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Reveiw Article

JAK/STAT AS A NOVEL TARGET FOR TREATMENT OF LEUKEMIA

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ABSTRACT

Several advances in recent year have focused on leukemia treatment. Primary treatments available for leukemia are Radiotherapy, Bone marrow transplant, Biotherapy, Surgery and Chemotherapy. BCR-ABL tyrosine kinase inhibitor E.g. Imatinib mesylate has revolutionized and set the landmark in this field. It is used as first line treatment in chronic myelogenous leukemia. But, due to resistance developed by the blood cells through the mutations in the BCR-ABL gene need for the newer target arises. The Janus kinase (JAK) and signal transduction and activator of transcription (STAT) pathway stands in a paradigm of how diverse extracellular signal can elicit rapid changes in gene expression in specific target. JAK/STAT is dominant pathway for signal transduction of erythropoietin, growth factor and cytokines receptors. Cytokines are major mediators for cell maturation and multiplication. When cytokines bound to the receptor Jaks gets autophosphorylates and in turn, phosphorylates STATs. Activated STAT is form dimer which is transported into nucleus where it shows gene regulatory effect. Due to mutations in JAK gene Janus kinase gets activated without Cytokines or other growth factors binding which leads to the Antiapoptic activity. The current review underlines the role of Jak/stat in pathophysiology of Leukemia and it's inhibitors as potential drug for leukemia treatment.

Keywords: Leukemia, Janus Kinase, Signal transducers and activators of transcription.

INTRODUCTION

Leukemia is blood disorder which is developed due to perturbed cell development process. Stem cells are converted into blood cells through various steps. Each step is regulated by cytokines and growth factors through their respective receptors present on cell surface. Any change in this regulation can lead to the leukemia.

Leukemia can be divided into four different types. It is classified as acute or chronic. In chronic leukemia, the leukemia cells are abnormal, but mature cells. The cells remain as such for too long and accumulate. These types of cells slowly multiply. Acute leukemia develops from immature cells, called "blasts," which have tendency to multiply frequently. In acute leukemia cells, they don't stop dividing like normal cells do. After being classified as acute or chronic, it is then classified the cells from which leukemia started. It can either be myelogenous or lymphocytic. Lymphocytic leukemia develops from cells called "lymphoblast" or "lymphocytes" in the blood marrow. The disease can be acute or chronic, called as chronic lymphocytic leukemia (CLL) and acute lymphocytic leukemia (ALL). There are several types of lymphocytic leukemia [1]. Myelogenous leukemia develops from myeloid cells. The disease can either be chronic or acute, referred to as chronic myelogenous leukemia (CML) and acute myelogenous leukemia (AML). There are several types of myelogenous leukemia [2].

There are various factors which is responsible for the development of leukemia. Radiation can induce leukemia dose dependently[5, 6, 7]. Human T-cell leukemia virus is retro virus and has tendency to develop T-cell leukemia[3]. Benzene and its derivative is also potential cause for development of leukemia[14]. Many NSAID's contains benzene in its core so, if taken for longer period of time can show leukemic cell proliferation. As cigarette smoke is also major source of benzene which is inhaled in lungs and transferred to blood which than accumulate into bone marrow leads to some mutations which can develops myeloproliferative disorders. Chromosomal aberrations and translocations are most often found in patient suffering from leukemia. DNA mutations are major cause of leukemia. The Bcr-Abl fusion gene is characteristic of chronic myelogenous leukemia (CML) and some cases of acute lymphoblastic leukemia (ALL)[5]. Overall, the incidence of leukemia is a complex result of the role of multiple factors, genetic predisposition, viruses, radiation, chemical substances may interact, with overlapping roles in the occurrence of leukemia.

Diagnosis is done by Bone marrow aspiration. a bone marrow aspiration and/or biopsy procedure will be carried out to actually look at the fluid and/or tissue ("solid marrow") in the marrow and evaluating the number, size, and shape of each of the cell types, as well as the proportions of mature and immature cells[8, 9]. Immunophenotyping or phenotyping by flow cytometry this test can be used to help diagnose leukemia and to determine which type of leukemia a person has [10, 11, 12].

