STAT3 Inhibitors: Finding a Home in Lymphoma and Leukemia

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ABSTRACT

The Janus kinase (JAK) and signal transducer and activator of transcription (STAT) pathway is an active mediator of cytokine signaling in the pathogenesis of solid and hematologic malignancies. The seven-member STAT family is composed of latent cytoplasmic transcription factors that are activated by phosphorylation intertwined in a network with activation that ultimately leads to cell proliferation. An activated kinase enzyme phosphorylates one STAT factor or more, which shuttle to the nucleus to regulate gene expression, promoting cell survival. Somatic STAT3 mutations have been recently reported in large granular lymphocytic leukemia, aplastic

anemia, and myelodysplastic syndrome. Furthermore, the relationship between BCL6 and STAT3 in diffuse large B-cell lymphomas, particularly on the activated B-cell subtype, needs to be further explored. The search for therapeutic STAT3 inhibitors that abrogate the JAK/STAT pathway is currently under way. Targeting the STAT pathway, which seems to be critical in tumorigenesis, is promising for multiple malignancies including lymphoma and leukemia. In this paper, we review mechanisms of action, failures, and successes of STAT3 inhibitors. *The Oncologist* 2014; 19:536–544

Implications for Practice: Constitutive and transient endogenous inhibitors of STAT3 maintain pathway homeostasis in the cell. The potential use of STAT3 inhibitors in hematological malignancies is reviewed due to recent discoveries in the field.

INTRODUCTION

The interleukin 6 (IL-6), Janus kinase (JAK), and signal transducer and activator of transcription (STAT) pathway (Fig. 1) is positioned at the crossroads between immunity and malignancy, and its key components have been implicated in both processes. The JAK family is composed of four sibling members (JAK1, JAK2, JAK3, and tyrosine kinase 2 [TYK2]) [1, 2]. After cytokines bind to a receptor, activated JAKs phosphorylate such receptors, generating a docking site for signal molecules such as STAT [2]. The STAT family is composed of seven sibling members (STAT1, STAT2, STAT3, STAT4, STAT5a, STAT5b, and STAT6) [3, 4]. These signal transducers can be targeted with inhibitors with therapeutic intent. Following therapeutic successes with IL-6 and JAK2 inhibitors, the ubiquitous STAT3 was a natural candidate for targeted drug development. Activated STAT3 is located at the point of convergence in a network with activation that leads to cell proliferation (Fig. 2). Once dimerized, STAT3 shuttles from the cytoplasm to the nucleus, where it ultimately binds to DNA, mediating growth and survival. Furthermore, STAT3 seemingly perpetuates proliferation in tumor and nontumor cells located in the microenvironment. At the apex of the cascade, the activation of a receptor triggers downstream signal activity.

IL-6 receptor monoclonal antibodies, for example, are active in suppressing inflammatory disease states such as rheumatoid arthritis as well as malignancies such as Castleman disease [5]. The JAK inhibitors lead the way, and ruxolitinib was the first U.S. Food and Drug Administration-approved small molecule used to treat myelofibrosis [6]. Downstream from JAK, the STAT3 transcription factor has a pivotal role in inflammation and carcinogenesis because it has a central location in the proliferation network where many pathways converge [7]. Consequently, STAT3 may also be activated downstream from other aberrant signaling oncogenic pathways such as Ras [8] and EGFR [9]. Moreover, IL-2 [10] and IL-10 [11] can also activate STAT3, among other STATs. Despite multiple possible combinations of receptors, four JAKs, and seven STATs, the IL-6–driven activation of STAT3 seems to be critical in carcinogenesis [7]. The search for STAT3 inhibitors as part of the process of drug development has resulted in a handful of clinical trials currently investigating small molecules that abrogate the IL-6/JAK/STAT pathway in an attempt to mediate inflammatory conditions and malignancies driven by it. In this paper, we review mechanisms of action, failures, and successes of STAT3 inhibitors, particularly in light of recently discovered

