Current Hematologic Malignancy Reports (2019) 14:570–576
https://doi.org/10.1007/s11899-019-00545-5

T-CELL AND OTHER LYMPHOPROLIFERATIVE MALIGNANCIES (J ZAIN, SECTION EDITOR)

Targeting the JAK/STAT Pathway in T Cell Lymphoproliferative Disorders

Geoffrey Shouse[1] · Liana Nikolaenko[1]

Published online: 18 November 2019

Abstract

Purpose of Review T cell lymphoproliferative disorders represent a diverse group of hematologic malignancies with poor prognosis underscoring the need for novel therapeutic approaches. Disruption of the JAK/STAT signaling pathway has been described in this group of blood cancers and may represent an approach for targeted therapy. Here, we summarize the current data describing the disruptions of JAK/STAT signaling in T cell malignancies and focus on the existing evidence for exploitation of this pathway with targeted therapies.

Recent Findings To date, preclinical studies have demonstrated the efficacy of JAK/STAT inhibition in the treatment of several T cell lymphoproliferative disorders. More recently, several early clinical trials have demonstrated promising results utilizing this approach as well. The benefit of the combination of JAK/STAT-targeted therapies along with immunotherapy and other molecularly targeted therapies is also discussed.

Summary There is substantial evidence that targeting the JAK/STAT pathway in T cell lymphoproliferative disorders could be of clinical benefit. There are several early clinical trials showing promise and many ongoing trials investigating the optimal utility of agents that inhibit this signaling pathway. In addition, targeting this pathway may provide a platform for further rational combination therapies.

Keywords JAK · STAT · T cell lymphoproliferative disorders · T-ALL · T cell lymphoma · NK cell lymphoma · AITL · PTCL · CTCL · ALCL

Introduction

The Janus kinase (JAK)/signal transducers and activators of transcription (STAT) signaling pathway is an evolutionarily conserved mechanism whereby extracellular signals can regulate gene expression. The JAK/STAT pathway is activated in response to the binding of cytokines and growth factor signaling molecules to cell surface receptors. The end result is changes in gene expression that are critical for normal development and differentiation and function of T cells including immunogenicity and the function of stem cells [1, 2]. Disruption of JAK/STAT signaling can lead to inflammatory and autoimmune diseases, immunodeficiency, and tumorigenesis including hematologic malignancies [3]. The prototypic hematologic malignancy associated with perturbation of the JAK/STAT pathway is polycythemia vera (PV), which is nearly ubiquitously associated with a missense mutation in the JAK2 gene, V617F, leading to unregulated activation of the JAK2 tyrosine kinase, resulting in panmyelosis, a neoplastic proliferation of erythroid, megakaryocytic, and granulocytic cell lines [4]. In addition to PV, dysregulation of the JAK/STAT pathway has been documented in various solid and hematologic malignancies and represents an attractive target for therapeutic exploitation [1, 2, 5, 6]. Given the requirement of intact JAK/STAT signaling for normal T cell function, it seems more than plausible that dysregulation of this pathway would be observed in T cell lymphoproliferative disorders [7]. In fact, dysregulation of JAK/STAT signaling has been described in many T cell malignancies including thymocyte

This article is part of the Topical Collection on *T-Cell and Other Lymphoproliferative Malignancies*

✉ Liana Nikolaenko
lnikolaenko@coh.org

Geoffrey Shouse
gshouse@coh.org

[1] Department of Hematology/Hematopoietic Cell Transplantation, City of Hope National Medical Center, 1500 E Duarte Road, Duarte, CA 91010, USA

(T) cell acute lymphoblastic leukemia (T-ALL) and T cell prolymphocytic leukemia (T-PLL) as well as angioimmunoblastic T cell lymphoma (AITL), extranodal T/NK cell lymphoma, monomorphic epitheliotrophic intestinal T cell lymphoma or enteropathy-associated T cell lymphoma (EATCL), hepatosplenic T cell lymphoma (HSTCL), cutaneous T cell lymphoma (CTCL) including mycosis fungoides (MF) and Sézary syndrome (SS), peripheral T cell lymphoma not otherwise specified (PTCL-NOS), anaplastic lymphoma kinase (ALK), negative anaplastic large cell lymphoma (ALCL), and T/NK cell large granular lymphocytic leukemia (LGL) [8]. This review will focus on the role of JAK/STAT signaling in T cell lymphoproliferative disorders with an emphasis on therapeutic exploitation of this pathway.

