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Review Article

Cytokine Signaling in Tumor Progression

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Conflict of Interest
The authors declare no potential conflicts of interest.

Abbreviations
Abl, Abelson kinase; ALL, acute lymphoblastic leukemia; AML, acute myelogenous leukemia; Bcl-2, B-cell lymphoma 2; Bcl-xL, B-cell lymphoma-extra large; CML, chronic myelogenous leukemia; ET, essential thrombocythemia; JH, JAK homology; MF, myelofibrosis; MPN, myeloproliferative neoplasm; PMF, primary myelofibrosis; PTK, protein tyrosine kinase; PV, polycythemia vera; SH2, Src homology 2; STAT, signal transducer and activator of transcription; TEL, transformation-specific leukemia; Tyk2, tyrosine kinase 2; V617F, valine 617 to phenylalanine 617

ABSTRACT

Cytokines are molecules that play critical roles in the regulation of a wide range of normal functions leading to cellular proliferation, differentiation and survival, as well as in specialized cellular functions enabling host resistance to pathogens. Cytokines released in response to infection, inflammation or immunity can also inhibit cancer development and progression. The predominant intracellular signaling pathway triggered by cytokines is the JAK-signal transducer and activator of transcription (STAT) pathway. Knockout mice and clinical human studies have provided evidence that JAK-STAT proteins regulate the immune system, and maintain immune tolerance and tumor surveillance. Moreover, aberrant activation of the JAK-STAT pathways plays an undeniable pathogenic role in several types of human cancers. Thus, in combination, these observations indicate that the JAK-STAT proteins are promising targets for cancer therapy in humans. The data supporting this view are reviewed herein.

Keywords: Cytokine; JAK-STAT; Cancer; Kinase inhibitor

INTRODUCTION

The importance of inflammation for tumorigenesis and malignant progression has become the considerable interests for good reasons. Inflammatory conditions can initiate or promote various accessary responses such as oncogenic transformation, and genetic and epigenetic changes in malignant cells that further enhance tumor progression. The presence of specific inflammatory cells and mediators, including cytokines and chemokines provoke cancer-related inflammation and cytokines apply broad immunoregulatory roles to human disease (1-3).

Over the last 25 years, it has been shown that the majority of cytokines transfer their signals via the JAKs and signal transducer and activator of transcriptions (STATs). The different JAKs associate constitutively with different cytokine receptors. Binding of specific ligands to such receptors induces conformational changes in the receptors, resulting in activation of JAKs. The activated JAKs subsequently induce phosphorylation of specific tyrosine-based motifs in the cytokine receptors, which provide docking sites for Src homology 2 (SH2)-containing STATs, as well as for other proteins with SH2 domains (4-6). Inactivating JAK3 mutations in humans are seen is a severe combined immunodeficiency syndrome, whereas mutations

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of tyrosine kinase 2 (Tyk2) result in another primary immunodeficiency such as autosomal recessive hyperimmunoglobulin E syndrome (7). These findings imply a critical role of JAK-STAT pathways in promoting normal immunity (2).

Conversely, activating mutations of JAKs are found in the connection with malignant transformation in humans as gain-of-function mutation of JAK2 in myeloproliferative disorders (8). Moreover, JAK3 and Tyk2 are also related with clinical disorders in humans and mouse models (9,10). In addition, recent evidences provide important roles for STAT family that potentiate candidates to induce a pro-carcinogenic inflammatory microenvironment as well as the initiation of malignant transformation and cancer progression (10). STAT3 is linked to inflammation-associated tumorigenesis initiated by genetic alterations in malignant cells and induced by various environmental factors such as chemical carcinogens, sunlight, infection, cigarette smoking, and stress (11). Thus, JAK-STATs have complex roles, either direct or indirect, in promoting cancer progression.

In this review, we will discuss the role of JAK-STAT pathways in promoting cancer development and progression. We will show that the involvement of JAK-STAT pathways in these processes can be either direct or indirect. We will also summarize the data regarding the creation and testing of pharmacological inhibitors of the JAK-STAT pathways for the treatment of various types of human cancers.