Leukemia symptoms can occur all of a sudden or gradually. Fever, infection is seen as WBC count gets down. Fatigue, physical exercise intolerance, abdominal pain, or generally feeling fullness, weight loss appears due to reduction in normal erythrocytes. Bleeding is conmen as platelet number is less.

The primary treatment available for leukemia is Chemotherapy, Radiotherapy, Biotherapy, Immunotherapy, Bone marrow transplant and Surgery. Radiation is used to kill cancer cells and shrink tumors. Biologic therapy is a treatment that uses the patient's immune system to fight cancer. Surgical removal of the spleen is also a treatment option for chronic leukemia. The spleen collects leukemic cells and they accumulate and results in enlargement of spleen. A bone marrow transplant is procedure to replace bone marrow that has been destroyed by treatment with high doses of anticancer drugs or radiation Transplantation may be autologous (an individual's own marrow saved before treatment), allogeneic (marrow donated by someone else), or syngeneic (marrow donated by an identical twin) [13]. Chemotherapy is the use of drugs that either kills cancer cells or preventing the cells from dividing.

Table 1: It shows Medications choice for leukemia [14, 15, 16, 17, 18]

Acute			Chronic	
ALL	**AML**	**APL**	**CLL**	**CML**
Prednisone	Cytarabine	ATRA	Cyclophosphamide + Vincristine + Prednisone	Imatinib
Methotrexate	Idarubicine	Arsenic trioxide	Fludarabine	Dasatinib
Asparaginase	Mitoxantron	Daunorunicin	Chlorambucil	Nilotinib
Doxorubicin		Idarubicine	Rituximab	Hydroxyurea
Daunorunicin			Alemtuzumab	Busulfan Interferon-α

ALL- Acute lymphocytic leukemia ;AML- Acute myelogenous leukemia ; APL- Acute promyelocytic leukemia ; CLL-Chronic lymphocytic leukemia ; CML – Chronic myelogenous leukemia ; ATRA-All trans retinoic acid;

Need for Novel target system

As per the table:1 most of the traditional antineoplastic agent used in Leukemia shows many life threatening side effect like myelosuppression, cardiac toxicity, peripheral neuropathy etc. Imatinib mesylate, targets the BCR-ABL kinase as well as a few structurally related kinases. This drug has proven to be effective in the treatment of CML patients. However, leukemic cells have evolved mechanisms to become resistant to this drug. A means to combat drug resistance is to target other prominent signaling components involved in the pathway or to inhibit BCR-ABL by other mechanisms.

Treatment of Imatinib-resistant leukemia cells with drugs that target Ras (farnysyl transferase inhibitors) or with the protein destabilizer geldanamycin has proven to be a means to inhibit the growth of resistant cells. Although the introduction of kinase inhibitors such as Imatinib mesylate has revolutionized the treatment of this disease, several clinical challenges persist. Some patients cannot tolerate the side effects from kinase inhibitors, and in others mutations arise in BCR/ABL rendering it resistant to the effect of kinase inhibitors. In addition, kinase inhibitors do not eradicate the leukemic stem cell, and thus patients need to take these drugs indefinitely [19].

