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Stat5 as a diagnostic marker for leukemia


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The Jak-Stat-Socs pathway is an important component of cytokine receptor signaling. Not surprisingly, perturbation of this pathway is implicated in diseases of hematopoietic and immune origin, including leukemia, lymphoma and immune deficiencies. This review examines the role of a key component of this pathway, Stat5. This has been shown to be activated in a variety of leukemias and myeloproliferative disorders, including downstream of a range of key oncogenes where it has been shown to play an important role in mediating their effects. Therefore, Stat5 represents a useful pan-leukemia/myeloproliferative disorder diagnostic marker and key therapeutic end point, as well as representing an attractive therapeutic target for these disorders.

KEYWORDS: cytokine signaling • diagnostics • hematology • Jak-Stat pathway • leukemia • myeloproliferation • oncology • Stat5 • therapeutics

Jak-Stat-Socs pathway

The Jak-Stat-Socs pathway represents an evolutionarily conserved signaling module widely engaged by growth factor and cytokine receptors to rapidly facilitate changes in gene expression in response to appropriate external stimulus [1–4]. Thus, the binding of many cytokines or growth factors to their cognate cell surface receptor triggers dimerization and structural changes in the receptor complex, which leads to the activation of one or more members of the Jak family of protein tyrosine kinases, which are prebound to the cytoplasmic domain of the receptor. This results in autophosphorylation of adjacent Jak proteins as well as phosphorylation of the receptor. The resultant phosphotyrosine residues on the receptor (and Jak) then serve as docking sites for members of the Stat family of transcription factors. These then become tyrosine phosphorylated, forming either homo- or heterodimeric complexes that translocate to the nucleus and bind to the promoter region of responsive genes to activate their transcription. Target genes include the Socs family of proteins (Socs1–7 and Cis), which generally act as a negative feedback system via direct competition of Stat binding, inhibition of Jak kinase activity or degradation of active receptor complexes [3,5–7].

Stat5 proteins

Mammals possess two Stat5 proteins, Stat5a and Stat5b, which have 96% homology and are encoded by adjacent genes [8]. These proteins were first identified as prolactin (PRL)-induced mammary gland factor that produced tissue-specific and hormonally controlled transcription of the β-casein gene promoter [9]. It is now known that Stat5 proteins are activated by a wide range of cytokine receptors (TABLE 1) [1]. This includes those utilizing the common γ-chain (γC) family, such as the IL-2 receptor (IL-2R), IL-4, IL-7R, IL-9R, IL-15R and IL-21R, those belonging to the IL-3R family, IL-3R, IL-5R and granulocyte-macrophage colony-stimulating factor receptor (GM-CSFR), the single-chain receptors for erythropoietin (EPO), thrombopoietin (TPO), growth hormone (GH), PRL and granulocyte CSF receptor (G-CSF), as well as the class II receptors for IFNα/β, IFNγ and IL-22 [9–14]. In addition, several receptor tyrosine kinases can activate Stat5 proteins, including those for EGF, PDGF and CSF-1 [15,16]. Furthermore, oncostatin M has been shown to activate Stat5 through a heterodimer with gp130 or IL-31 [17,18], whilst thymic stromal lymphoprotein (TSLP) achieves this via a heterodimer between TSLPR and IL-7Rα [19].
Activation of Stat5 proteins then results in activation of a range of key genes, depending on the cellular context [20]. These include those encoding Bcl-XL, cyclin D1, Myc, p21, telomerase and Pim-1 [21–29]. These proteins play key roles in processes like cell survival and proliferation through effects on apoptosis and/or the cell cycle. Therefore, perturbation of Stat5 activation has the ability to disrupt these key cellular processes.