Mechanisms of JAK/STAT Signaling

The JAK/STAT signaling pathway involves the transduction of signals from members of the type I and type II cytokine-receptor superfamily through JAK tyrosine kinases and STAT transcription factors that mediate changes in gene expression [3]. The cell surface receptors include those for multiple cytokines, interferons, as well as growth factors such as erythropoietin, thrombopoietin, growth hormone, and prolactin [3]. Upon binding to their ligand, the receptors will either homo- or heterodimerize, or in some cases become hetero-multimer complexes. This process allows the previously bound JAK molecules to be activated through transphosphorylation. Phosphorylated JAK proteins then recruit and activate STATs that dimerize and translocate to the nucleus where they act as sequence-specific DNA binding transcription factors by binding to regulatory elements of specific genes and altering gene expression [1]. In humans, the JAK family consists of four genes: JAK1, JAK2, JAK3, and tyrosine kinase 2 (TYK2). Each JAK protein contains four conserved domains. The adenosine triphosphate (ATP)-dependent tyrosine kinase domain, a non-functional pseudokinase domain, a Src homology (SH) 2 domain responsible for binding to phosphorylated tyrosine residues, and a four point one, ezrine, radixin, moesin (FERM) domain which facilitates JAK protein binding to the cytoplasmic domain of cell surface receptors [1, 3].

The STAT family is comprised of seven genes and includes STAT1, STAT2, STAT3, STAT4, STAT5A, STAT5B, and STAT6 [1]. STAT proteins contain six known conserved domains. The amino terminal domain and coiled coil domain are important for protein-protein interaction and dimerization, while the DNA binding domain is important for binding specific regulatory sequences leading to signal transduction by activating or repressing transcription of target genes. The conserved SH2 domain binds phosphotyrosine and allows STAT recruitment to phosphorylated JAK. Additional domains regulate nuclear transport and recruitment of transcriptional machinery once STAT proteins are bound to DNA [9]. In addition to functioning as DNA binding transcription factors, STAT molecules have also been identified as regulators of epigenetic modifications through binding of heterochromatin. Additional protein regulators of JAK and STAT functions include suppressor of cytokine signaling (SOCS) molecules, which compete with STATs for binding to receptors as well as protein inhibitors of activated STATs (PIAS), which interfere with STATs binding to regulatory DNA domains, thereby decreasing the signal transduction through STATs. The signal transduction pathway can be suppressed by protein tyrosine phosphatases (PTP) that remove the activating phosphates from phosphotyrosines on the cell surface receptors, JAK proteins, and STAT proteins, thereby modifying the signaling cascade [1, 3, 5, 9].

Activation and Targeting of the JAK/STAT Pathway in T Cell Lymphoproliferative Disorders

T cell lymphoproliferative disorders define a broad spectrum of hematologic malignancies, often with an aggressive clinical course, inadequate response to therapy, and poor prognosis [8]. Alterations of the JAK/STAT signaling pathway have been described extensively in most of the T cell lymphoproliferative disorders [1, 2, 5, 6]. Activating mutations can be identified at all levels of the signaling cascade including the cytokine receptors, JAKs and STATs, as well as regulatory proteins including PTPs. In addition, in many T cell malignancies, JAK and STAT activation can be observed even in the absence of activating mutations in the pathway and could provide therapeutic target for molecular inhibitors [2]. The presence of activated JAK and STAT molecules is estimated by measuring the amount of phosphorylated JAK and STAT proteins. It has been demonstrated in several cell lines that JAK and STAT phosphorylation levels are much higher in T cell malignancies than in control cells due to the activation of the pathway [2]. The presence of this activity can predict response to targeted inhibition by JAK inhibitors. Ruxolitinib is the only JAK inhibitor currently FDA approved for myeloproliferative neoplasms; however, several other agents are undergoing testing in this disease including momelotinib, gandotinib, pacritinib, fedratinib, and itacitinib [10]. Therapeutic targeting of an activated JAK/STAT pathway is an attractive approach to treating T cell malignancies though the data to support this approach is still preliminary. To date, multiple studies have demonstrated the efficacy of inhibiting the JAK/STAT pathway in controlling the growth of T cell lymphoproliferative disorders both in vitro and in vivo in mouse models. In addition, various clinical trials are ongoing, testing these agents in various T cell malignancies.

Natural Killer/T Cell Lymphomas

Mutations in JAK3, STAT3, and STAT5B have been described at varying frequencies in NKTCLs. For instance, STAT3 mutations are found at rates of 8–26% in various sequencing studies of primary NKTCLs [11–14], while NKTCL cell lines harbor STAT3 mutations in up to 50% of cases [13, 15]. One study from Singapore [16] reported JAK3 mutations in 35% of cases, but there were no mutations reported in 105 cases of a Chinese population of NKTCL [14]. Other studies have reported frequencies in the range of 5.1 to 35.4% in NKTCL [17–19]. Mutations occur primarily in the pseudokinase domain leading to ongoing JAK3 activation in the absence of ligand [16, 19]. In addition, receptor-type tyrosine-protein phosphatase kappa (PTPRK), which normally dephosphorylates and deactivates STAT3, is expressed at low levels in a significant proportion of NKTCL cases leading to STAT3 activation. Decreased PTPRK expression has been shown to correlate with advanced-stage disease and poor outcomes [20, 21]. Another study identified SOCS1 mutations in 3.7% of cases, also leading to potential loss of SOCS1 function and subsequent disinhibition of STAT3 [22].