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Figure 1. The IL-6/JAK/STAT pathway. The endogenous inhibitors of the latter are shown including SOCS3 and PIAS. Knocking the SOCS off cancer: SOCS3 and PIAS keep STAT3-mediated proliferation in balance under normal conditions. Inflammation is needed to deploy an attack against pathogens and cancer; nevertheless, inflammation will be halted when the noxious agents are no longer present, hence restoring balance. Otherwise, cell death follows from uncontrolled pathway activation. Src is part of a family of nonreceptor tyrosine kinases, called Src family kinases, that can also activate the STAT pathway. The IL-6 receptor complex comprises the membrane-bound IL-6 receptor α chain and the gp130 receptor chain. Tocilizumab, an anti-IL-6R antibody, binds to the membrane-bound IL-6R portion of the receptor complex. Selective inhibition of IL-6 trans-signaling may provide higher efficacy with lower toxicity than complete IL-6 inhibition; therefore, agents that selectively target IL-6/soluble IL-6R trans-signaling may be attractive.

Abbreviations: IL, interleukin; JAK, Janus kinase; PIAS, protein inhibitor of activated STAT3; SOCS, suppressors of cytokine signaling; STAT, signal transducer and activator of transcription.

somatic STAT3 mutations in large granular lymphocytic leukemia [12] and the interplay between BCL6 and STAT3 in diffuse large B-cell lymphomas [13].

IL-6: AT THE CROSSROADS BETWEEN IMMUNITY AND MALIGNANCY

IL-6 is one of the first discovered members of the ever growing family of cytokines, the latest recognized addition of which is IL-37 [14]. IL-6 is a prototype of the many cytokines that induce STAT3 activation through JAK phosphorylation [15]. The integrity of the IL-6/JAK/STAT3 pathway (Fig. 1) is needed both for immunity against pathogens and for prevention against autoimmunity-related disorders [7]. IL-6, binding the specific membrane-bound IL-6 receptor α chain and the common gp130 receptor chain or interacting with gp130 in combination with a soluble form of the IL-6 receptor, governs various cellular responses, including those of T cells and neutrophils [7]. Paracrine IL-6, produced by stromal cells adjacent to cancer cells, prompts expression of autocrine IL-6. Consequently, it is not surprising that STAT3 levels are highest at the edges of tumors adjacent to stromal tissue [7]. In malignant mouse models, mice deficient in IL-6 were unable to

develop tumors [15]. This preclinical finding provides a rationale for developing drugs that abrogate the IL-6 pathway, including IL-6 blockade with IL-6 ligand-binding antibodies (CNTO-328) and IL-6R blocking antibodies (tocilizumab), which are found in dissimilar conditions such as inflammatory rheumatoid arthritis and malignancies such as Castleman disease [5]. It has been suggested that chronic inflammation, including the activation of STAT3, induces immunosuppression [16]. Furthermore, the inflammatory/anti-inflammatory balance seems to be reciprocally regulated by STAT1/STAT3 [17], and disturbances of such balance can impair immune responses, thereby decreasing immune surveillance. The anti-inflammatory response in macrophages, for example, seems to be driven by STAT3 activation [18]. In Castleman disease, the salutary effects of IL-6 blockade with siltuximab (CNTO-328) have been reported. In one phase I study, 12 of 23 patients (52%) achieved objective tumor responses secondary to siltuximab [19]. In addition to IL-6, many other cytokine members can trigger activation of the same pathway, including epidermal growth factor, fibroblast growth factor, platelet-derived growth factor, and oncostatin M [15], resulting in a cascade that promotes tumor progression (Fig. 1).

Figure 2. Activation of STAT3 simplified as an hourglass. Multiple pathways unify and use STAT3 as a central molecular hub. Activated STAT3, located at the waist of the hourglass as the converging bottleneck point of many of networks, ultimately binds to DNA, mediating growth and survival through activation of multiple genes.