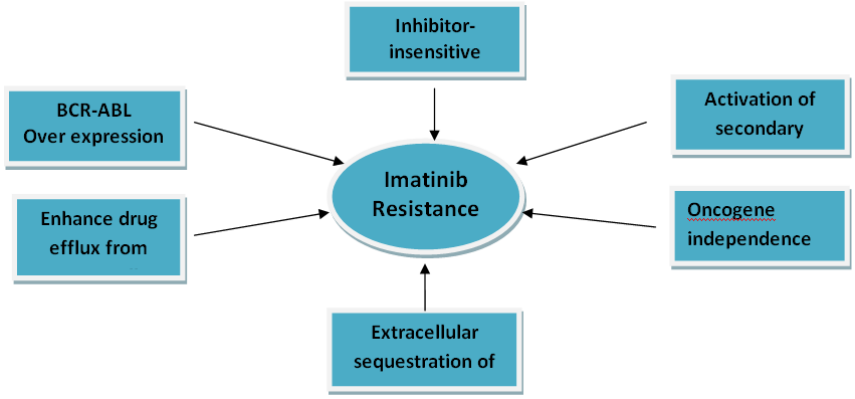


Fig. 1: It shows resistance developed by blood cells to the Imatinib (BCR-ABL kinase inhibitor) [19]

JAK\STAT inhibitor as novel target for leaukemia

The Janus kinase (JAK)-signal transducer and activator of transcription (STAT) pathway plays a critical role in the signaling of a wide array of cytokines and growth factors leading to various cellular functions, including proliferation, growth, Hematopoiesis, and immune response[20,21].

As a stem cell matures it undergoes changes in gene expression with which cell anatomy and physiology changes and makes it closer to specific cell line. This change in gene expression is associated with presence of specific proteins on the cell membrane and its expression. These proteins may be referred as receptor or ligand binding domain and with different receptor and functioning of it makes it closer to its specific cell line.

Red and White blood cells production is regulated in healthy human. When stem cell factor binds to its receptor it triggers proliferation and renewal of cell. After proliferation many glycoprotein growth factor regulates the maturation of the cells which makes it closer to desired cell line or needed cell line. Three more factors that stimulate the production of cells are called colony-stimulating factors (CSFs)

and include granulocyte-macrophage CSF (GM-CSF), granulocyte CSF (G-CSF) and macrophage CSF (M-CSF). These factors act on progenitor cell or the mature cell. Growth factors initiate signal transduction pathways which alters transcription factors and activates genes that determine the differentiation of blood cells [24].