THE JAK-STAT PATHWAYS

As referred to above, cytokine receptors are non-covalently associated with the JAK family member of cytoplasmic protein tyrosine kinases (PTKs) (2,4,5). JAK kinases are so called, because they have 2 tandem kinase-like domains, one true kinase domain and one pseudo-kinase domain, and thus reminiscent of the 2-headed mythical Roman god Janus (2,12). There are 4 common members of the JAK family, which are JAK1, JAK2, JAK3, and Tyk2 (10). Most JAK family members are ubiquitously expressed except JAK3 predominantly expressed in hematopoietic cells.

As mice deficient for individual JAK family members show different phenotypes, it is presumed that each kinase has a distinct function (4). JAK family members show very similar structures and functions and are more than 1,000 amino acids, which consist of unique 7 JAK homology (JH) regions (JH1 to JH7), and these form the alleged domains of JAK family members (**Fig. 1A and 1B**) (2).

It is likely that the usage of different combinations of JAKs by different cytokine receptors enables a diversity of signaling responses. The dimerization or clustering of the signaling chains allows the JAKs to cross-phosphorylate each other, thus stimulating their kinase activity. The activated JAKs then phosphorylate the cytokine receptors on specific tyrosine residues to generate binding sites for proteins with SH2 domains (**Fig. 1A**). Some of the tyrosine phosphorylated sites recruit SH2 domain-containing latent transcription factors known as STATs (5,12).

There are 7 known STATs (1–4, 5a, 5b, and 6) (4,12). The specificity of particular STATs for a particular receptor is determined by the recognition of distinctive phosphotyrosine sequences on the activated receptors by the SH2 domain of the STATs. Recruitment of

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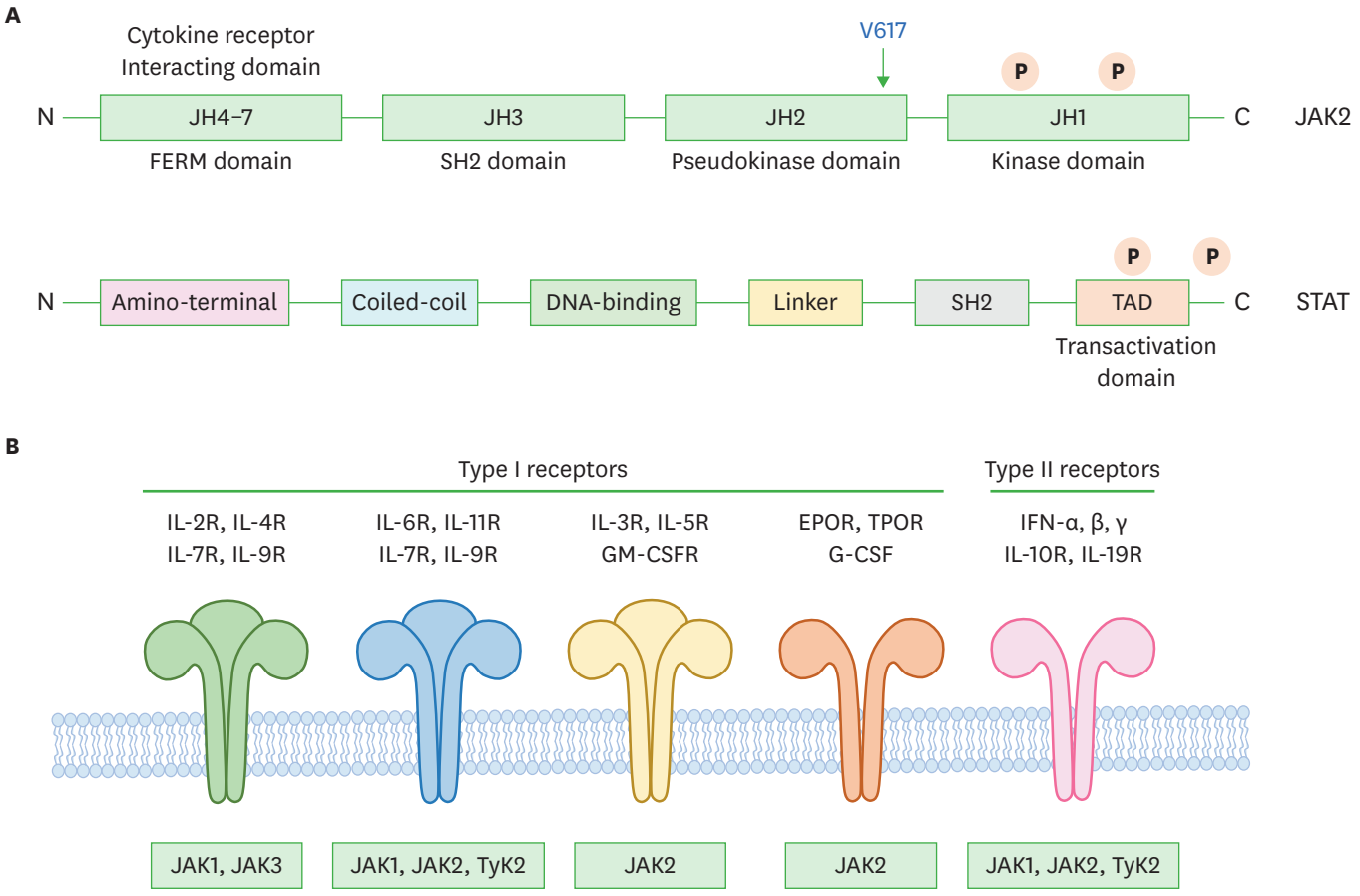