Successful therapeutic targeting of the JAK/STAT pathway in NKTCL has been demonstrated with several preclinical studies. Initial in vitro studies with the JAK3 inhibitor tofacitinib were encouraging and demonstrated the induction of apoptosis in NKTCL cell lines [16, 17]. However, the clinical applications have been limited due to the cross-inhibition of other JAK family members. JAK3 is the JAK family member primarily expressed in hematopoietic cells. JAK3 is responsible for carrying the signal downstream from interleukin-2 receptor subunit gamma upon cytokine binding, playing a vital role in lymphoid cell development and homeostasis [23, 24]. To overcome this, a more selective JAK3 inhibitor, PRN371, has shown to be highly effective at inhibiting the growth of NKTCL cell lines harboring JAK3-activating mutations [25••]. Efficacy with PRN371 was demonstrated in an in vivo model of NKTCL in mice, where the PRN371-treated tumors showed suppression of the JAK3 signaling pathway. Importantly, it was noted that NKTCL cells harboring STAT3-activating mutations were not sensitive to the inhibitor, demonstrating their intrinsic resistance to upstream JAK inhibition [25••]. Since STAT3-activating mutations bypass the need for upstream signaling from JAK kinases, JAK inhibition is ineffective in these cases. As such, knowledge of the mutation present predicts utility of targeted JAK inhibition. Additionally, JAK3 targeting may be effective in NKTCL cases not harboring mutations in the JAK/STAT pathway since JAK activation was seen in the absence of mutation in 87% of tested tumors in one study [17, 21]. In several NKTCL cell lines, mutations in the JAK/STAT pathway were not identified; however, JAK/STAT phosphorylation and activation of the pathway were identified. The presence of STAT phosphorylation predicted response to JAK inhibition [17, 21]. This adds an additional layer to the metrics available to predict response to JAK inhibition.

The potential for combinatorial therapies in NKTCL exists as well. For instance, STAT3 activation has been correlated with increases in expression of programmed death-ligand 1 (PD-L1) in NKTCL [21] which has been shown to promote evasion of immune surveillance. This raises the possibility of combining therapy with anti-programmed death 1 (PD1) or PD-L1-targeting antibodies along with small molecule inhibitors of the JAK/STAT pathway. In support of this, all 7 patients in a case series of relapsed NKTCL showed response to treatment with the PD1 antibody, pembrolizumab [26••], emphasizing a potential of improved responses with combination of immunotherapy and JAK/STAT-targeted therapy in NKTCL.

A recent evaluation of ANKL mutational landscape demonstrated mutations in STAT3 in 21% as well as epigenetic modifiers in 50% of cases [27•]. PTPs that normally downregulate STAT3, including PTPRK, PTPN4, and PTPN23, were found to have inactivating mutations as well. Copy number gains in the JAK1, JAK2, STAT3, STAT5A, and STAT5B genes were also identified. Drug sensitivity profiling demonstrated a role for JAK/STAT signaling as well as sensitivity to BCL2 inhibition. Interestingly, a synergy was demonstrated in NKTCL cell lines with the combination of the small molecule inhibitor of JAK2, ruxolitinib, and the BCL2 inhibitor, venetoclax. This novel combination has potential clinical utility in this highly aggressive malignancy [27•].

In LGL, STAT3 mutations have been identified in 30–40% of cases, while 4% of cases carry mutations in STAT5B. These mutations tend to occur in the SH2 domain leading to the enhanced transcriptional activity of these proteins [28–31]. STAT3 mutations are associated with more symptomatic disease and often require multiple lines of therapy [28, 32], while STAT5B mutations seem to be associated with an unusually aggressive and uniformly fatal disease course [30]. Similarly, STAT3 mutations are identified frequently in AITL, HSTCL, ALCL, GDTCL, and PTCL [5, 13, 32–37]. HSTCL is also reported to harbor STAT5B mutations in 31% of cases [13, 36, 37].

Peripheral T Cell Lymphomas

Activating mutations, particularly in STAT5B, have been described in PTCL and are seen in approximately one-third of different PTCL subtypes, including cutaneous as well as breast implant–associated large cell lymphoma (BIA-ALCL) [38•]. Another study of primary PTCL samples demonstrated mutations in STAT3 in 3.8%, JAK3 in 3.8%, and SOCS1 in 7.7% of cases [22].

Mutations in JAK/STAT signaling molecules have also been described in cutaneous T cell lymphomas (CTCL) [39].

