The role of JAK and STATs asimmune-regulatory and Transcriptional Regulatory, in immune system, as Potential Therapeutic and Preventive Target in Cancer and Autoimmunity

By DR ZELALEM KIROS BITSUE MD, PhD IMMUNOLOGY
United States of Africa Health Organization "AHO"
School of Public Health, Tehran University of Medical Sciences

Abstract: As our understanding of the mechanisms involved in innate immunity expands, new roles of STATs in these processes become evident. Currently the possibility of targeting the JAK-STAT pathway autoimmune disease has now become a reality.

The JAK/STAT signaling pathway is used by numerous cytokines and is critical for initiating innate immunity, orchestrating adaptive immunity, and ultimately constraining immune responses. Cytokines are of paramount importance in regulating the development, differentiation, and function of myeloid cells and T cells; thus, unrestrained activation of the JAK/STAT pathway has pathological implications for autoimmune diseases. Dysregulation of the JAK/STAT pathway has pathological implications in autoimmune and neuro-inflammatory diseases.

Many of the cytokines involved in MS/EAE, including IL-6, IL-12, IL-23, IFN-g, and GM-CSF, use the JAK/STAT pathway to induce biological responses. Thus, targeting JAKs has implications for treating autoimmune inflammation of the brain.

To date, Janus kinase-signal transducer and activator of transcription (JAK-STAT) signaling has been proposed to be crucial in various developmental pathways, especially in promoting astrogliogenesis. Inhibition of the JAK/STAT pathway has clinical efficacy in multiple preclinical models of MS, suggesting the feasibility of the JAK/STAT pathway as a target for neuro-inflammatory diseases.

In this article, I describe the role of Stat as Transcriptional Regulation, SOCS Proteins Control Inflammatory Responses by Regulating Stat Signaling, Negative Regulation of STATs by SOCS, New roles for STATs in helper T cell subsets, Role of STATs in Treg cell function as well as the JAK/STAT pathway as a target for cancer and neuro-inflammatory diseases.

Key Words:JAK and STATs, Immunoregulatory,Transcriptional Regulatory, Cancer and Autoimmunity

The Table of Contents

1. Introduction
2. Overview of a Stat Signaling Module
3. Stat Structure and Function
4. STAT Activation
5. Stat Transcriptional Regulation
6. SOCS Proteins Control Inflammatory Responses by Regulating Stat Signaling
7. STAT Nuclear Import
8. STAT Nuclear Export

9. Negative Regulation of STATs by SOCS
10. New insights into the immunoregulatory roles of JAKs and STATs
11. New roles for STATs in "old" helper T cell subsets
12. Role of STATs in Treg cell function
13. Roles of STATs in "new" helper cell subsets
- STATs and CD8 memory
- STAT5 in B cells

14. STATs and Innate Immunity

15. Conclusions

16. Reference

Introduction

Type I and II cytokine receptors are a conserved family, consisting of _40 members, that includes the receptors for interleukins, interferons, and hormones such as growth hormone, leptin, and erythropoietin and colony stimulating factors (CSF) such as granulocyte-CSF and granulocyte-macrophage CSF(1-3),Unlike other receptors with intrinsic enzyme activity(e.g., kinase or phosphatase), cytokine receptors are associated with a tethered kinase. These cytoplasmic kinases comprise the four members of the Jak family: Jak1, Jak2, and Tyk2 bind to an array of receptors, whereas Jak3 binds to only one receptor, the common gamma chain, or gc. Mutations of JAK3 or TYK2 in humans lead to specific primary immunodeficiency syndromes designated severe combined immunodeficiency (SCID) and autosomal- recessive hyperimmunoglobulin E syndrome (AR-HIES)(4-6). Additionally, the roles of the four Jak proteins have been elucidated through the generation of genetically deficient mice, and specific functions of each Jak member have been assigned(7).Because of their kinase activity, Jak proteins are potential targets for small molecule inhibition. For Jak3, its restricted association with gc has made Jak3 an attractive therapeutic target as an immunosuppressive drug thatcan primarily target activated T cells(8).Upon cytokine binding to their cognate receptor, the receptorassociatedJaks are activated and in turn phosphorylate tyrosine residues in the receptor cytoplasmic domain. This eventprovides a docking site for proteins with Src homology 2 domains,one important class of which is the Stat family of transcription factors. With seven members in all (Stat1, Stat2, Stat3, Stat4, Stat5a, Stat5b, and Stat6), these DNA-binding proteins provide a rapid membrane to nucleus mechanism for regulation of gene expression(9)