JAK2: A “JAK OF ALL TRADES”

Ruxolitinib is an orally available ATP-competitive inhibitor selective for the protein tyrosine kinases JAK1 and JAK2 and is the most advanced JAK1/JAK2 inhibitor in development for the treatment of myeloproliferative neoplasms. Ruxolitinib was, in fact, approved by the U.S. Food and Drug Administration on November 16, 2011, for the treatment of patients with intermediate- or high-risk myelofibrosis [20]. Approval was based on a randomized phase III clinical trial that compared ruxolitinib with placebo. The primary endpoint achieved was a reduction in splenic volume, with the secondary endpoint showing improvement from baseline symptomatology [20]. Recent results suggest that ruxolitinib may provide myelofibrosis patients with a survival advantage compared with matched historical controls [21]. A recent report showed ruxolitinib-induced complete cytogenetic remission in

a patient with JAK2-positive chronic eosinophilic leukemia, proof-of-concept of JAK2 inhibition having a potentially central role in mediating positive responses in a subset of diseases [22]. As stated above, the suggested mechanism of action of ruxolitinib is attenuation of cytokine signaling by inhibition of JAK1 and JAK2 (wild-type or mutated forms), resulting in antiproliferative and proapoptotic effects [6]. The V617F mutation is seen in many myeloproliferative neoplasms and induces the constitutive activation of JAK2, stimulating cell proliferation in a cytokine-independent fashion. Accordingly, a recent phase II trial tested ruxolitinib in 38 patients with relapsed and refractory leukemias [23], 12 of whom had a JAK2 (V617F) mutation. Three of 18 patients that had developed acute myeloid leukemia in the setting of a myeloproliferative neoplasm before enrollment showed a significant response, with either complete remission or complete remission with insufficient recovery of blood counts [23]. JAK proteins, with their cellular ubiquity and promiscuity, have potential roles as master regulators of cell proliferation in many conditions, including lymphomas [24–27]. Younes et al. [26], for example, showed promising results in a phase I trial with the oral JAK2 inhibitor SB1518 in 34 patients with relapsed or refractory Hodgkin or non-Hodgkin lymphoma, displaying 3 patients with partial responses and 15 patients with stable disease. Inhibiting these proteins seems to be a promising mechanism for arresting associated carcinogenesis and inflammation, activity that is being investigated in inflammatory conditions such as rheumatoid arthritis [28] and psoriasis [29].

High levels of STAT3 expression were preferentially seen in the activated B-cell and the BCL6-negative germinal center B-cell lymphomas. Furthermore, activation of the STAT3 signaling pathway by immunohistochemistry was found to be associated with shorter survival in 185 patients with diffuse large B-cell lymphoma treated with R-CHOP.

THE JAK FAMILY

JAKs were first discovered in the 1990s and were thought of as “just another kinase” (i.e., JAK) because of uncertainty surrounding their actual roles [1]. The JAK family is composed of four sibling members: JAK1, JAK2, JAK3, and TYK2 [1]. Their similar molecular structure, with seven homologous domains, makes them a family. The name “Janus” is derived from the enigmatic two-faced Roman god who simultaneously faced the future and the past and who was usually found guarding doors, representing beginnings and transitions; hence, the month of January was named in honor of Janus. The catalytic tyrosine kinase Jak Homology (JH1) domain and pseudokinase (JH2) domain fold at the carboxy-terminus of the JAK structure [30]. These two domains, exclusive to the JAK family, are reminiscent of the duality of the Roman deity, creating the rationale for the name, “Janus kinases” [1]. The ubiquitous presence of JAK2 proteins suggested that commercial potential from novel anticancer drugs could result from their broad spectrum of activity. JAK2 is seemingly the “tip of the iceberg,” composed of highly conserved pathways driven by

oncogene addiction. The COMFORT-I trial is a randomized placebo-controlled trial of the JAK1/2 inhibitor ruxolitinib in 309 patients with intermediate-2 or high-risk myelofibrosis. The initial publication mainly reported that ruxolitinib-treated patients achieved clinically meaningful improvements in quality of life [31]; nevertheless, survival data were not available at the time of publication. A subsequent publication with more prolonged follow-up reported improved survival with ruxolitinib (27 deaths) despite the fact that the “ruxolitinib now versus ruxolitinib later” trial design allowed all patients randomized to placebo (41 deaths) to cross over to ruxolitinib at a median time to crossover of 41 weeks [32]. This significantly longer survival ($p = .03$) seen with ruxolitinib versus placebo is encouraging [32] and begs the question of whether abrogation of the JAK/STAT pathway further downstream, with STAT3 inhibitors instead of JAK2 inhibitors, may be even more beneficial (Fig. 3). Clinical trials testing JAK2 inhibitors in other subsets of disease are awaited [33]. It is currently unknown whether the development of an inhibitor of one of the other three members of the JAK family will supersede the putative importance of JAK2. Gain-of-function domain mutations in JAK3, for example, have been documented in 4 of 36 patients with adult T-cell leukemia/lymphoma [34]. Whether inhibition of JAK and STAT will have equal weight in the therapeutic equation for the fight against cancer is not yet known (Fig. 3).