Stat5 ablation in mice produced major defects in response to PRL, GH and a range of hematopoietic cytokines. Stat5a knockout mice were principally defective in PRL-mediated mammmopoiesis and lactogenesis [30,31], while knockdown of the orthologous zebrafish stat5.1 also produced phenotypes that mirrored those of PRL receptor knockdowns [LEWIS ET AL., MANUSCRIPT SUBMITTED]. Stat5a knockout mice also displayed subtle defects in T-cell proliferation in response to IL-2 and GM-CSF-induced proliferation of bone marrow-derived macrophages [31–33]. By contrast, Stat5b knockouts were phenotypically similar to GH-deficient mice, with reduced bodyweight, skeleton size and loss of sexual differentiation responses [31,34,35]. These mice also demonstrated a decrease in the number of natural killer (NK) cells and diminished proliferation of T cells in response to IL-2 and IL-15 [36,37]. A subsequent Stat5a/b double-knockout mouse exhibited exacerbated PRL, GH and much more severe hematopoietic defects; the latter manifested by an absence of NK cells, dramatically reduced numbers of pro-B cells and fewer myeloid colonies [31,36,38]. This suggests some functional redundancy between Stat5a and Stat5b, especially with respect to the hematopoietic cytokine receptors. Further studies have revealed that these mice are best considered as ‘knockdowns’, forcing a re-evaluation of the role of Stat5. Recently generated complete Stat5a/b knockouts showed over 99% perinatal lethality in day 18.5 fetuses with severe hematopoietic defects, including anemia, leukopenia and substantially reduced numbers of both T and B cells [39,40]. These phenotypes were also largely recapitulated in zebrafish stat5.1 knockdown embryos [LEWIS ET AL., MANUSCRIPT SUBMITTED].

Stat5 proteins have also been observed to be activated in a range of disease states, including malignancy. These encompass cancers of the breast, head and neck, prostate, melanoma, as well as leukemia and myeloproliferative disorders [25]. The remainder of this review provides an overview of these disorders, and the role of Stat5 as a diagnostic marker, pathogenic factor and potential therapeutic target.

**Leukemia & myeloproliferative diseases**

Normal hematopoiesis is the process whereby hematopoietic stem cells give rise to multilineage progenitor cells that differentiate into specific subsets of cells; erythroid, myeloid or lymphoid. This process is highly regulated by cytokines that control checkpoints of the cell cycle. Disruption in the regulation of appropriate signaling can lead to uncontrolled expansion of hematopoietic cells, leading to disease [3,41,42]. These include a range of malignancies, including acute myeloid leukemia (AML), acute lymphoblastic leukemia (ALL), acute promyelocytic leukemia (APL), chronic lymphocytic leukemia (CLL), chronic myelogenous leukemia (CML) and erythroleukemia, as well as disorders characterized by an overproliferation of myeloid cell populations, such as polycythemia vera (PV), essential thrombocythemia (ET) and idiopathic myelofibrosis (Table 2) [3,43–49]. Given the key role by the Jak-Stat pathway downstream of the raft of cytokines regulating hematopoiesis, it is not surprising that mutation or dysregulation of this pathway can contribute to many of these hematopoietic diseases. In particular, the signal transducers, Stats, appear to be activated in many of these diseases.

**Stat5 as a marker of leukemia**

Constitutive activation of Stats has now been identified in primary samples from a range of malignancies, including leukemias, with Stat1, Stat3 and Stat5 predominantly activated [50]. Stat5 activation is found in patients with AML [51–53], ALL [50,51], CML, erythroleukemia and megakaryocytic leukemia [55–7]. Importantly, introduction of antisense oligonucleotides targeting Stat5 proteins into primary CML or AML blasts decreased proliferation and increased apoptosis, providing prime face evidence for a pathological role for Stat5 [54]. While the underlying cause of dysregulated Stat5 activation is not always known, a clear relationship with an upstream oncoprotein has been identified in many cases.

A common illustrative example is the BCR-ABL oncogene. This results from the translocation t(9;22)(q34;q11), otherwise known as the Philadelphia chromosome, is the most common cause of CML. This translocation leads to the fusion of BCR to

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**Table 1. Cytokines activating Stat5.**