Stat Structure and Function

Stats are proteins of 750 to 850 amino acids that contain the following domains: amino terminal, coiled-coil, SH2, nonlinker, DNA binding, and transcriptional activation do-remains. The crystal structure of two Stats, Stat1 andStat3, bound to DNA has been solved (reviewed in(1),but the

structures did not include the amino-and carboxy-terminal portions of the molecules. The SH2 domain is an essential feature for Stat activation and function, docking the protein to tyrosine phosphory-lated receptor subunits. Additionally though, Stat2 and perhaps also Stat1 associate with the unactivated, nonphosphorylated IFNAR prior to ligand binding. The receptor-bound Stats are then phosphorylated by Jaks on a conserved tyrosine residue and the SH2 domains mediate dimerization through reciprocal phosphotyro sine/SH2 interactions. The Stat SH2 domain may also be important for association with the activating Jak.

The phosphorylated Stat dimer bound to DNA forms a nutcracker-like structure with the SH2 domains forming the hinge. The central portion (approximately aa 320-480) of the dimer forms a barrel with an immunoglobulin fold similar to NF-B and p53 and is responsible for DNA binding, although the residues that directly contact DNA are limited. Stat homodimers bind a motif termed a GAS (activated sequence) element (TTN5-6AA). Unlike other cytokines, IFN induces the formation of a complex comprising Stat1, Stat2, and IRF9 that binds the IFN stimulated response element (ISRE), AGTTN3TTTC. While the importance of tyrosine phosphorylation and dimerization of Stat proteins is clear, the mechanisms that regulate nuclear import and export are an area of intense investigation. Accumulation of Stat proteins in the nucleus is clearly controlled by nuclear export via Ran-dependent interaction with chromosome region maintenance (CRM)1/exportin 1(10).
A Leu-rich motif in the DNA binding domain of Stat1 (amino acids 400-409), conserved in other Stats, is critical for nuclear export. DNA binding of the phosphory-lated Stat dimer is proposed to mask the NES, whereas Stat dephosphorylation and dissociation from DNA per-mits recognition of this site, allowing nuclear export. It should be noted that a different NES (amino acids 302-314) has also been mapped(11).Inhibition of nuclear export alone is not sufficient to cause Stat nuclear accumulation; Stats are imported by the nuclear import receptor, importin-5, and Ran. This requires Stat dimerization, and tyrosine phosphorylation alone is not sufficient(10).Stat1 L407 appears to function as nuclear localization signal (NLS),as mutations in this region of the protein interfere withimportin binding and nuclear import of phosphorylatedStat dimers(12),(13),(10). However, a bonafide, autono-mously functioning Stat NLS hasyet to be defined. Addi-susceptibiltionally, nuclear trafficking of nonphosphorylated Stat monomers may occur by mechanisms distinct from those that govern movement of dimers(14),(13).

STAT Activation

A large array of cytokines and growth factors utilize the JAK/STAT network to transduce their cognate signal to the nucleus, for example IL-6, IL-10, cardiotrophin 1 (CT-1) and G-CSF induce STAT3 activity, while interferons (IFN) utilize predominantly STAT1 and STAT2. Ligand binding to the extracellular domain of JAK associated cytokine receptors induces receptor dimerisation and JAK autophosphorylation. JAKs then transphosphorylate the cytoplasmic domain of the cytokine receptor and create a docking site for the SH2 domain of STATs. (15). Once STATs bind to the intracellular receptor chain, they are phosphorylated by JAKs at distinct tyrosine residues, causing the bound STATs to be released from the receptor and