A WHOLE IS COMPOSED OF ITS PARTS: WHEN JAK MET STAT

The initial depiction of the JAK/STAT pathway, now a paradigm for how protein-to-protein interactions convey information from outside the cell to regulate gene expression, steered research in the direction of similar mechanisms, including the fact that interferon [35] and other cytokines could trigger a similar response through activation of a common molecular cascade. The activity of this cascade is initiated by activation of growth factor receptors, including tyrosine kinase receptors, type I and type II cytokine receptors, and non-tyrosine kinase receptors, by ligand or agonist binding (Fig. 1) that, in turn, actuates JAKs via transphosphorylation interchanges. Subsequently, JAK-induced phosphorylation of STAT proteins that are recruited to activated receptors produces STAT-STAT homodimers, such as STAT3-STAT3 [36], or heterodimers, such as STAT3-STAT1 [37]. This occurs via a reciprocal phosphorylated interaction of tyrosine and Src homology 2 (SH2) among the STATs. Once dimerization occurs, STATs accumulate within the nucleus via importin protein to regulate stimulation or inhibition of gene transcription, leading to proliferation and activation of other cellular responses [38]. Dephosphorylated STATs are shuttled from the nucleus back to the cytoplasm by exportin through the nuclear pore complex [38].

THE STAT FAMILY

It was not until the 1990s that the STAT factors, initially thought to be IL-6-induced acute-phase reactants and interferon-responsive factors, were discovered to be latent cytoplasmic proteins participating in gene regulation in the context of cytokine activation [39]. The mammalian STAT family has seven members: STAT1, STAT2, STAT3, STAT4, STAT5a, STAT5b, and STAT6 [40]. These STATs are involved in cell proliferation, embryogenesis, differentiation, cell motility, and

Figure 3. When JAK met STAT: The different possible value of molecular hubs in myeloproliferative and lymphoproliferative disorders. STAT3 and JAK2 might have different weights when leveling off the balance within normal homeostasis and malignant development. Abrogation of the JAK/STAT pathway further downstream, with STAT3 inhibitors instead of JAK2 inhibitors, may be even more beneficial in a particular malignancy compared with other cancers, although this question will need to be answered in future clinical trials.

apoptosis. Despite the fact that STAT5a and STAT5b are encoded by separate genes, they have a high degree of homology [40]. The structure of STAT3, based on functional modular domains, begins with an N-terminal domain, a coiled-coil domain, a DNA-binding domain, a linker, and a single SH2 domain and ends with the transactivation domain [40]. STAT3 has a tyrosine residue at position 705 (Y705), placed between the SH2 domain and the transactivation domain, that, on phosphorylation, triggers dimerization via a reciprocal phosphorylated tyrosine-SH2 interaction [38], as explained above.

STAT3 AND JOB SYNDROME

Job syndrome, or hyperimmunoglobulin E syndrome, was originally described in 1966 in two red-haired girls and obtained its name from the biblical figure, Job, who had “sore boils from the sole of his foot unto his crown” (Job 2:7). Since then, the presence of these “cold” boils [41], devoid of the typical signs of inflammation, suggested anomalous activity in the inflammatory cascade. Phenotypically, Job syndrome is characterized by eczema, sinopulmonary infections, and local susceptibility to recurrent staphylococcal abscesses [41], although systemic dissemination of infection is not a feature. Subsequently, Job syndrome was named “hyperimmunoglobulin E syndrome” when individuals with the syndrome were