Figure 1. Schematic representation of JAK-STAT structure. (A) The domain structure of JAKs and STATs. Four JAKs consist of the domains JH1 to JH7 based on their sequence similarity including 2 tyrosines after cytokine stimulation. JH1 is kinase domain and JH2 is the pseudo-kinase domain. The JH6 and JH7 domains introduce the binding of JAKs to main receptors. STATs consist of 7 specific domains, which are involved with various responses resulting in the regulation of protein modification by tyrosine and serine phosphorylation, methylation, sumoylation, and acetylation. (B) Classification of cytokine receptors which are type I and II according to their ligands and the association with JAKs to deliver their signals to the downstream.
FERM, 4.1, ezrin, radixin, moesin; TAD, transactivation domain; GM-CSFR, granulocyte-macrophage colony-stimulating factor receptor; EPOR, erythropoietin receptor; TPOR, thrombopoietin receptor; G-CSF, granulocyte-colony stimulating factor; IFN, interferon.

a STAT to an activated receptor brings the STAT close to the activated JAK, which can then phosphorylate the STAT (4). This leads to a conformational change in the STAT that allows it to bind to another STAT and form a STAT dimer. STATs can form homodimers or heterodimers. The phosphorylated STAT dimer then dissociates and enters the nucleus to initiate the transcription of particular genes (4). These STAT-regulated genes contribute to the growth and differentiation of specific subsets of lymphocytes.

As cytokines have so many powerful effects, the activation of cytokine signaling pathways must be tightly controlled; breakdown in control can lead to significant pathological effects. A variety of cytokine-specific inhibitory mechanisms ensure that cytokine signaling pathways can be efficiently terminated (3,13). As cytokine receptor signaling depends on tyrosine phosphorylation, dephosphorylation of receptor complexes by protein tyrosine phosphatases is one important means of signal termination. A variety of protein tyrosine phosphatases have been implicated in the dephosphorylation of cytokine receptors, JAKs or STATs; these include CD45, SH2 domain-containing phosphatase-1 (SHP-1) or SHP-2, and the T-cell protein tyrosine phosphatase (TCPTP) (14,15).

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Cytokine signaling can also be terminated by a negative feedback process involving specific inhibitors induced by cytokine activation. One class of inhibitors contains the suppressors of cytokine signaling (SOCS) proteins, which terminate signaling in variety of ways, including promoting the ubiquitination and subsequent degradation of receptors, JAKs and STATs (16). Another class of inhibitory proteins consists of the protein inhibitors of activated STAT (PIAS) proteins, which also seem to be involved in promoting the degradation of receptors and pathway components (17).

Among the genes known to be transcriptionally upregulated by mammalian STAT proteins are some encoding cell survival factors, such as the B-cell lymphoma 2 (Bcl-2) family of proteins, others involved in cell proliferation, such as cyclin D1 and Myc, and some implicated in angiogenesis or metastasis, such as vascular endothelial growth factor (16,18). Since it is conceivable that upregulation of genes promotes cancer formation, it has been presumed that upregulation of these genes mediates the physiological effects of STAT activation on cell behavior and, also, may promote cancer formation.