NGS studies have demonstrated the presence of activating point mutations in JAK1 in 0.9% of cases, JAK3 in 2.7%, STAT3 in 0.9%, and STAT5B in 3.6% [40]. In addition, copy number gains of JAK2 have been reported in 13% of cases, STAT3 in 60% of cases, and STAT5B in 60% of cases [40]. These copy number gains have been shown to result in increased expression levels of the associated proteins. Importantly, CTCL cell lines harboring JAK3-activating mutations have shown sensitivity to targeted JAK inhibition [41, 42].

The JAK/STAT-targeted therapies have been evaluated in preclinical studies of CTCL and PTCL as well. Inhibition of STAT5B in primary PTCL patient-derived cell lines with a neuroleptic drug, pimozide, induced apoptotic cell death via TRAIL/DR4-dependent extrinsic apoptotic pathway, emphasizing another potential [38•].

BIA-ALCL is a rare form of T cell lymphoma and the risk of developing this disease after breast implantation is about 0.35–1 per million implants [43]. A comprehensive next-generation sequencing, conducted on BIA-ALCL patient sample, identified sequence variants leading to JAK/STAT activation in 10 out of 11 patients, providing insight into the possible pathologic mechanism for tumorigenesis in BIA-ALCL [44].

T Cell Acute Lymphoblastic Leukemia and Adult T Cell Leukemia

Several studies in T-ALL have demonstrated mutations throughout the JAK/STAT pathway as well as in associated regulatory proteins [2]. JAK1 mutations have been identified in 6.5–27% of cases [45–47], while JAK3 mutations are found in 7.5% [48]. JAK3 mutations are associated with an aggressive early T-ALL phenotype [49]. TYK2 mutations are also detected in 21% of cases [50]. Mutations in the interleukin 7 receptor (IL-7R) detected in 7.5–21% of cases have been shown to result in constitutive activation of the JAK/STAT pathway [51, 52]. Deactivating mutations in PTPN2 and PTPRC are detected in 6% of cases and are associated with activation of JAK1 and STAT5B signaling, respectively [53–55]. In T-PLL, a similar distribution of mutations throughout the JAK/STAT pathway has also been described [2]. These include JAK1 mutations in 8–12% of cases, JAK3 in 30–42%, interleukin 2 receptor gamma (IL2RG) in 2%, and STAT5B mutations in 36% [56–58].

T-ALL harboring IL7R mutations shows significant sensitivity to JAK1/2 inhibition by ruxolitinib. Interestingly, the combination of ruxolitinib with the BCL2 inhibitor, venetoclax, showed synergistic effects of inhibiting leukemic growth in a murine model [59••]. In addition, the JAK2 small molecule inhibitor TG101209 showed efficacy in vitro against several T-ALL cell lines [60]. Ruxolitinib was also able to overcome glucocorticoid resistance in a subset of T-ALL samples harboring JAK/STAT activation in response to IL7 [61].

In HTLV-associated adult T cell leukemia (ATL), JAK/STAT pathway activation involving phosphorylation of JAK1/3 and STAT3/STAT5B was identified in the presence and absence of JAK/STAT-activating mutations [62]. The combination of the Bcl-xL inhibitor navitoclax with the JAK1/2 inhibitor ruxolitinib showed synergistic efficacy in studies using mouse models of human ATL [62, 63]. Cerdulatinib showed efficacy in a murine model of ATL as well [64].

Clinical Application of JAK/STAT-Targeted Therapies in T Cell Lymphoproliferative Disorders

Clinical evaluation of the efficacy of JAK/STAT-targeted therapies in T cell malignancies is lacking. To date, only a few studies have demonstrated positive results. For instance, in a phase 2 study of the dual spleen tyrosine kinase (SYK)/JAK1/3/TYK2 inhibitor, cerdulatinib, 43% of patients with relapsed and refractory PTCL showed response to treatment and two-thirds of responders had a complete response. In CTCL, the retinoic acid derivative ECPIRM was shown to have efficacy in inducing apoptosis and cell cycle arrest in CTCL cell lines through inhibition of JAK/STAT signaling [65]. In another phase 2 study, the small molecule inhibitor of JAK, ruxolitinib led to a 38% and 40% overall response rate (ORR) in patients with activating JAK/STAT mutations or evidence of JAK/STAT pathway activation, respectively [66••].

There are also several ongoing clinical trials targeting the JAK/STAT pathway in T cell malignancies, which include NCT03613428, a phase I/II study combining ruxolitinib with the combination of vincristine, prednisone, and asparaginase in relapsed and refractory T-ALL. NCT01712659 is a phase II study investigating the response rates of ATL to ruxolitinib. NCT01431209 is another phase II study investigating the efficacy of ruxolitinib in relapsed lymphomas, including NKTCL, as is NCT02974647. Tofacitinib is being evaluated in NKTCL in the phase I/II study NCT0359899 in combination with Chidamide in patients with relapsed refractory NKTCL as well. NCT03601819 in a phase Ib study evaluating the efficacy of the JAK inhibitor pacritinib in PTCL and CTCL.