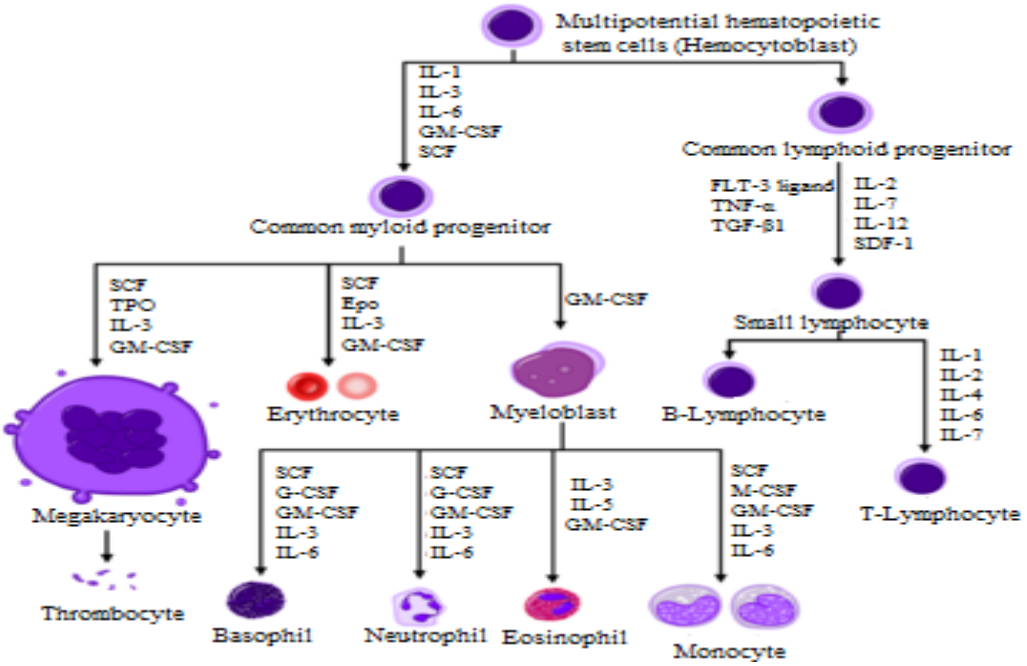
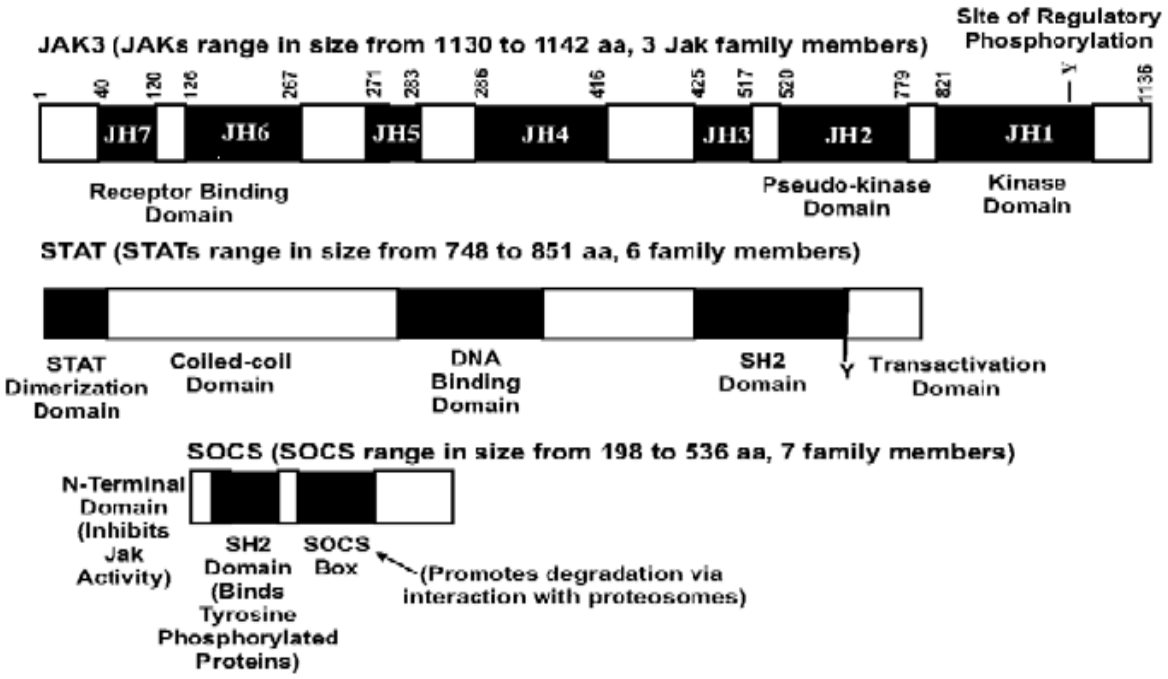


Fig. 2: It shows involvement of cytokines in blood cell development [22, 23]

Diagram including some of the important cytokines that determine which type of blood cell will be created. SCF= Stem Cell Factor; Tpo= Thrombopoietin; IL= Interleukin GM-CSF= Granulocyte Macrophage-colony stimulating factor; Epo= Erythropoietin M-CSF= Macrophage-colony stimulating factor; G-CSF= Granulocyte-colony stimulating factor ;SDF-1= Stromal cell-derived factor-1; FLT-3 ligand= FMS-like tyrosine kinase 3 ligand ;TNF-α = Tumor necrosis factor-alpha; TGF-β = Transforming growth factor beta.

The binding of cytokines and growth factors to their corresponding receptors activates JAK, which then phosphorylates the receptor and STAT proteins on specific tyrosine residues. STATs then dimerize, translocate to the nucleus, bind to the consensus DNA sequence of 5'-TT(N_{4-6})AA-3' and initiate the transcription of target genes [25, 26].