found to display marked elevated levels of immunoglobulin E [42]. Genotypically, the autosomal dominant form of Job syndrome is characterized by mutations in the DNA-binding, SH2, or transactivation domains of STAT3 [43], which seem to diminish STAT3 activity in all affected cells (keratinocytes, dendritic cells, T cells, B cells, and macrophages). This mechanism explains the phenotype seen in this entity and serves as a good example of how STAT3 affects not only tumor cells but also their microenvironment. Rarely, autosomal recessive homozygous TYK2 mutations have been documented in patients with hyperimmunoglobulin E syndrome [44], and it is important to mention that TYK2 is a nonreceptor tyrosine kinase that is a member of the JAK family. The relatively common autosomal and rare recessive mutations in Job syndrome both seem to impair Th17 activity [45], and the incomplete penetrance [46] of these aberrations may account for the susceptibility to infection, among the wide spectrum of clinical abnormalities, seen in this syndrome. Interestingly, patients with hyperimmunoglobulin E syndrome have an increased risk of non-Hodgkin lymphoma [47].

ENDOGENOUS STAT3 INHIBITORS: BRAKES OF PROLIFERATION AND CELLULAR FUNCTIONS

Persistent STAT activation and loss of its natural inhibitors have been documented in several malignancies [48]. A regulated STAT pathway under normal conditions results from a tightly kept balance between stimulation and inhibition. The activity of STAT3, for example, can be upregulated by tyrosine kinase-mediated phosphorylation or downregulated by phosphatases, including cytoplasmic and nuclear phosphatases [49] that, through dephosphorylation, suppress JAK-STAT signaling. In addition, transcription of SOCS3 is induced by activated STAT3. This feedback inhibitor (Fig. 1) seems to function in preventing perpetuation of pathway activation [50, 51]. The protein inhibitor of activated STAT3 (i.e., PIAS3) [52] regulates oncogenic transcription and modulates nuclear DNA binding transcription factors (Fig. 1). When the balance of activating and inhibitory pathways impinging on STAT3 is upset, proliferation and other cellular activities may be deregulated [48]. This situation is reminiscent of other molecular pathways that automatically trigger regulatory feedback loops, as in the mammalian target of rapamycin [53] and estrogen receptors [54].

DEVELOPED STAT3 INHIBITORS: FAILURES AND SUCCESSES

STAT3 inhibition can occur by indirect or direct mechanisms [55]. Indirectly, many agents target upstream constituents of the STAT3 pathway. In addition to EGFR and Src inhibitors, an ever-growing list of tyrosine kinase inhibitors is being studied in preclinical models, and a handful of other types of STAT3 inhibitors are slowly populating the list of agents under clinical evaluation (Table 1). STAT3 abrogation also occurs by inhibition of upstream tyrosine kinases, through therapeutics such as tyrphostins [56], cucurbitacin, and the cucurbitacin analogs JSI-124 [57] and withacnistin [58]. Curcumin (diferuloylmethane) also apparently inhibits deregulated STAT3 activation [59]. These agents are still at the preclinical stage and have not yet been tested in clinical trials.

STAT3 SH2 Domain (Dimerization) Inhibitors

These peptide and nonpeptide agents block reciprocal docking between the SH2 domain of one STAT monomer and the pTyr motif of the other STAT monomer, preventing protein-protein dimerization. Protein-protein interactions generally have large surface areas, which make it quite challenging to find suitable small molecules to disturb such interactions [55]. ISS 610 is a peptidomimetic analog of pTyr that binds to the STAT3 SH2 domain [60]. Another similar example is the small molecule oxazole S3I-M2001 [61], which demonstrates greater activity preclinically than ISS 610 [55]. Nonpeptide or peptidomimetic approaches compensate for the limitations of a pure peptide strategy, which includes low biological activity, poor membrane permeability (particularly impaired by the pTyr moiety), modest stability, and relative nonspecificity for STAT3 [55]. Nonpeptide STAT3 SH2 inhibitors include the small molecules STA-21 [62], S3I-201 [63], catechol (1,2-dihydroxybenzene) [64] and Stattic (STAT3-inhibitory compound) [65]. These agents are presently under evaluation at the preclinical level.

STAT3 DNA-Binding Domain Inhibitors

Examples of agents that block STAT3-DNA interactions include the platinum compounds IS3 295 [66], tetrachloride [67], CPA-1 [67], and CPA-7 [67]. These agents are still in preclinical exploration.