Conclusion

T cell malignancies represent a complex and variable set of hematologic diseases with treatment challenges and poor prognosis. As such, the need for novel therapeutic approaches cannot be overstated. As delineated above, the JAK/STAT pathway is activated in a majority of T cell malignancies, either through the presence of activating mutation, increased

protein expression, or loss of expression of negative regulators. The importance of the JAK/STAT pathway in T cell lymphoproliferative disorders is underscored by the significant pre-clinical and early clinical data, indicating the efficacy of JAK and STAT-targeted therapies [67]. Ongoing clinical trials may yield further evidence of the clinical utility of this approach. Overcoming the inherent resistance to JAK inhibition in the presence of activating STAT mutations will also be necessary to optimize the efficacy of this targeted treatment approach. Overall, the most promising therapies may lie in combinatorial strategies employing immunotherapy and modulators of apoptosis and epigenetic changes along with JAK/STAT-targeted therapies [21, 26••, 27, 62, 63]. Further clinical validation of these approaches may elucidate novel treatment paradigms in this complex set of diseases.

Compliance with Ethical Standards

Conflict of Interest The authors declare that they have no conflict of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

References

Papers of particular interest, published recently, have been highlighted as:
• Of importance
•• Of major importance

1. O'Shea JJ, Schwartz DM, Villarino AV, Gadina M, McInnes IB, Laurence A. The JAK-STAT pathway: impact on human disease and therapeutic intervention. Annu Rev Med. 2015;66:311–28.
2. Springuel L, Renauld JC, Knoops L. JAK kinase targeting in hematologic malignancies: a sinuous pathway from identification of genetic alterations towards clinical indications. Haematologica. 2015;100(10):1240–53.
3. Rawlings JS, Rosler KM, Harrison DA. The JAK/STAT signaling pathway. J Cell Sci. 2004;117(Pt 8):1281–3.
4. James C, Ugo V, Le Couedic JP, Staerk J, Delhommeau F, Lacout C, et al. A unique clonal JAK2 mutation leading to constitutive signalling causes polycythaemia vera. Nature. 2005;434(7037):1144–8.
5. Pencik J, Pham HT, Schmoellerl J, Javaheri T, Schlederer M, Culig Z, et al. JAK-STAT signaling in cancer: from cytokines to non-coding genome. Cytokine. 2016;87:26–36.
6. Groner B, von Manstein V. JAK STAT signaling and cancer: opportunities, benefits and side effects of targeted inhibition. Mol Cell Endocrinol. 2017;451:1–14.
7. Seif F, Khoshmirsafa M, Aazami H, Mohsenzadegan M, Sedighi G, Bahar M. The role of JAK-STAT signaling pathway and its regulators in the fate of T helper cells. Cell Commun Signal. 2017;15(1):23.
8. Matutes E. The 2017 WHO update on mature T- and natural killer (NK) cell neoplasms. Int J Lab Hematol. 2018;40(Suppl 1):97–103.
9. Finbloom DS, Larner AC. Regulation of the JAK/STAT signalling pathway. Cell Signal. 1995;7(8):739–45.
10. Vainchenker W, Leroy E, Gilles L, Marty C, Plo I, Constantinescu SN. JAK inhibitors for the treatment of myeloproliferative neoplasms and other disorders. F1000Res. 2018;7:82.
11. Zhang Y, Li C, Xue W, Zhang M, Li Z. Frequent mutations in natural killer/T cell lymphoma. Cell Physiol Biochem. 2018;49(1):1–16.
12. Dobashi A, Tsuyama N, Asaka R, Togashi Y, Ueda K, Sakata S, et al. Frequent BCOR aberrations in extranodal NK/T-cell lymphoma, nasal type. Genes Chromosom Cancer. 2016;55(5):460–71.
13. Kucuk C, Jiang B, Hu X, Zhang W, Chan JK, Xiao W, et al. Activating mutations of STAT5B and STAT3 in lymphomas derived from gammadelta-T or NK cells. Nat Commun. 2015;6:6025.
14. Jiang L, Gu ZH, Yan ZX, Zhao X, Xie YY, Zhang ZG, et al. Exome sequencing identifies somatic mutations of DDX3X in natural killer/T-cell lymphoma. Nat Genet. 2015;47(9):1061–6.
15. Lee S, Park HY, Kang SY, Kim SJ, Hwang J, Lee S, et al. Genetic alterations of JAK/STAT cascade and histone modification in extranodal NK/T-cell lymphoma nasal type. Oncotarget. 2015;6(19):17764–76.
16. Koo GC, Tan SY, Tang T, Poon SL, Allen GE, Tan L, et al. Janus kinase 3-activating mutations identified in natural killer/T-cell lymphoma. Cancer Discov. 2012;2(7):591–7.
17. Bouchekioua A, Scourzic L, de Wever O, Zhang Y, Cervera P, Aline-Fardin A, et al. JAK3 deregulation by activating mutations confers invasive growth advantage in extranodal nasal-type natural killer cell lymphoma. Leukemia. 2014;28(2):338–48.
18. Kimura H, Karube K, Ito Y, Hirano K, Suzuki M, Iwata S, et al. Rare occurrence of JAK3 mutations in natural killer cell neoplasms in Japan. Leuk Lymphoma. 2014;55(4):962–3.
19. Sim SH, Kim S, Kim TM, Jeon YK, Nam SJ, Ahn YO, et al. Novel JAK3-activating mutations in extranodal NK/T-cell lymphoma. Nasal Type Am J Pathol. 2017;187(5):980–6.
20. Chen YW, Guo T, Shen L, Wong KY, Tao Q, Choi WW, et al. Receptor-type tyrosine-protein phosphatase kappa directly targets STAT3 activation for tumor suppression in nasal NK/T-cell lymphoma. Blood. 2015;125(10):1589–600.
21. de Mel S, Soon GST, Mok Y, Chung TH, Jeyasekharan AD, Chng WJ, et al. The genomics and molecular biology of natural killer/T-cell lymphoma: opportunities for translation. Int J Mol Sci. 2018;19(7):1931.
22. Song TL, Nairismagi ML, Laurensia Y, Lim JQ, Tan J, Li ZM, et al. Oncogenic activation of the STAT3 pathway drives PD-L1 expression in natural killer/T-cell lymphoma. Blood. 2018;132(11):1146–58.
23. Hofmann SR, Lam AQ, Frank S, Zhou YJ, Ramos HL, Kanno Y, et al. Jak3-independent trafficking of the common gamma chain receptor subunit: chaperone function of Jaks revisited. Mol Cell Biol. 2004;24(11):5039–49.
24. Johnston JA, Kawamura M, Kirken RA, Chen YQ, Blake TB, Shibuya K, et al. Phosphorylation and activation of the Jak-3 Janus kinase in response to interleukin-2. Nature. 1994;370(6485):151–3.
25.•• Nairismagi M, Gerritsen ME, Li ZM, Wijaya GC, Chia BKH, Laurensia Y, et al. Oncogenic activation of JAK3-STAT signaling confers clinical sensitivity to PRN371, a novel selective and potent JAK3 inhibitor, in natural killer/T-cell lymphoma. Leukemia. 2018;32(5):1147–56 **The investigators demonstrate the efficacy of specific JAK3 inhibition thereby overcoming a potential limitation of off-target effects of prior pan-JAK inhibitors.**
26.•• Kwong YL, Chan TSY, Tan D, Kim SJ, Poon LM, Mow B, et al. PD1 blockade with pembrolizumab is highly effective in relapsed or refractory NK/T-cell lymphoma failing l-asparaginase. Blood. 2017;129(17):2437–42 **Demonstration of the efficacy of PD1-based immunotherapy in treating NK/T cell lymphoma.**