Four JAK family kinases, including JAK1, JAK2, JAK3, and TYK2 [27,28] and seven STAT family members, including STAT1, STAT2, STAT3, STAT4, STAT5a, STAT5b, and STAT6 [29] have been identified. JAK 3 found in lymphoid cells and all other are very ubiquitous. The JAKs are structurally has two domain C-terminal kinase domain (JH1) followed by a pseudokinase domain (JH2), which lacks the catalytic activity but has a critical regulatory function. JAKs also have a Src homology 2 (SH2) domain and an N-terminal band four-point-one, ezrin, radixin, moesin (FERM) domain that is critical for mediating the association with cytokine receptors [30,31]. STAT proteins contain a SH2 domain for dimerization and a DNA-binding domain. The amino acid sequence diversity and their tissue-specific distributions account for the diverse roles of STATs in response to extracellular cytokines.



Structure of the JAK, STAT and SOCS proteins. The JAK family of proteins is centrally involved in cytokine-mediated signal transduction (see Kisseleva et al 49 and Krebs and Hilton50 and references therein). The JAK family consists of JAK1, JAK2, JAK3 and TYK2. The JAK family of kinases contains seven JAK homology (JH) regions. Shown in this diagram is the JAK3 protein with the amino-acid residues indicated in the JH regions. The JH1 region is the kinase domain that contains a regulatory tyrosine residue. The STAT family of proteins consists of at least seven STAT proteins, which all have a STAT dimerization domain, a coiled-coil domain, a DNA-binding domain, an SH2 domain for interaction with tyrosine-phosphorylated proteins and finally a transactivation domain. The SOCS (suppressor of cytokine signaling proteins) consists of at least six SOCS proteins and a CIS (cytokine-inducible SH2-containing) protein. These proteins contain an amino-terminal domain which inhibits JAK activity, an SH2 domain which binds tyrosine-phosphorylated proteins and a SOCS box which

Fig. 3: It shows structure of the Jak, stat, and socs [35]

Abnormal constitutive activation of JAK-STAT pathways has been implicated in various cancers and immune disorders. For example, STAT3 is persistently activated in many tumors, including major carcinomas and some hematologic tumors. Activating mutations in JAK2 have been linked to leukemia.

Table 2: It shows role of Jak in Hematopoiesis

Jak Type	Relevant Phenotypes	Cytokines affected	Reference
Jak 1	• Impaired lymphoid development • Defective responses to class 2cytokines and those using gc or gp130 receptor subunits	IL-2, IL-4, IL-6, IL-7, IL-9, IL-10, IL-15, LIF, all interferons	32
Jak 2	• No definitive erythropoiesis	EPO, TPO, IL-3, IL-5, GM-CSF, IFN-g	33
Jak 3	• Defective lymphoid development • Dysregulated myelopoiesis	IL-4, IL-7, IL-9, IL-15	34

Table 3: It shows role of Stat in Hematopoiesis

Stat Type	Relevant Phenotypes	Cytokines Affected	Reference
STAT 1	Interferon responses absent: —innate immune responses absent —highly sensitive to viral/microbial infection —IFN-responsive genes not activated	IFNs only	38
STAT 2	Type 1 interferon responses impaired	IFN-a/b	
STAT 3	Embryonic lethal		39
STAT 4	IL-12 responses absent Decrease production of high IFN-g, low IFN-g Ra Th1 cells Decrease priming for high level IFN-g production Decrease lymphocyte proliferation Decrease enhancement of NK cell-mediated cytotoxicity Increase Th2 cells	IL-12 only	40,41
STAT 5a/b	Proliferation signaling affected: Decrease CFU-Mix, Eos, G, GM, Pre-B Decrease peripheral T cells Absence of NK cells	IL-2, IL-3, IL-7, GM-CSF, G-CSF	42,43
STAT 6	L-4 responses absent: -Absence of IL-4 producing Th2 cells -Block in B-cell IgE class switching < lymphocyte proliferation (partial),< expression of IL-4-induced cell surface markers	IL-4 only	44,45

TEL-JAK2 fusion due to chromosomal translocation was identified in a small set of human T cell acute lymphoblast leukemia patients. Inhibitors of JAK-STAT pathways are currently being sought in the areas of oncology and immune disorders.