STAT3 Gene Expression Oligonucleotide Inhibitors

These strategies include decoy oligodeoxynucleotides, which mimic the consensus STAT DNA binding sequence, thereby competing for STAT DNA binding and subsequently resulting in the downregulation of STAT-dependent gene transcription. In addition, agents such as small interfering RNA and antisense RNA have been used to inhibit STAT3 [55] via antisense oligonucleotides that bind mRNA, resulting in subsequent degradation. An ongoing phase I trial in our clinic using the latter strategy is enrolling patients with advanced, refractory cancer into a dose-escalation study of an antisense oligonucleotide inhibitor of STAT3 (ClinicalTrials.gov identifier NCT01563302).

STAT3 N-Terminal Domain Inhibitors

The STAT N-terminal domain is thought to aid protein-protein interactions between STAT3 and other transcription factors and the formation of STAT3 tetramers [55]. Synthetic analogs perturbing the N-domain structure are in development [68].

Regarding the toxicity of STAT3 inhibitors, it is important to note that mice homozygous for Stat3 deletion (Stat3^{-/-}) are not viable, suggesting a probable role for STAT3 in embryonic development [69]. In addition, animals with hematopoietic-restricted deletion of Stat3 develop a lethal inflammatory condition resembling Crohn disease, resulting in death in early adulthood [70]. By contrast, mice heterozygous for Stat3 (Stat3^{+/-}) are fertile and phenotypically normal [69], suggesting that STAT3 inhibition might have a good safety profile as a therapeutic target; results from ongoing clinical trials are eagerly awaited. Clinically, Goh et al. reported at the 2012 American Society of Clinical Oncology annual meeting that OPB-51602 (Table 1), a small molecule inhibitor of STAT3 phosphorylation, was well tolerated and showed evidence of clinical activity via reduction in metabolism by PET-CT on day

Table 1. Selected STAT3 inhibitors in interventional studies at ClinicalTrials.gov

Condition	Study drug	Phase	Identifier	No. of patients ^a	Responses	Grade 3 dose-limiting toxicity
Head and neck cancer [74]	STAT3 decoy	0	NCT00696176	NA	NA	NA
Atypical nevi	BSE-SFN	0	NCT01568996	18	NA	NA
Advanced cancer	ISIS-STAT3Rx	1	NCT01563302	80	NA	NA
Hepatocellular carcinoma	AZD9150	1/1b	NCT01839604	73	NA	NA
Advanced cancer	OPB-31121	1	NCT00955812	30	8/17 SD	Lactic acidosis, diarrhea, vomiting
Glioblastoma multiforme	WP1066	1	NCT01904123	21	NA	NA
Advanced cancer	OPB-51602	1	NCT01423903	80	4/8 ^b	Diarrhea, hyponatremia, neuropathy
CLL/SLL	Pyrimethamine	1/2	NCT01066663	26	NA	NA

^aEstimated enrollment.^bInitial results reported at the 2012 American Society of Clinical Oncology annual meeting. Four of eight patients receiving the 4-mg/day dose experienced reduction in tumor metabolism shown by positron emission tomography on day 15. ClinicalTrials.gov accessed January 4, 2014.

Abbreviations: BSE-SFN, broccoli sprout extracts and sulforaphanes; CLL/SLL, chronic lymphocytic leukemia or small lymphocytic lymphoma; NA, not applicable or not available at the time of publication; SD, stable disease.

15 in four of eight patients [71]. Kurzrock et al. reported no responses in 30 patients exposed to OPB-31121 with extensive first-pass CYP3A4 hepatic metabolism and dose-limiting grade 3 vomiting and diarrhea as toxicity [72]. Of note, the OPB agents are not exclusively STAT3 inhibitors. OPB-31121 inhibits STAT3 and STAT5 phosphorylation [73]. Relevant to our review, OPB-31121 has been shown in preclinical models to be effective against multiple myeloma, Burkitt lymphoma, and leukemia [73]. Phase 0 STAT3 inhibitor trials have been developed because Sen et al. [74] reported downregulation of STAT3 target gene expression after using a STAT3 decoy in head and neck cancers. A pilot study is evaluating broccoli sprout extracts, which have demonstrated STAT3 inhibitor properties, and sulforaphanes, which seem to decrease ultraviolet radiation-mediated DNA damage. This group is assessing STAT1 and STAT3 expression in patients with atypical nevi, and results are awaited (Table 1).