27.• Dufva O, Kankainen M, Kelkka T, Sekiguchi N, Awad SA, Eldfors S, et al. Aggressive natural killer-cell leukemia mutational landscape and drug profiling highlight JAK-STAT signaling as therapeutic target. Nat Commun. 2018;9(1):1567 **Demonstration of JAK-STAT signaling as a therapeutic target in aggressive forms of NK cell leukemia, a disease with very poor outcomes.**

28. Jerez A, Clemente MJ, Makishima H, Koskela H, Leblanc F, Peng Ng K, et al. STAT3 mutations unify the pathogenesis of chronic lymphoproliferative disorders of NK cells and T-cell large granular lymphocyte leukemia. Blood. 2012;120(15):3048–57.

29. Koskela HL, Eldfors S, Ellonen P, van Adrichem AJ, Kuusanmaki H, Andersson EI, et al. Somatic STAT3 mutations in large granular lymphocytic leukemia. N Engl J Med. 2012;366(20):1905–13.

30. Rajala HL, Eldfors S, Kuusanmaki H, van Adrichem AJ, Olson T, Lagstrom S, et al. Discovery of somatic STAT5b mutations in large granular lymphocytic leukemia. Blood. 2013;121(22):4541–50.

31. Rajala HL, Mustjoki S. STAT5b in LGL leukemia–a novel therapeutic target? Oncotarget. 2013;4(6):808–9.

32. Ohgami RS, Ma L, Merker JD, Martinez B, Zehnder JL, Arber DA. STAT3 mutations are frequent in CD30+ T-cell lymphomas and T-cell large granular lymphocytic leukemia. Leukemia. 2013;27(11):2244–7.