INVOLVEMENT OF JAK FAMILY KINASES IN CANCER

Several lines of evidence have directly implicated the JAK-STAT pathways in the pathogenesis of cancers. Abnormal translocations or mutations involving certain genes coding for JAKs have been observed in leukemias and other hematologic malignancies in humans. Moreover, JAK-STATs are hyperactivated in a variety of hematological malignancies and solid tumors, and such abnormal activations are likely involved in the pathogenesis of these diseases (34,35).

Discovery of mutations in JAK2, in particular JAK2 valine 617 to phenylalanine 617 (V617F) mutation in myeloproliferative neoplasms (MPNs) such as polycythemia vera (PV), essential thrombocythemia (ET), and primary myelofibrosis (PMF) has caused remarkable interest in examining the direct involvement of JAK-STAT pathways in cancer (19). These mutations result in a constitutively active kinase domain, leading to gain-of-function and tumor development. The V617F mutation happens in the pseudokinase domain of JAK2 and results in an impaired ability of the pseudokinase domain to regulate negatively the kinase domain (the active part of an enzyme) (20). JAK2 V617F mutation exists in most PV patients and about half of PMF patient as well as ET have a JAK2 V617F mutation, even though different levels of allele burden (21). Although JAK2 V617F is mostly related with MPNs, abnormally activated JAK2 mutation have been recognized in a few patients with MPN without a JAK2 V617F mutation. These mutations include JAK2 mutations residing in exon 12 and mutations in the myeloproliferative leukemia virus oncogene (MPL) receptor (MPL W515L) (**Fig. 2**) (21). All these mutations result in abnormal proliferation and survival of stem cells and hypersensitivity or independence from hematopoietic cytokines (6,22). Enforced expression of these mutant proteins in mice, either by transgenesis or by retroviral transfer in bone marrow stem cells, cause PV, ET, and post-PV/ET myelofibrosis (MF) phenotypes implying a direct causal role for these mutations in MPNs (23,24).

Recently, several published studies identified a genetic haplotype that affect the development of JAK2 V617F mutation and MPN through somatic mutation (25,26). These reports suggested that the JAK2 V617F mutation is not causing MPN, but rather is a contributing factor for disease existence (25,27). Identification of the abnormalities that lead to the