translocate to the nucleus where they bind specific sequences such as the IFN activated sequence (GAS) in the promoters of target genes (15).Once bound to DNA, the NTD is responsible for recruiting RNA Pol II and co-factors such as the histone acetyl transferase p300(16).There are currently around 36 known cytokine receptor combinations that respond to 38 cytokines which utilize distinct combinations of JAKs and STATs(17).The selective use of receptor combinations outlined in allow a certain specificity for signaling but it is currently unknown precisely how cytokines exert differing responses utilizing the same JAK and STAT combinations. The JAK/STAT pathway can also be stimulated by G-protein coupled receptors such as the angiotensin II receptor and this may be mediated through Rho family GTPases(18).Another mode of JAK/STAT activation is via non-receptor tyrosine kinases such as Src, Fer, Abl, Etk and Lck which all induce STAT3 activity(19-22). The IL-6 family of cytokines comprises IL-6, IL-11, leukaemia inhibitory factor (LIF), oncostatin M (OSM), ciliaryneurotrophic factor (CNTF), cardiotrophin-1 (CT-1) and cardiotrophin-like cytokine (CLC). IL-6 cytokine receptors are comprised of the signal transducer gp130 in combination with IL-6R, IL-11R, LIF-R or OSM-R. All IL-6 cytokines potently activate STAT3 and this is followed by internalization and degradation of gp130(23).Serum levels of IL-6, soluble gp130, LIF and CT-1 have all been shown to be elevated in patients suffering from heart failure and these levels correlate with the severity of left ventricular dysfunction, suggesting that the IL-6/STAT3 axis may have a role to play in myocardial cell death(24-28).
Dimerization of STATs appears to be essential for DNA binding and retention in the nucleus. Traditionally it was thought that inactive STATs were present as monomers and only undergo dimerization after phosphorylation, however accumulating evidence suggests that unphosphorylated STATs are present in the cytosol as dimmers or higher order multimers(29).Unphosphorylated STAT1 dimers are formed by reciprocal interactions of their N-terminal domains, coiled-coil and DNA binding domains in an anti-parallel conformation (30).Phosphorylation promotes dimerization through the SH2 domains in a parallel confirmation which is essential for DNA binding and nuclear retention and these parallel and anti-parallel conformations appear to be mutually exclusive (31),(32).Recently it has been shown that tyrosine phosphorylation of STAT1 is dispensable for DNA binding *per se*, however phosphorylation promotes the parallel conformation which increases DNA binding activity by more than 200 fold(32).

Stat Transcriptional Regulation

The Stat C terminus contains an autonomously functioning transcriptional activation domain (TAD), and alternativelyspliced isoforms of Stat1, Stat3, and Stat4 lackingthis domain have attenuated transcriptional activity.TruncatedStat5 polypeptides lacking the TAD arethoughtto be generated by proteolysis and are unstable(33).While the mechanisms by whichthese domains regulate transcription are incompletelydefined, serine phosphorylation within the TAD typicallypromotes transcriptional activity and enhances the ex-impression of selected genes(34),(35).This site,a putative mitogen-activated protein kinase phosphorylation motif,

encom-passes serine 727 in Stat1 and Stat3. Stat4, Stat5a, andStat5b have similar residues in analogous positions, but identity of the kinase(s) responsible for these modifications remains a subject of some controversy. None-theless,TAD phosphorylation could allow for regulationand crosstalk by different receptors. The mechanismunderlying this regulation presumably involves the re-cruitment of other transcription factors and coactiva-tors. Factors shown to bind the TAD include CBP/p300,c-Jun, MCM5, and BRCA1(1),CBP/p300also binds other parts of the Stat molecule, and theN-myc interacting protein (Nmi-1) facilitates this associ-ation. Stat2, however, recruits a different histone acetyl-transferase,GCN5 in complex with TAF130.Stats also interact with a wide variety of other factors;in addition to p48/IRF9, these factors include NF-B,SMADs, Sp1, USF-1, c-Jun, PU.1, C/EBP, glucocorticoid receptor, NcoA-1, YY-1, TFII-1, and HMG-I(Y).Some of these interactions are mediated by the Statcoiled-coil domain, but the Stat linker domain is alsoinvolved in transcriptional control. Additionally, theaminoterminus of the Stats forms a hook-like domain,which may facilitate Stat interactions and cooperativebinding to tandem imperfect Stat binding sites. Thus,despitewhatwe have learned about Stats and transcriptional regulation, it is very clear that we are only begin-ning to understand these processes and the relevantinteractions.