In the JAK/STAT signaling Pathway, ligand binding to cytokine receptors results in dimerisation of receptor subunits either it will form homo dimer or hetero dimer depending on the type of cytokine or ligand binds to cytokine receptor e.g. when erythropoietin binds to its receptor results in homo dimer formation and if interferons or interleukins bind to its receptor leads to hetero dimer formation. Ligand binding is followed by association of two cytoplasmic subunits of receptor with Jak, Which brings the two JAKs into close proximity, aiding their transphosphorylation. The activated JAKs can then phosphorylate STATs near C-terminus which has conserved tyrosine residue. After phosphorylation two molecules of STAT form dimer by interacting with a conserved SH-2 domain. In unstimulated cell STAT remains in cytoplasm but after dimerisation it is transported to nucleus by importin-5 a mechanism. Activated Stat then binds to DNA and starts transcription and further signaling leads to further maturation and functioning of cell.

JAK/STAT signaling is negatively regulated by three different mechanisms. First includes suppressors of cytokine signaling (SOCS), second is protein inhibitors of activated stats (PIAS) and third is protein tyrosine phosphatases (PTPs). SOCS proteins contain an SH2 domain same as that of STAT and a SOCS box at their C-terminus. They contain inhibitory domain near SH-2 domain at N-terminal. Activated STATs binds to SOCS gene and transcribe SOCS protein which binds to activated Jak as this protein has SH-2 domain which is binding site for Jak and by its inhibitory activity this protein blocks activity of phosphorylated Jak. The SOCS can also bind to phosphotyrosines residues on the receptors and block the recruitment of STATs to these receptors. The PIAS protein family consists of five members: PIAS1, PIAS3, PIASxa, PIASxb, and PIASy. They bind to activated STAT dimers and prevent their DNA binding. They contain a Zn-binding 'RING finger' domain in their central domain, a well-conserved SAP (SAF-A/Acinus/PIAS) domain at the N-terminus, and a less well- conserved carboxyl domain. SHP-1, a tyrosine phosphatase can also regulate JAK/STAT signaling by dephosphorylating JAK. Here, the SH2 domains of SHP-1 bind phosphorylated JAK and/or phosphorylated receptors to block JAK/STAT signaling. [46, 47]

JAK/STAT pathway plays an important role in the establishment of cell fate. For example, IL-12 regulates the maturation of CD4+ T cells to Th1 cells by activation of STAT-4. STAT-4 Knockout mice don't respond to IL-12 and produce Th2 cells. Similarly from knockout mice study role of STAT-6 in maturation of CD4+ cell to Th2 cell established.

Aberrant activation of Jaks and Stats

The most direct evidence implicating dysregulation of the Jak-Stat pathway in hematopoietic malignancies was the identification of Tel-Jak2 fusions in lymphoid and myeloid leukemia [48, 49]. In early B-precursor acute lymphoblastic leukemia, t(9;12)(p24;p13) translocations were responsible, whereas in the case of atypical chronic myeloid leukemia there was a complex t(9;15;12)(p24;q15;p13) translocation. In each case, the helix-loop-helix oligomerization domain of the transcription factor Tel is fused to the catalytic JH1 domain of Jak2 (Figure 5) and during fusion of two domain TEL- JAK regulatory domain JH-2 is partially or completely being eliminated. As previously explained JH2 domain required for regulatory activity. Change in this regulatory domain leads to constitutive association and hence activation of the kinase and constitutive activation of Stat proteins [50, 51].