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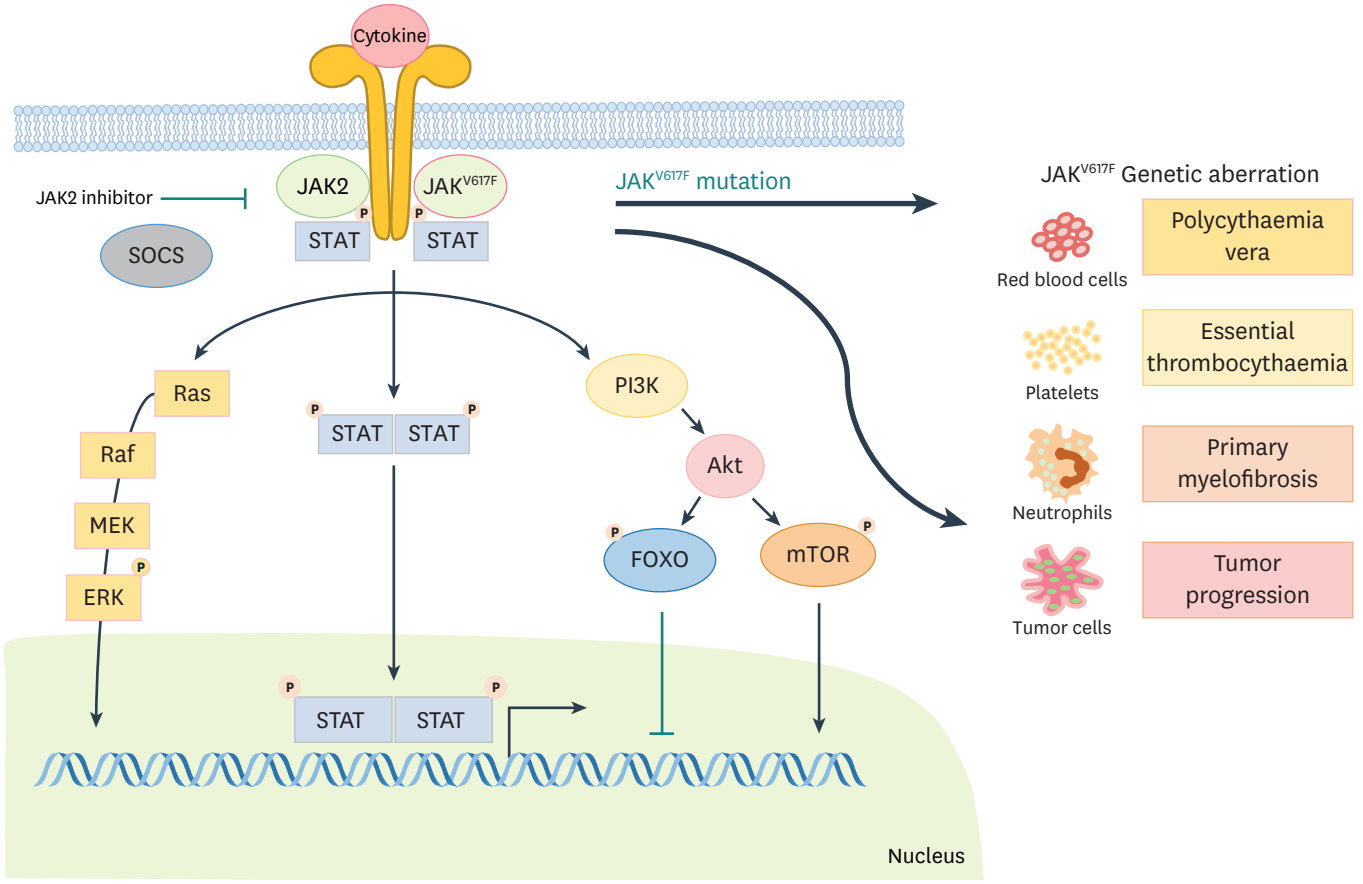

Figure 2. Schematic representation of the JAK-STAT pathway. The cytokine receptor induces activation of JAKs after cytokine stimulation following the phosphorylation of STATs. Furthermore, phosphorylated STATs undergo dimerization and translocate to the nucleus to activate target gene transcription. Genetic aberration in JAKs provoke serious diseases such as PV, ET, PMF as well as cancer.
SOCS, suppressors of cytokine signaling; PI3K, phosphatidyl inositol 3 kinase; Akt, protein kinase B; FOXO, Forkhead box protein O; mTOR, mammalian target of rapamycin.

existence of MPN and the occurrence of JAK2 V617F mutations, and to the distinct clinical entities of PV, ET, and PMF in humans, is a subject of intense investigation (28,29).

It has been reported that acute lymphoblastic leukemia (ALL), acute myelogenous leukemia (AML), and acute megakaryoblastic leukemia (AMKL) are also affected by JAK2 mutations (30). Point mutations of V617F enhance cell proliferation and survival via tyrosine phosphorylation of JAK2. Rare cases of point mutations in JAK3/STAT5 phosphorylation causing AMKL have been reported contrast to high prevalence of patients with JAK2 alterations. Interestingly, JAK3 mutations have been reported in solid cancers such as breast cancer or gastric cancer (31).

Another abnormal translocation, which results in production of the E26 transformation-specific leukemia (TEL)-JAK2 fusion protein, has been identified in myeloid and lymphoid malignancies in humans (32). Direct evidence that this abnormal JAK protein with constitutive activation of its kinase domain can induce leukemia-like syndromes was obtained by the creation of TEL-JAK2 transgenic mice, which exhibited uncontrolled expansion of $CD8^+$ T cells (32,33). Studies to understand how the TEL-JAK2 fusion protein promotes leukemogenesis have shown that the constitutive activity of JAK2 in the fusion

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protein results in phosphorylation/activation of STAT proteins (STAT1, STAT3, and STAT5) (32,34). The ability to induce myelo- and lymphoproliferative diseases in STAT5a/b-deficient mice, using a bicistronic retrovirus encoding both TEL-JAK2 and STAT5a, established the critical role of STAT5 in the pathogenesis of TEL-JAK2-induced syndromes (35). The TEL-JAK2 fusion protein induces the transformation of a hematopoietic pro-B cell line (Ba/F3), seemingly through constitutive STAT3 and STAT5 activation (36,37).