<table>
<thead>
<tr>
<th>Cytokine receptor chain</th>
<th>Cytokine</th>
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<tbody>
<tr>
<td>Common γ-chain (γc)</td>
<td>IL-2</td>
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<tr>
<td></td>
<td>IL-7</td>
</tr>
<tr>
<td></td>
<td>IL-9</td>
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<td></td>
<td>IL-15</td>
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<td></td>
<td>IL-12</td>
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<tr>
<td>IL-3 family</td>
<td>IL-3</td>
</tr>
<tr>
<td></td>
<td>IL-5</td>
</tr>
<tr>
<td></td>
<td>Granulocyte-macrophage colony-stimulating factor</td>
</tr>
<tr>
<td>Single-chain receptors</td>
<td>Erythropoietin</td>
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<tr>
<td></td>
<td>Thrombopoietin</td>
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<td></td>
<td>Growth hormone</td>
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<td></td>
<td>Prolactin</td>
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<tr>
<td></td>
<td>Granulocyte colony-stimulating factor</td>
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<tr>
<td>Class II receptors</td>
<td>IFNα/β</td>
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<tr>
<td></td>
<td>IFNγ</td>
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<tr>
<td></td>
<td>IL-22</td>
</tr>
<tr>
<td>Growth factors</td>
<td>Stem cell factor</td>
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<tr>
<td></td>
<td>FLT-3</td>
</tr>
<tr>
<td></td>
<td>PDGF</td>
</tr>
<tr>
<td></td>
<td>EGF</td>
</tr>
</tbody>
</table>
the ABL kinase, which increases the tyrosine kinase activity of ABL and also brings new domains to the ABL kinase including an SH2-binding site [55]. It has been shown to activate several downstream pathways, including Stat3, which leads to dysregulated cellular transformation and proliferation [56–58]. It has been well documented in vitro that BCR-ABL-positive cell lines display constitutive phosphorylation and subsequent activation of Stat5, which are not observed in BCR-ABL negative cell lines [59–62]. A truncated version of Stat5B, which deletes Tyr699 and the activation domain, is able to dimerize with endogenous Stat5 and inhibit cell growth in BCR-ABL expressing cells [63]. In addition, this truncated isoform increases cell sensitivity to cytotoxic agents [63]. This has been borne out in vivo, with Stat5 knockout mice demonstrating reduced sensitivity to the effects of BCR-ABL [40,64], as are Jak2-deficient fetal liver cells [65], indicating a role for the Jak2-Stat5 pathway.

Stat5 is also activated by a range of other activated tyrosine kinases. Tel-Jak2 fusion proteins have been observed in patients with three different types of leukemia: pre-B cell ALL, T-cell ALL and atypical CML [66–68]. The fusion (p9;12)(p24;p13) consists of the oligomerization domain of TEL and both the kinase and pseudo-kinase domain of Jak2 [66], and displays constitutive activation of its tyrosine kinase activity [68,69], which leads to the strong constitutive activation of Stat5 [68,70]. Similar results have also been obtained with TEL-PDGFR. In each case, the transformation properties have been shown to be largely dependent on Stat5 [45,71,72]. Stat5 is also activated by activated forms of various tyrosine kinases (including FLT3 [73]) and in viral oncogenesis (including HTLV-1-mediated T-cell leukemia [23]). Further emphasizing its role in leukemia, Stat5 is itself a partner in a leukemic oncogene fusion with retinoic acid receptor-α (RARα) [74,75], a member of the superfamily of nuclear hormone receptors [76]. The Stat5b-RARα fusion, observed in APL, contributes to myeloid maturation arrest by binding to retinoic acid response elements and augmenting activation of Stat5 [74,75]. Finally, methylation of the SOCS1 promoter has been observed in 60% of AML patients [77] and 67% of CML patients [78]. Given that Socs1 negatively regulates the Jak-Stat pathway, including Stat5, it is likely that the reduced expression of Socs1 caused by the methylation may also contribute to dysregulation of Stat5.

The increased proliferation and survival of hematopoietic cells in response to Stat5 activation is most probably linked to transcriptional regulation of downstream targets of Stat5. However, Stat5 has been shown to repress transcription. This was demonstrated most recently by the observation that DNA methylation of the Stat5a promoter is necessary for NPM1-ALK-mediated transformation, because Stat5a is normally able to bind to the enhancer region of NPM1-ALK to trigger-selective suppression of this gene [79]. In addition, the Stat5b-RARα fusion has been shown to interact with a co-repressor complex, which inhibits binding of this complex to RARα, in turn enhancing repressor activity and disrupting hematopoietic differentiation [80].