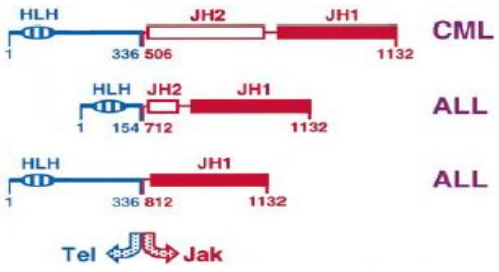


Fig. 4: It shows Tel-Jak2 fusions observed in myeloid (CML; chronic myeloid leukemia) and lymphoid (ALL; acute lymphoblastic leukemia) leukemias [48, 49]

The relative position of the fusion, as well as the helix-loop-helix (HLH) and Jak homology (JH) domains are shown.

However JAK-STAT can be activated by oncogenic viruses in normal hematopoietic cell by expressing oncogenic tyrosine kinase. Oncogenic viruses elicit the effect through many cytokine kinases which involves Jak or directly Activates Stat (Figure 5) [53].

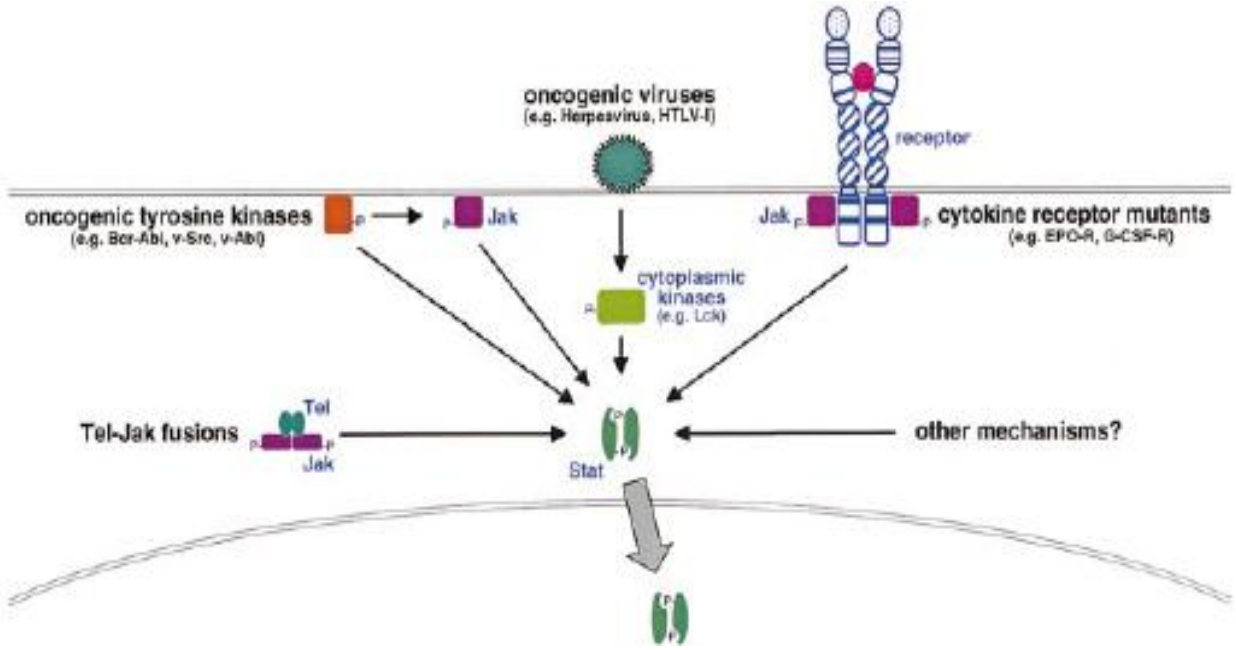


Fig. 5: It shows mechanisms of aberrant stat activation in hematopoietic malignancy disease.[64]

Stat gets activated by different mechanism which is consequently results in differentiation of cells uncontrollably which has defects in one or other way.