THE LYMPHOMA-STAT3 CONNECTION: A POSSIBLE HOME

STAT3 has been identified as a novel B-cell lymphoma 6 (*BCL6*) target gene [13]. The *BCL6* DNA recognition motif has been found to bind the STAT transcription factors [75]. The *BCL6* gene has been identified in chromosomal translocations involving 3q27 in diffuse large-cell lymphomas [76]. Rearrangement of the *BCL6* gene correlated with a favorable clinical outcome as a prognostic marker in diffuse large-cell lymphoma [77]. Structural aberrations of the noncoding region of the *BCL6* gene have been seen in 6.4% of follicular lymphomas and 45% of diffuse large cell lymphoma [78, 79]. Immunohistochemistry results in biopsies of patients with lymphoma reveal detectable BCL6 protein independent of the presence of *BCL6* gene rearrangements [78]. B-cell and T-cell lymphocytes communicate via cytokines. Cytokines, which signal via the JAK-STAT pathway [80], that are secreted by activated T-cell lymphocytes promote the differentiation of B cells into plasma cells. BCL6 is a transcriptional repressor expressed in germinal center B cells [78] and has a role during B-cell differentiation and germinal center development. Germinal center B cells, for

example, normally migrate and differentiate into plasma cells to establish humoral immunity [81]. These results suggest that deregulated BCL6 expression may play a role in lymphoma-genesis by preventing postgerminal center differentiation. Recently, it has been suggested that a critical connection among BCL6 (a transcriptional repressor), p53 (a tumor suppressor), and STAT3 exists [82]. Diffuse large B-cell lymphoma, like most diseases under molecular scrutiny, are a heterogeneous collection of multiple subsets, including activated B-cell-like lymphoma and germinal center B-cell lymphoma. The latter is a relatively more common phenotype and expresses high levels of BCL6. In contrast, activated B-cell-like lymphomas are less common, chemotherapy refractory, and aggressive and express low levels of BCL6, high levels of nuclear factor- κ B, and high levels of phosphorylated STAT3, which seems to be continuously activated [83]. BCL6 is the most common transcriptional repressor expressed in non-Hodgkin lymphoma [83]. Moreover, the survival of activated B-cell-like lymphoma cell lines seems to depend on gain-of-function oncogenic mutations of MYD88, which activate interferon- β autocrine production and the JAK/STAT and nuclear factor- κ B pathways [84]. Ding et al. [13] documented that constitutively activated STAT3 promotes cell proliferation in the activated B-cell subtype of diffuse large B-cell lymphomas. High levels of STAT3 expression were preferentially seen in the activated B-cell and the BCL6-negative germinal center B-cell lymphomas [13]. Furthermore, activation of the STAT3 signaling pathway by immunohistochemistry was found to be associated with shorter survival in 185 patients with diffuse large B-cell lymphoma treated with R-CHOP (rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone) chemotherapy [85]. Interestingly, phosphotyrosine-STAT3 was associated with worse event-free survival only in patients with non-germinal center B-cell subtypes [85].

The literature reports a handful of agents that could potentially serve as a platform for rational combinatorial clinical trials using STAT3 inhibitors as a backbone [86].