### Table 2. Stat activation in leukemia and myeloproliferative diseases.

<table>
<thead>
<tr>
<th>Disease type</th>
<th>Transforming kinase</th>
<th>Stat activated</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acute myeloid leukemia</td>
<td>FLT3</td>
<td>Stat1, Stat3, Stat5</td>
</tr>
<tr>
<td></td>
<td>c-Kit, Jak3, v-abl, v-mpl</td>
<td></td>
</tr>
<tr>
<td>Acute lymphoblastic leukemia</td>
<td>Tel-Jak2, Tel-PDGFR</td>
<td>Stat1, Stat5</td>
</tr>
<tr>
<td>Chronic myelogenous leukemia</td>
<td>BCR-ABL p185, p210, Tel-Jak2, Jak2-PCMV</td>
<td>Stat5</td>
</tr>
<tr>
<td>Erythroleukemia</td>
<td></td>
<td>Stat1, Stat5</td>
</tr>
<tr>
<td>Megakaryocytic leukemia</td>
<td></td>
<td>Stat5</td>
</tr>
<tr>
<td>T-cell leukemia</td>
<td>HTLV-1</td>
<td></td>
</tr>
<tr>
<td>B-cell lymphoma</td>
<td>BCR-ABL p185, p210</td>
<td>Stat5</td>
</tr>
<tr>
<td>Myeloproliferative disease</td>
<td>Jak2 (V617F), Tel-Jak2, Tel-PDGFR</td>
<td>Stat5</td>
</tr>
</tbody>
</table>

### Stat5 as a marker of myeloproliferative diseases

Enhanced Stat5 activation has also been observed in several proliferative diseases. One example of this is PV, a disease characterized by erythrocytosis, thrombocytosis, leukocytosis and splenomegaly [81], resulting from cytokine hypersensitivity, particularly to EPO [82]. It has been postulated that a somatic point mutation in the pseudo-kinase domain of Jak2 (V617F) is the underlying cause of PV, and also the related ET and idiopathic myelofibrosis [48,83], because over 95% of PV, 60–70% ET and 50% myelofibrosis patients were found to be positive for this mutation via allele-specific PCR [47,48,84–88]. Mutation of the pseudo-kinase domain relieves autoinhibition of Jak activity [89], which subsequently activates the downstream Stat5 protein, as observed in cell models and primary samples [44,47].

A similar result is observed with several other mutations. For example, truncations of G-CSF receptor lead to hyperproliferation at the expense of differentiation, with a propensity for leukemia development [90]. This correlates with sustained activation of Stat5, which plays a lead role in the hyperproliferation, with other pathways playing a lesser role [91]. In addition, truncating mutations in the EPO receptor have been linked to erythrocytosis, in which there is an isolated proliferation of bone marrow cells of the erythroid lineage due to hypersensitivity to
EPO [92–94]. These truncations lead to prolonged tyrosine phosphorylation of both Jak2 and Stat5 [95], probably due to the loss of binding of the negative regulator SHP-1. Finally, a point mutation in MPL has been identified in 9% of Jak2 V617F-negative myelofibrosis patients and leads to increased Stat5 activation [96], further testifying to the generality of this phenomenon.

Stat5 is also implicated in the myeloproliferation mediated by a range of mutations involving receptor tyrosine kinases. These include FGFR1 fusions, which involve translocations of chromosome band 8p11 [97]. These lead to an aggressive myeloproliferative syndrome (EMS), which is characterized by eosinophilia, lymphadenopathy and progression to acute leukemia [98]. One of the most common translocations is the fusion of the N-terminal of ZNF198 to the catalytic domain of FGFR1 [99,100]. Many Stats are activated by ZNF198-FGFR1 [101]; however, only the dominant negative version of Stat5 was able to inhibit the ability of ZNF198-FGFR1 to survive in low cytokine conditions, due to an essential role in BclXL induction by the fusion protein [97]. In addition, fusion of the FIP1L1 to PDGFRα, which results from a deletion on chromosome 4q12, is found in 56% of patients with idiopathic hypereosinophilic syndrome [102], whilst several novel mutations have been identified that lead to myeloproliferative disease, including an internal tandem repeat involving exons 11 and 12 of c-Kit found in 7% of childhood AML [103].

**Mechanisms of pathogenic action**

From the aforementioned studies, it is clear that Stat5 may be considered both a diagnostic and prognostic marker. Modulation of Stat5 in vivo has provided insights into the mechanism of action in the disease. For example, expression of constitutively active versions of Stat5 alone is sufficient to induce multilineage leukemia in mice [104] and a myeloproliferative disorder in zebrafish [105]. This is mediated via an enhancement in the self-renewal of hematopoietic stem cells [106], including the CD34+ cell population, interestingly with an erythroid bias [107]. Importantly, Stat5 also appears to mediate long-term maintenance of leukemic stem and progenitor cells, although the mutation used in this study could potentially give off-target effects [108].