33. Bamford S, Dawson E, Forbes S, Clements J, Pettett R, Dogan A, et al. The COSMIC (Catalogue of Somatic Mutations in Cancer) database and website. Br J Cancer. 2004;91(2):355–8.

34. Odejide O, Weigert O, Lane AA, Toscano D, Lunning MA, Kopp N, et al. A targeted mutational landscape of angioimmunoblastic T-cell lymphoma. Blood. 2014;123(9):1293–6.

35. Crescenzo R, Abate F, Lasorsa E, Tabbo F, Gaudiano M, Chiesa N, et al. Convergent mutations and kinase fusions lead to oncogenic STAT3 activation in anaplastic large cell lymphoma. Cancer Cell. 2015;27(4):516–32.

36. McKinney M, Moffitt AB, Gaulard P, Travert M, De Leval L, Nicolae A, et al. The genetic basis of hepatosplenic T-cell lymphoma. Cancer Discov. 2017;7(4):369–79.

37. Nicolae A, Xi L, Pittaluga S, Abdullaev Z, Pack SD, Chen J, et al. Frequent STAT5B mutations in gammadelta hepatosplenic T-cell lymphomas. Leukemia. 2014;28(11):2244–8.

38.• Simpson HM, Furusawa A, Sadashivaiah K, Civin CI, Banerjee A. STAT5 inhibition induces TRAIL/DR4 dependent apoptosis in peripheral T-cell lymphoma. Oncotarget. 2018;9(24):16792–806 **Demonstration of the utility of STAT5 inhibition in PTCL.**

39. Bastidas Torres AN, Najidh S, Tensen CP, Vermeer MH. Molecular advances in cutaneous T-cell lymphoma. Semin Cutan Med Surg. 2018;37(1):81–6.

40. Park J, Yang J, Wenzel AT, Ramachandran A, Lee WJ, Daniels JC, et al. Genomic analysis of 220 CTCLs identifies a novel recurrent gain-of-function alteration in RLTPR (p.Q575E). Blood. 2017;130(12):1430–40.

41. da Silva Almeida AC, Abate F, Khiabanian H, Martinez-Escala E, Guitart J, Tensen CP, et al. The mutational landscape of cutaneous T cell lymphoma and Sezary syndrome. Nat Genet. 2015;47(12):1465–70.

42. McGirt LY, Jia P, Baerenwald DA, Duszynski RJ, Dahlman KB, Zic JA, et al. Whole-genome sequencing reveals oncogenic mutations in mycosis fungoides. Blood. 2015;126(4):508–19.

43. Kricheldorff J, Fallenberg EM, Solbach C, Gerber-Schafer C, Rancso C, Fritschen UV. Breast implant-associated lymphoma. Dtsch Arztebl Int. 2018;115(38):628–35.

44.• Blombery P, Thompson E, Ryland GL, Joyce R, Byrne DJ, Khoo C, et al. Frequent activating STAT3 mutations and novel recurrent genomic abnormalities detected in breast implant-associated anaplastic large cell lymphoma. Oncotarget. 2018;9(90):36126–36 **BIA-ALCL is shown to harbor a high frequency of STAT3 mutations.**

45. Jeong EG, Kim MS, Nam HK, Min CK, Lee S, Chung YJ, et al. Somatic mutations of JAK1 and JAK3 in acute leukemias and solid cancers. Clin Cancer Res. 2008;14(12):3716–21.

46. Flex E, Petrangeli V, Stella L, Chiaretti S, Hornakova T, Knoops L, et al. Somatically acquired JAK1 mutations in adult acute lymphoblastic leukemia. J Exp Med. 2008;205(4):751–8.

47. Roberts KG, Morin RD, Zhang J, Hirst M, Zhao Y, Su X, et al. Genetic alterations activating kinase and cytokine receptor signaling in high-risk acute lymphoblastic leukemia. Cancer Cell. 2012;22(2):153–66.

48. Bains T, Heinrich MC, Loriaux MM, Beadling C, Nelson D, Warrick A, et al. Newly described activating JAK3 mutations in T-cell acute lymphoblastic leukemia. Leukemia. 2012;26(9):2144–6.

49. Zhang J, Ding L, Holmfeldt L, Wu G, Heatley SL, Payne-Turner D, et al. The genetic basis of early T-cell precursor acute lymphoblastic leukaemia. Nature. 2012;481(7380):157–63.

50. Sanda T, Tyner JW, Gutierrez A, Ngo VN, Glover J, Chang BH, et al. TYK2-STAT1-BCL2 pathway dependence in T-cell acute lymphoblastic leukemia. Cancer Discov. 2013;3(5):564–77.