Lenalidomide further increases interferon- β production, inducing cell death, in activated B-cell-like lymphoma cell lines; this did not occur in other types of diffuse large B-cell lymphoma [84]. This finding suggests that lenalidomide might have a role in MYD88 mutant activated B-cell-like lymphoma. The chaperone heat shock proteins (i.e., HSP90) seem to sustain cell proliferation through stabilization of several client oncogenic pathways during signal transduction from membrane receptors to the nucleus. The latter function might explain the relationship between heat shock proteins and STAT3 [87]. Some multitarget oral tyrosine kinase receptor inhibitors, such as sunitinib malate [88], inhibit STAT3, platelet-derived growth factor, KIT, AKT, vascular endothelial growth factor, and others. Histone deacetylase inhibitors, the benefit of which may be partially exerted through their inhibition of the *BCL6* oncogene [82], might be attractive combinatorial agents to pair with STAT3 inhibitors in lymphomas. An example of the effects of histone deacetylase inhibitors in lymphoproliferative disorders is vorinostat, an agent approved by the U.S. Food and Drug Administration for the treatment of cutaneous T-cell lymphoma [89]. That said, epigenetic mechanisms implicated in acetylation of histones regulating gene expression are complex [90]. Histone deacetylase inhibitors, which decrease acetylation of histones and cause DNA compaction while blocking transcription of multiple genes, have broad activity that likely goes beyond *BCL6* inhibition. Survivin, an inhibitor of apoptosis, is a target of the STAT3 pathway that is active in anaplastic large-cell lymphoma and that predicts poorer prognosis as an independent prognostic marker in both ALK-positive and ALK-negative groups [91].

T-cell large granular lymphocytic leukemia has recently been found to have SH2 domain mutations in STAT3 as frequent as 40% (31 of 77 patients).

STAT3 AND LEUKEMOGENESIS

T-cell large granular lymphocytic leukemia has recently been found to have SH2 domain mutations in STAT3 as frequent as 40% (31 of 77 patients) [12], which suggests a possible role for STAT3 inhibitors in such a lymphoproliferative disorder. Andersson et al. [92] performed exome sequencing in three STAT mutation-negative patients with T-cell large granular lymphocytic leukemia and found an activated STAT3 pathway by RNA expression or pSTAT3 analysis in all three samples. Jerez et al. [93] studied 50 patients with chronic lymphoproliferative disorders of natural killer cells and 120 patients with T-cell large granular lymphocytic leukemias and found STAT3 gene mutations (in exons 21 and 20, encoding the Src homology 2 domain) in approximately one-third of patients. Phenotypically, wild-type and STAT3 mutants shared many clinical features, thus it was suggested that perhaps other mechanisms of STAT3 activation play a role in these conditions. Importantly, STAT3 inhibitors produced apoptosis in both wild-type and STAT3 mutants [93]. Interestingly, the same group,

led by Jerez et al. [94], screened 140 patients with adult-acquired aplastic anemia and 367 patients with myelodysplastic syndrome and found STAT3 mutations in 7% and 2.5%, respectively. STAT3-mutant patients with aplastic anemia showed a trend toward better therapeutic response to immunosuppressive agents [94]. An immune-mediated myelosuppression hypothesis has been proposed in aplastic anemia and myelodysplastic syndrome suggesting that STAT3 mutations may produce persistent proliferation of cytotoxic autoimmune T-cell clones, as seen in large granular lymphocytic leukemia, which has also been associated with autoimmune phenomena [95]. Constitutive phosphorylation and activation of STATs have been demonstrated in various leukemias [96, 97] including acute myelogenous leukemia [98], acute promyelocytic leukemia [99], acute lymphoblastic leukemia [100], chronic lymphocytic leukemia [101], and chronic myelogenous leukemia [102]. Hossain et al. [103] recently showed that silencing STAT3 in acute myeloid leukemia cells in a mouse model stimulates systemic antitumor immunity and antigen-specific activation of CD8⁺ T cells. Intravenously delivered CpG-STAT3 small interfering RNA showed a direct immunogenic effect on leukemic cells [103]. The leukemic regression may be due to “immune editing” by the strongly immunosuppressive acute myeloid leukemia microenvironment rather than direct tumor cell killing [104]. Results from STAT3 clinical trials in patients with hematological malignancies are eagerly awaited.

CONCLUSION

STAT3 inhibitors have great potential for development as novel targeted agents. Their positive attributes include a low toxicity profile and a mechanism of action amenable to use in various solid and hematological malignancies, particularly in lymphomas and leukemia, despite the fact that their true clinical role still needs to be elucidated. Although many of the molecules are in preclinical testing, the potential for STAT3 as a target is emerging, given its role in many tumors such as lymphoma and leukemia.

AUTHOR CONTRIBUTIONS

Conception/Design: Javier Munoz, Navjot Dhillon, Stephanie S. Watowich, Filip Janku, David S. Hong

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DISCLOSURES

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