Besides TEL-JAK2, different JAK2 fusion proteins are involved with atypical chronic myelogenous leukemias (CMLs), including pericentriolar material 1 (PCM1)-JAK2 or B-cell receptor (BCR)-JAK2 fusions (38). Similarly, in the setting of acute leukemias, JAK2 fusion proteins have been reported (38). The oncogenic potential of such PTK fusion proteins was featured by translocations leading to production of TEL-platelet-derived growth factor receptor (PDGFR) or TEL-Abelson kinase (Abl) with chronic myelomonocytic leukemia (CMML) or ALL, respectively (39-41).

Another important hematologic malignancy in which JAK-STAT pathways appear to play roles in pathogenesis is multiple myeloma. Studies have shown that constitutive activation of STAT3 occurs in bone marrow mononuclear cells from patients with multiple myeloma (42,43). Similarly, STAT3 was found to be activated in IL-6-independent multiple myeloma cell lines and such activation was associated with activation of JAK1, JAK2, or JAK3 (43). STAT3 inhibitors were found to downregulate B-cell lymphoma-extra large (Bcl-xL) expression and increase Fas-mediated apoptosis (44). In addition, they were shown to suppress cell proliferation and inhibit JAK2 kinase activity, as well as extracellular signal-regulated kinase (ERK2) and STAT3 phosphorylation, in IL-6-dependent multiple myeloma cell lines.

STAT3 was also shown to be constitutively activated in solid tumors. These include primary breast carcinoma cells, breast cancer cell lines, and primary melanoma cells (45,46). STAT3 is also constitutively activated in prostate carcinomas (46). Blockade of activated STAT3 in prostate cancer cells expressively suppressed their growth and tumorigenicity. Constitutive activation of STAT3 has also been described in squamous cell carcinomas of the head and neck, and such an activation decreases apoptosis through increased Bcl-xL expression (47-49). In addition, correlation between increased levels of the activated form of phosphorylated STAT3 and cyclin D1 levels was found in one study in which 51 primary tumor samples (50).

Thus, in combination, these results clearly established that constitutive and aberrant activation of JAK-STAT pathways can have a direct pathogenic role in various hematological malignancies, as well as in certain types of solid tumors, in humans.

INDIRECT PARTICIPATION OF JAK-STAT PATHWAYS IN HUMAN MALIGNANCIES

There is also indication that the JAK-STAT pathways can participate indirectly in the pathogenesis of human malignancies. Indeed, JAKs regulate signaling pathways activated by a variety of cytokines and growth factors such as various interleukins; granulocyte-macrophage colony-stimulating factor receptor (GM-CSFR), granulocyte-colony stimulating factor (G-CSF), and erythropoietin (10). As a result, members of the JAK family activate

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normal mitogenic pathways and this feature may contribute to creation of the oncogenic state. For instance, JAK kinases activate the Ras-Raf-mitogen activated protein kinase (MAPK) cascade that is implicated in malignant transformation and neoplastic cell growth (51). JAK kinases have also been linked to malignant transformation by other oncogene proteins such as v-Abl (52). The capacity of v-Abl to transform cells is directly linked to its ability to induce constitutive activation of STAT5 and STAT6, and v-Abl-dependent STAT activation correlates with its ability to activate JAK1, JAK2, and JAK3, depending on the cellular context and cell type involved (52).

Another mechanism by which JAK kinases appear to promote malignant cell survival and growth is modulation of apoptosis via regulation of the activities of anti-apoptotic the Bcl-2 family proteins. JAK kinases regulate the levels of Bcl-xL, Bcl-2, and Bcl-2-associated X protein (Bax), independently of their effects on STATs and other associated pathways such as the phosphatidyl inositol 3 kinase (PI3K) and the Ras-MAPK pathways (53,54). JAKs also regulate apoptosis and p53 dependent cell cycle arrest.

