathogenesis of leukemia and represent potential targets for therapeutic intervention.

F. miRNET

MiRNET analysis reveals intriguing regulatory insights into the genes JAK1 and STAT3, particularly in the context of the identified miRNA hsa-miR-17-5p. For JAK1, hsa-miR-17-5p emerges as a predicted regulator, suggesting a potential mechanism for modulating JAK1-mediated signaling pathways. Since JAK1 plays a pivotal role in cytokine signaling and is implicated in leukemia progression, the downregulation of JAK1 by hsa-miR-17-5p could influence critical cellular processes such as proliferation and survival. Similarly, miRNET analysis indicates that STAT3 is also a predicted target of hsa-miR-17-5p, hinting at a regulatory axis between this miRNA and STAT3. Given STAT3's significance in leukemogenesis and its association with adverse prognosis in leukemia, the modulation of STAT3 expression by hsa-miR-17-5p underscores the potential impact of this miRNA on leukemic cell growth and survival pathways. Therapeutically, targeting the hsa-miR-17-5p/JAK1 or hsa-miR-17-5p/STAT3 axes could offer promising avenues for leukemia treatment, either through miRNA-based therapeutics aimed at restoring miRNA levels or through interventions targeting downstream signaling pathways. Overall, understanding the regulatory roles of hsa-miR-17-5p in modulating JAK1 and STAT3 sheds light on novel mechanisms underlying leukemia pathogenesis and unveils potential therapeutic targets for further exploration.

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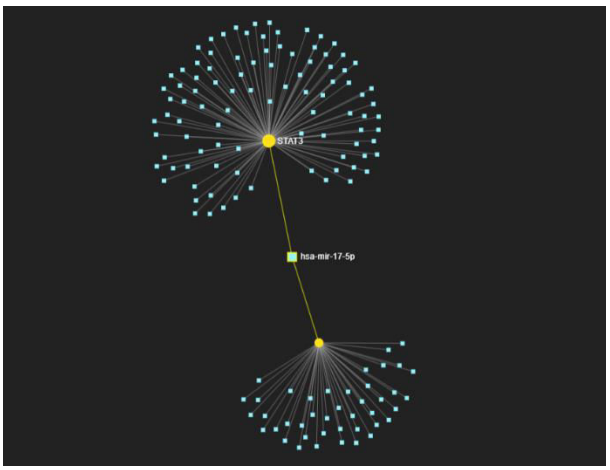

Fig.7 regulatory axis between this miRNA and STAT3

G. Molecular Docking

Using Discovery Studio Visualizer, a powerful molecular docking software, we conducted simulations to explore the potential interactions between JAK1 protein (PDB ID: 6GGH) and FDA-approved drugs for leukemia. Among the screened drugs, Thioguanine emerged as the most promising candidate, exhibiting a calculated binding affinity score of -0.540554. Thioguanine, a chemotherapy medication used to treat leukemia, particularly acute myeloid leukemia (AML), demonstrated strong interactions with the binding site of JAK1, suggesting its potential efficacy in modulating JAK1-mediated signaling pathways implicated in leukemia pathogenesis. Thioguanine's SMILES notation is CC1=C(C(=O)N=C(N1)N)S.

Additionally, we investigated the interactions of other FDA-approved drugs with JAK1 to assess their potential as therapeutic agents for leukemia. Atovaquone, Arsenic Trioxide (Trisenox), Azacitidine (Onureg), Cytarabine, Clofarabine, Mercaptopurine, Nelarabine, Prednisone, Dasatinib (Sprycel), and Vincristine Sulfate were among the compounds screened in our study. However, Thioguanine demonstrated the most favorable binding characteristics, suggesting its superiority as a targeted therapy for leukemia, particularly in the context of JAK1-mediated signaling pathways.

The selection of Thioguanine as the finalized drug candidate stems from its ability to effectively target key proteins involved in leukemia progression. By binding to JAK1, Thioguanine may disrupt downstream signaling cascades associated with aberrant cytokine signaling, thereby inhibiting leukemic cell proliferation and survival. Furthermore, Thioguanine's favorable binding affinity with JAK1 underscores its potential as an effective therapeutic agent for leukemia treatment.

Overall, our findings highlight Thioguanine as a promising targeted therapy for leukemia, with potential implications for improving patient outcomes. Further preclinical and clinical studies are warranted to validate its efficacy and safety profile, ultimately advancing its potential as a novel therapeutic option for leukemia patients.

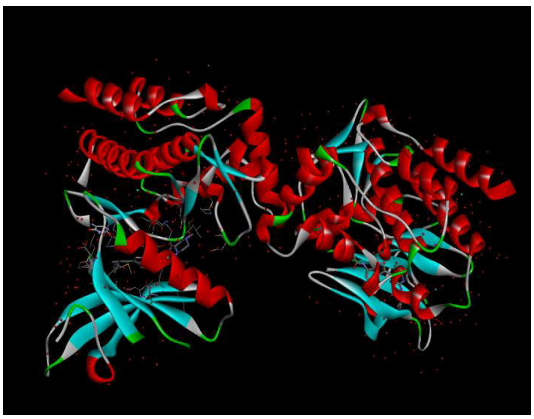

Fig.8 6GGH Structure

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IV. CONCLUSION

In this study, we conducted a comprehensive computational investigation into the genetic targets and regulatory networks involved in leukemia metastasis, with a focus on immune responses and molecular pathways. Through an interdisciplinary approach integrating literature review, gene identification, coexpression analysis, pathway mapping, miRNA profiling, and molecular docking simulations, we gained novel insights into the complex mechanisms driving leukemia progression.

Our analysis identified 25 genes frequently implicated in leukemia metastasis, with JAK1 and STAT3 emerging as central players in a molecular network regulating immune responses and signaling pathways. Pathway analysis highlighted the roles of JAK1 in Human T-cell leukemia virus 1 infection and STAT3 in Acute myeloid leukemia, underscoring their significance in leukemia pathogenesis. Furthermore, miRNA analysis revealed potential regulatory mechanisms involving hsa-miR-17-5p targeting JAK1 and STAT3, offering therapeutic implications for leukemia treatment.

Through molecular docking simulations, we evaluated the interactions between JAK1 and FDA-approved drugs for leukemia, identifying Thioguanine as a promising candidate with strong binding affinity and potential efficacy in modulating JAK1-mediated signaling pathways. Our findings suggest that Thioguanine holds promise as a targeted therapy for leukemia, particularly in the context of JAK1-mediated pathways, and warrants further preclinical and clinical investigation to validate its efficacy and safety profile.

Overall, this study provides valuable insights into the molecular landscape of leukemia metastasis and highlights potential therapeutic targets and interventions for improving patient outcomes. By elucidating the intricate mechanisms underlying leukemia progression, our findings contribute to the development of targeted therapeutic strategies tailored to individual patients, ultimately advancing the field of leukemia research and treatment.

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