51. Shochat C, Tal N, Bandapalli OR, Palmi C, Ganmore I, te Kronnie G, et al. Gain-of-function mutations in interleukin-7 receptor-alpha (IL7R) in childhood acute lymphoblastic leukemias. J Exp Med. 2011;208(5):901–8.

52. Zenatti PP, Ribeiro D, Li W, Zuurbier L, Silva MC, Paganin M, et al. Oncogenic IL7R gain-of-function mutations in childhood T-cell acute lymphoblastic leukemia. Nat Genet. 2011;43(10):932–9.

53. Kleppe M, Lahortiga I, El Chaar T, De Keersmaecker K, Mentens N, Graux C, et al. Deletion of the protein tyrosine phosphatase gene PTPN2 in T-cell acute lymphoblastic leukemia. Nat Genet. 2010;42(6):530–5.

54. Kleppe M, Soulier J, Asnafi V, Mentens N, Hornakova T, Knoops L, et al. PTPN2 negatively regulates oncogenic JAK1 in T-cell acute lymphoblastic leukemia. Blood. 2011;117(26):7090–8.

55. Porcu M, Kleppe M, Gianfelici V, Geerdens E, De Keersmaecker K, Tartaglia M, et al. Mutation of the receptor tyrosine phosphatase PTPRC (CD45) in T-cell acute lymphoblastic leukemia. Blood. 2012;119(19):4476–9.

56. Bellanger D, Jacquemin V, Chopin M, Pierron G, Bernard OA, Ghysdael J, et al. Recurrent JAK1 and JAK3 somatic mutations in T-cell prolymphocytic leukemia. Leukemia. 2014;28(2):417–9.

57. Bergmann AK, Schneppenheim S, Seifert M, Betts MJ, Haake A, Lopez C, et al. Recurrent mutation of JAK3 in T-cell prolymphocytic leukemia. Genes Chromosom Cancer. 2014;53(4):309–16.

58. Kiel MJ, Velusamy T, Rolland D, Sahasrabuddhe AA, Chung F, Bailey NG, et al. Integrated genomic sequencing reveals mutational landscape of T-cell prolymphocytic leukemia. Blood. 2014;124(9):1460–72.

59.•• Senkevitch E, Li W, Hixon JA, Andrews C, Cramer SD, Pauly GT, et al. Inhibiting Janus kinase 1 and BCL-2 to treat T cell acute lymphoblastic leukemia with IL7-Ralpha mutations. Oncotarget. 2018;9(32):22605–17 **The investigators demonstrate the efficacy of combination therapy with JAK1 inhibition and BCL-2 inhibition.**

60. Cheng Z, Yi Y, Xie S, Yu H, Peng H, Zhang G. The effect of the JAK2 inhibitor TG101209 against T cell acute lymphoblastic leukemia (T-ALL) is mediated by inhibition of JAK-STAT signaling and activation of the crosstalk between apoptosis and autophagy signaling. Oncotarget. 2017;8(63):106753–63.

61. Delgado-Martin C, Meyer LK, Huang BJ, Shimano KA, Zinter MS, Nguyen JV, et al. JAK/STAT pathway inhibition overcomes IL7-induced glucocorticoid resistance in a subset of human T-cell acute lymphoblastic leukemias. Leukemia. 2017;31(12):2568–76.

62. Waldmann TA. JAK/STAT pathway directed therapy of T-cell leukemia/lymphoma: inspired by functional and structural genomics. Mol Cell Endocrinol. 2017;451:66–70.
63. Zhang M, Mathews Griner LA, Ju W, Duveau DY, Guha R, Petrus MN, et al. Selective targeting of JAK/STAT signaling is potentiated by Bcl-xL blockade in IL-2-dependent adult T-cell leukemia. Proc Natl Acad Sci U S A. 2015;112(40):12480–5.
64. Ishikawa C, Senba M, Mori N. Anti-adult T cell leukemia/lymphoma activity of cerdulatinib, a dual SYK/JAK kinase inhibitor. Int J Oncol. 2018;53(4):1681–90.
65. Yang H, Ma P, Cao Y, Zhang M, Li L, Wei J, et al. ECPIRM, a potential therapeutic agent for cutaneous T-cell lymphoma, inhibits cell proliferation and promotes apoptosis via a JAK/STAT pathway. Anti Cancer Agents Med Chem. 2018;18(3):401–11.
66.•• Moskowitz AJ, Jacobsen E, Ruan J, Schatz JH, Obadi O,Motylinski K, et al. Durable responses observed with JAK inhibition in T-cell lymphomas. ASH annual meeting; 2018 Dec 1–4; San Diego. [Abstract 2922]. **Clinical evidence of the efficacy of JAK inhibition in TCL.**
67. Waldmann TA, Chen J. Disorders of the JAK/STAT pathway in T cell lymphoma pathogenesis: implications for immunotherapy. Annu Rev Immunol. 2017;35:533–50.