Lastly, the JAK-STAT pathways can indirectly favor malignant transformation by promoting immune cell-mediated inflammation at sites of tumor development. While immunity can help prevent or terminate the oncogenic process, it is now becoming abundantly clear that inflammation at tumor sites can also have pro-oncogenic effects. This activity is mediated through multiple mechanisms by way of the ability of some immune cells, in particular macrophages, to secrete growth factors that promote tumor cell growth, to stimulate blood vessel development that enhances blood perfusion and arrival of nutrients at tumor sites and to suppress anti-tumor-specific immune reactions (55).

JAKS AS CLINICAL DRUG TARGETS

Considering the evidence that activation of JAK-STAT pathways plays a role, direct or, at times, indirect in malignant transformation of hematopoietic and non-hematopoietic cells, there has been significant interest in developing and using pharmacological inhibitors of the JAK-STAT pathways to treat these disorders (**Table 1**). In support of this, JAK-specific kinase inhibitors have been shown to inhibit cell proliferation in several systems (56).

At first, the quinazoline derivatives such as WHI-P131 and WHI-P154, which were therapeutic agent for glioblastoma, are also considered to potential activity against JAK3 (57-59). However, in retrospect, these compounds were neither selective nor potent JAK3 inhibitors (60). Other inhibitors such as tyrphostin AG 490 (Sigma-Aldrich, St. Louis, MO, USA) or PNU156804 (Pfizer Inc., New York, NY, USA) were also observed to inhibit JAK3 and show significant effects *in vitro*, but, again, their selectivity was not confirmed *in vivo* (61,62). Another study showed that CP-690,550 (Tofacitinib; Pfizer Inc.) had high affinity for JAK3, with little effect on unrelated kinases (63,64). But the clinical efficiency of this compound remains unproven.

More significantly, the discovery of an activating mutation (JAK2 V617F) in hematological malignancies like MPNs, PV, ET, and PMF led to the accelerated development of JAK2 inhibitors, of which are in clinical studies. Various JAK2 inhibitors such as pacritinib (SB1518; S*BIO Pte Ltd., Singapore, Singapore), XL019 (Exelixis, Inc., South San Francisco, CA, USA), ruxolitinib (INCB018424; Incyte Corporation, Wilmington, DE, USA), TG101348

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Table 1. Type of JAK-STAT inhibitors

Type	Name	Efficacy	Clinical stage
JAK2 inhibitor	SB1518 (pacritinib)	Hematological malignancies, CIMF, MF, MDS	Phase III
	XL019	MPD, MF	Phase I/II
	TG101348	MF, renal impairment	Phase I/II
	INCB018424 (ruxolitinib)	Prostate cancer, multiple myeloma, AML, CML, IBC, advanced hematologic malignancies, MF	Phase II/III
	CEP701 (lestaurtinib)	AML, pancreatic cancer, prostate cancers, Neuroblastoma	Phase II
	Dasatinib	JAK2 mutant dependent PV, CML, prostate cancer	Phase IV
JAK3 inhibitor	WHI-P131	Glioblastoma	N/A
	WHI-P154	Glioblastoma	N/A
	Tyrphostin AG 490	Pre-B acute leukemia (ALL)	N/A
	PNU156804	Block allograft rejection	N/A
	CP-690,550 (tofacitinib)	RA, psoriasis, inflammatory bowel disease, organ transplant rejection, ulcerative colitis, ankylosing spondylitis	Phase III
	NC1153	Block allograft rejection	N/A
STAT3 inhibitor	Sorafenib	HCC, RCC, breast cancer, thyroid cancer	Phase II/III
	Sunitinib	GIST, esophageal cancer, RCC, pNET	Phase II/III
	Bendamustine	CLL, multiple myeloma, non-Hodgkin's lymphoma	Phase II/III
	Napabucasin	Colon cancer, rectal cancer, colorectal cancer	Phase II

CIMF, chronic idiopathic myelofibrosis; MDS, myelodysplastic syndrome; MPD, myeloproliferative disorder; IBC, inflammatory breast cancer; N/A, not applicable; RA, rheumatoid arthritis; HCC, advanced hepatocellular carcinoma; RCC, advanced renal cell carcinoma; GIST, gastrointestinal stromal tumor; pNET, pancreatic neuroendocrine tumor; CLL, chronic lymphocytic leukemia.