At a mechanistic level, it appears that tetrameric forms of the Stat5 protein are required for pathogenesis, perhaps leading to more robust activation of certain genes or expansion of the standard repertoire [104]. Most data are consistent with a pro-survival role for the protein: for example, by inducing genes such as BclXL [25]. However, there is evidence that it also plays a role in enhancing/extending cell progression by inducing myc [27,28] and telomerase [29], or by cooperating with loss of p53 [109]. Interestingly, recent studies also suggest a possible role outside the nucleus [110], possibly involving PI3K [111]. In addition, recent studies have demonstrated PI3K-independent activation of Akt via Stat5 [112]. However, it is important to recognize that other pathways act in concert with Stat5.

For example, PI3K with BCR-Abl [58], PI3K and PLCγ with Tel-PDGFR [71], and PI3K and Erk with truncated G-CSF receptors [91].

**Stat5 as a marker for therapeutic intervention**

Stat5 also serves as both a marker of (successful) therapeutic intervention, as well as a target in its own right. This includes first-generation therapies for CML, such as imatinib [53,133,134] or PD180970 [62], as well as those used against resistant CMLs, such as dasatinib (BMS-354825) [115] and sorafenib [116]. The same paradigm is true for the FLT3 inhibitor GTP14564 [117], the multikinase (FLT3/KIT) inhibitor SU5416 [118], the second-generation KIT inhibitor PKC412 [119], and even curcumin in the therapy of HTLV-1-induced T-cell leukemia [120].

Again focusing on the BCR-ABL oncoprotein: a key indicator of the likely success of therapies is their ability to suppress constitutive Stat5 activation. Imatinib is a potent inhibitor of BCR-ABL that has proved to be successful with 80% of CML patients demonstrating complete cytogenetic response after treatment [121,122]. It targets the ATP binding site of the kinase [123,124], thereby stabilizing the inactive form of BCR-ABL [121], inhibiting autophosphorylation and downstream responses, including Stat5 phosphorylation [123]. However, there is a high incidence of resistance to this compound, with at least 30 different point mutations identified that block the ability of the compound to bind the kinase [125,126], while gene amplification and subsequent overexpression serve as an alternate route for generating resistance [125]. As a result, a second generation of inhibitors has been created [127–129]. This includes BMS-354825, which is 100-times as potent, is active against most resistant BCR-ABL mutants in vitro [128] and also blocks Stat5 signaling, inhibits cell proliferation and induces apoptosis [115].

There are many ongoing studies to identifying specific pan-Jak2 inhibitors based on the molecular structure of the Jak2 and Jak3 kinase domains, and they are refining the original tyrosine phosphorylation inhibitors [130,131]. In addition, there are currently screens underway in an attempt to identify specific inhibitors of Jak2V617F, which will provide an optimal therapeutic as only the disease allele will be targeted [132].

Underpinning the key role of Stat5 is the recent realization that one mechanism by which cells lose sensitivity to imatinib is to utilize alternate pathways to activate the protein, such as via secretion of GM-CSF and subsequent autocrine activation [133]. Moreover, targeting Stat5 by RNAi leads to a reduction in proliferation to the same extent as BCR-ABL RNAi in cell culture, and could reduce colony formation from primary CML [134].

**Expert commentary**

Leukemia poses a significant health burden, with approximately 44,000 new cases diagnosed in the USA in 2007, striking more than 10-times as many children as adults, while
MPDs present serious concerns for an older cohort of patients. Current advances in both basic science and pharmaceutical technologies have seen rapid advances in our understanding of both leukemia and MPD at the molecular level in recent years. In particular, these insights have led to the generation of drugs to help combat these diseases, including the tailoring of therapies to specific patients depending on their molecular profile. Thus, we have already seen the revolution of specific kinase inhibitors, such as to BCR-ABL, and now second-generation compounds that overcome the problems of resistance. However, with so many molecular changes now known to contribute to these diseases, and the increasing incidence of resistance to these drugs, more specific therapies are required. Activation of Stat5 has been demonstrated in a large number of leukemias and MPDs, and thus represents a useful diagnostic marker of both leukemia and MPD. Moreover, since Stat5 is a point of common convergence for a range of different pathologic alterations, it is also a sensible therapeutic target for these diseases.