Evidence for Jak-Stat involvement

The data given above are correlative but there are few evidence found about involvement of Jak/Stat in study. For example, Ba/F3 cells are dependent on IL-3 for their survival but Tel-Jak fusion protein makes it IL-3 independent as Jak constitutively gets activated with or without IL-3 in medium[48, 50].

Retrovirus expressing this fusion when transplanted to mice develop a fatal mixed myeloproliferative and T-cell lymph proliferative disorder with a latency of 2 to 10 weeks [50].

Currently available Janus kinase inhibitor

Janus Kinase inhibitors shows its effect by reversibly or irreversibly inhibiting enzymes of family Janus kinase which interferes with JAK-STAT pathway.

Some Jak inhibitors are still under clinical trials for many blood disorders like polycythemia vera, thrombocythemia, Myelofibrosis [65].

Lestaurtinib is JAK2 inhibitor used in acute myelogenous leukemia (AML). Tofacitinib JAK3 inhibitor used in for psoriasis,[66] and rheumatoid arthritis[68,69]. Ruxolitinib[71] against JAK1/JAK2 for psoriasis,[66] myelofibrosis,[72,73] and rheumatoid arthritis[74]Pacritinib (SB1518)[75,76],CYT387 [77], LY3009104 [71] and TG101348 are the other example of Jak inhibitors which are in use for blood disorders and inflammatory diseases.

Currently available Stat inhibitors

Stat inhibitors are effective in many disorders which are arises due to constitutive activation of Stat due to environmental or genetic factor. Cryptotanshinone, Cucurbitacin I, Niclosamide, SD 1008, Stattic are few examples of stat inhibitors.

There are many drugs available in market which were originally approved for other disorders and later found to be stat inhibitor. Niclosamide, Nifuroxazide, Pyrimethamine are few of them. Pimozide, which was earlier approved for Tourette's syndrome in USA[80], but later on it was found that it is stat-5 inhibitor which can be used in the disorder related to constitutive STAT-5 activation and is useful in Chronic myelocytic leukemia.

Future directions

It is very much clear from this review that Jak/Stat pathway is disturbed in leukemia. It is also evident that Jak-Stat gets constitutively activated in many other malignancies However, the significance of altered Jak-Stat activation in the other disorders remains less clear. Now-a-days knockout mice with important component of Jak/Stat can elicit the importance of this pathway in various disorders. Much remains to study about Jak/Stat structure and it effect on functioning as well as its interaction with other signaling scheme.

CONCLUSION

Leukemia is disorder related to the blood cell and its development. During the developmental stage of blood cells due to genetic or other reasons growth of blood cells arrest in immature state, where it is unable to work their functions properly as well as has tendency to multiply rapidly. These cells are called blast cells, which are responsible for the development of leukemia. Jak/stat is the signal transduction pathway for the majority of growth factors, colony stimulating factor, erythropoietin, interleukin and various other mediators. Any modification in this process leads to serious consequences. Janus kinase is also called non receptor kinase, has capacity to phosphorylate it self when ligand binds to the receptors, which in turn phosphorylates the stat. Stat is than dimerize and get transported into nucleus where it bound to DNA and regulates the gene expression. Stat has SH-2 domain which is phosphorylated by Jak. Expression of Jak is controlled by gene JAK. Any mutation in this gene leads to the impaired function of Jak. Jak get activated without receptor activation by ligand or its kinase activity becomes uncontrolled which is responsible for cell survival and consequently Antiapoptic effect. Jak inhibitor inhibits the activation of Jak by

directly binding to it or indirectly blocking its kinase activity. There are many Jak inhibitors approved for anti-inflammatory effect and many are in phase-III trial for leukemia treatment. Stat inhibitors as it blocks the Stat by preventing dimerization or inhibiting transport of stat in nucleus or preventing the binding of the stat to DNA. Jak/stat pathway is potential target system for the leukemia and other blood disorders like polycythaemia Vera, myelofibrosis, and lymphomas.

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