(Sanofi, Paris, France), and lestaurtinib (CEP701; Abcam Biochemicals, Cambridge, UK) are under being examined to develop for hematological malignancies (65-70). Clinical studies of ruxolitinib are being conducted for prostate cancer, multiple myeloma, AML, and CML (71,72). Lestaurtinib is a U.S. Food and Drug Administration (FDA)-designated orphan drug for AML, which was considered by targetting Fms-like tyrosine kinase 3 (FLT3) and tropomyosin-related kinase A (TrkA) (73-76). However, lestaurtinib was also reported to inhibit JAK2. Consequently, phase II clinical trials are testing this drug in AML patients with JAK2 mutations (70,77). Furthermore, although imatinib (Gleevec®, STI571; Novartis Oncology, East Hanover, NJ, USA) show activity towards JAK2, efficacy of imatinib was tested in clinical trials for PV (78). Finally, dasatinib (Sprycel®, BMS-354825; Bristol-Myers Squibb, Princeton, NJ, USA), a PTK inhibitor approved for CML after imatinib, is a potential inhibitor of Src family PTKs and BCR-Abl (79). Dasatinib is less efficacious *in vivo* model of JAK2 mutant dependent PV model though *in vitro* dasatinib inhibit myeloid and erythroid colony growth in peripheral blood cells (80). Dasatinib can inhibit JAK2 activity *in vitro* at least at high-doses and more clinical trials are underway to determine how it inhibits JAK2 mutation-driven proliferation. Moreover, several FDA-approved tyrosine kinase inhibitors already in the clinic, including sorafenib (Nexavar®, BAY43-9006; Bayer HealthCare Pharmaceuticals Inc., Wayne, NJ, USA) and sunitinib (Sutent®, SU11248; Pfizer Inc.), were found to inhibit STAT3 signaling indirectly, resulting in tumor cell cycle arrest and apoptosis (81,82). Sorafenib inhibits of phosphotyrosine site of STAT3 and decreases expression of anti-apoptotic protein myeloid cell leukemia 1 (Mcl-1), a member of Bcl-2 family (82,83). Sunitinib has further been found to inhibit STAT3 activity in tumor-associated immune cells, modulating the tumor immunological microenvironment in favor of cancer therapy (84). It inhibits immunosuppressive myeloid lineage-derived suppressor cells (MDSCs) and regulatory T cells both in mouse models and in human clinical trials (85,86). Although the inhibition of STAT3 signaling contributes to the anti-tumor activities of sorafenib and sunitinib, their precise molecular mechanisms of action in terms of STAT3 inhibition remain to be determined. In sum, targeting of JAKs-STATs — a central regulatory node on which many oncogenic and inflammatory pathways converge — hold great promise for cancer therapy. In addition to

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the inhibitory functions for the tumor cell proliferation and survival, such JAK2 or STAT3 inhibitors may convert inflammation in the tumor microenvironment from tumor-promoting to tumor-suppressing. This possibility deserves consideration.

CONCLUSION

Significant progresses have occurred over the recent years in the field of JAK-STAT signaling. The original identification of the components of the JAK-STAT pathways led to the development of important basic research studies that have provided valuable information for mechanisms by which different combinations of JAK kinases and their substrates participate in the regulation of malignant cell growth, survival and death. Depending on the specific JAK kinase involved and the downstream effectors activated, different biological outcomes can occur. While it is clear that JAK-STAT pathways negatively regulate neoplastic cell proliferation under certain circumstances, activation of JAKs or STATs promotes malignant transformation and neoplastic cell growth in most of cases. The tumor-promoting activity of JAKs and STATs is highly relevant both to hematologic malignancies and to solid tumors, and has provided potential targets for the development of specific anti-tumor therapies. The several reports of JAK2 inhibitors in the treatment of various cancer models were a remarkable scientific and clinical advance in the field of leukemia. The studies of these drugs have provided a model for the development of other small molecules that target kinases involved in the pathogenesis of malignancies. It is likely that continuation and expansion of current research efforts will provide additional important information that could be applied towards the future development of novel anticancer therapies.

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