Five-year view

Over the next 5 years, we anticipate that Stat5 (and other Stat proteins) will become a key diagnostic and prognostic marker. It will be increasingly targeted for therapeutic intervention. This may be indirect, by targeting molecules that either mediate its effects or regulate it. For example, antibodies to CD44 (a key target of Stat5 downstream of BCR-ABL) attenuates CML-like leukemia in both human cell lines and murine recipients [135,136]. Alternatively, monoclonal antibodies or antagonists directed against receptors lying upstream of Stat5 may be used, especially given the success of an IL-6 superantagonist in blocking the constitutive activation of Stat3, inducing apoptosis and inhibiting growth in a myeloma cell line and a patient with plasma cell leukemia [137–139]. Tocilizumab, a humanized murine monoclonal antibody, was recently released, which displaces IL-6 from the IL-6Rα complex at extremely high affinity and will be extensively utilized for inflammatory diseases in the near future [140,141]. In addition, inhibitors of both tyrosine and serine/threonine kinases, which phosphorylate and thus activate Stat5 (e.g., Jak kinases) are likely to play an important therapeutic role. Finally, downstream regulators of Stat5, including Socs and PIAS proteins or the tyrosine phosphatases SHP-1 and SHP-2, could also be targeted.

However, direct targeting of Stat5 remains an exciting possibility. We have already discussed the successful targeting of Stat5 RNAi in a conditional cell culture model to inhibit BCR-ABL-dependent cell proliferation in a dose-dependent manner [134]. Another candidate to directly block Stat5 activity would be a SH2-like peptide, which is able to recognize and bind phosphotyrosine residues of Stats [142,143]. This approach has again been successfully demonstrated for Stat3 with the use of an SH2 domain-binding phosphotyrosol (PY*LKTK), which was able to block Stat3 DNA binding activity and subsequent gene regulation both in vitro and in vivo [142]. Alternatively, antisense oligodeoxyribonucleic acids have been shown to successfully target Stat3 to reduce proliferation of leukemia and lymphoma cells [144], and thus are worth considering for Stat5. Short double-stranded decoy oligonucleotides are another alternative [144]. However, targeting transcription factors intracellularly remains a challenge, with problems of delivery and control of off-target effects representing key issues. This suggests that it may not be realistic that specific Stat5 inhibitors will be sufficiently developed for therapeutic use within the next 5 years – although certainly in the 5 years after that.

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Key issues

- Stat5 is normally transiently activated by a variety of cytokines, with a role in hematopoiesis.
- Stat5 proteins are often constitutively activated in leukemias and myeloproliferative diseases.
- Stat5 is activated by known leukemic oncoproteins, such as BCR-ABL and Tel-Jak2, or known mediators of myeloproliferation, including mutants of Jak2 EPOR and G-CSFR.
- The ability to suppress activation of Stat5 correlates well with the success of therapeutics in treating leukemias and myeloproliferative diseases.
- Specific targeting Stat5 represents an attractive therapeutic strategy for multiple disease states.

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Papers of special note have been highlighted as:
• of interest
• of considerable interest


• Recent comprehensive review of the role of the Jak-Stat-Socs pathway in cytokine signaling and disease


• Comprehensive analysis of the Jak-Stat literature.


Some speculations on the requirement of Stat5 in lymphoid development and Abelson induced oncogenesis.


Well-written review on the role of Stats in hematological malignancy.


• Definitive study on the specific activation of Stats in primary patient samples.


Peeters P, Raynaud SD, Cools J et al. Fusion of TEL, the ETS-variant gene 6 (ETV6), to the receptor-associated kinase Jak2 as a result of t(9;12) in a lymphoid and t(9;15;12) in a myeloid leukemia. Blood 90(7), 2535–2540 (1997).


Stat5 as a diagnostic marker for leukemia

- **Key paper providing compelling evidence for the role of Stat5 in leukemia.**


- **Critical review articles**


Tocilizumab inhibits signal transduction mediated by both mIL-6R and sIL-6R, but not by the receptors of other members of IL-6 cytokine family. Int. Immunopharmacol. 5(12), 1731–1740 (2005).


Useful review highlighting current strategies of targeting Stat3 in cancer therapy.

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