SOCS Proteins Control Inflammatory Responses by Regulating Stat Signaling

Upon cytokine stimulation, a family of cytokine-induced inhibitors termed suppressors of cytokine signaling (Socs proteins) is rapidly induced. The predominant function of Socs proteins is to block the generation of the Stat signal from a cytokine receptor(36),(37). Importantly, the genes encoding the Socs proteins are direct targets of Stat proteins; the Jak-Stat cascades thereby control their own signaling output by feedback inhibition. Although there are eight Socs proteins, genetic evidence from mice and cells lacking Socs1 and Socs3 unequivocally shows that these two Socs proteins are necessary to reduce the overall signaling output from their target receptors(36),(37). The Socs1- and Socs3-mediated modulationin signaling from cytokine receptors therefore has profoundeffects on the regulation of immunity and inflammationby affecting the activation, development, and homeostatic functionsof all lineages involved in immune and inflammatoryresponses.A major question in understanding the activities of Stat-Socs modules concerns the biochemical mechanism of how Socs proteins block cytokine-receptor signaling. Each of the eightSocs proteins have two major domains, an SH2 domain and a Socs box that complexes with elongins B and C, a cullin and Rbx2, to form a E3 ubiquitin ligase(38),(39).

The Socs SH2 domains bind phosphorylated tyrosine residues in their substrates. The best characterized Socs substrates are specific tyrosine residues in the cytoplasmic tails of cytokine receptors. In addition, the Socs SH2 domain has the potential to bind other phosphotyrosine residues and thereby regulate the activity of a wide range of proteins. The current model of Socs function postulates that the E3 activity of a Socs protein will target the substrate to be ubiquitinated and then directed to the proteosome for degradation. However, genetic studies using mice that lack the Socs box of Socs1 or Socs3, but that are engineered to retain the SH2 domains of each protein, indicate that the SH2 and Socs box domains don't always function in concert because the phenotypes of mice lacking the Socs box of Socs1 or Socs3 are dramatically less severe than the corresponding conventional knockouts

(40),(41).These data suggest that the SH2 domain of Socs1 and Socs3 alone can block cytokine-receptor signaling. Thus, the mechanistic relationship between the SH2 and Socs box domains remains unresolved, as does the contribution of E3 ligase activity to Socs function.
A second outstanding question concerns the mechanism by which a Socs protein, tethered to a specific residue of a cytokine receptor, inhibits the generation of activated Stats. An obvious possibility is that a Socs protein directs its receptor substrateto be degraded. At least for gp130, a substrate of Socs3, thismdoes not seem to be the case(42).Another possibility is that Socs proteins promote ubiquitination of Stat proteins in the vicinity of the receptor; however, this does not agree with the restricted requirement for the Socs box of Socs1 or Socs3 compared to the absolute requirement for the intact proteins and their SH2 domains. A third possibility is that a tethered Socs protein inhibits the activity of tethered JAK proteins through effective concentration-type effects that remain uncharacterized(43),(44),(37).At this stage, the biochemical mechanism(s) of Socsmediated inhibition of Stat signaling remains unknown.

STAT Nuclear Import

In the last few years we have gained a much more detailed understanding as to how the phosphorylated STATs are transported to the nucleus. Work from UweVinkemer's group and others has shown that once phosphorylated, STAT dimers are transported to the nucleus in both an energy-dependent and an energy independent manner (45).Importins such as importin α5 bind to phosphorylated STAT dimers and transport them through nuclear pore complexes with a conserved sequence in the coiled-coil domain essential for nuclear import(46).Conversion of RanGTP to RanGDP in the nucleus allows STATs to re-enter the cytosol, utilizing exportins such as chromosomal region maintenance 1 (CRM1)(47).The CRM1 binding site in STAT1 is located within the DNA binding domain, suggesting that CRM1 is prohibited from binding when STAT1 is bound to chromatin(47).Using protein microinjection techniques, Marg et al. demonstrated that unphosphorylated STAT1 could move freely between the cytoplasm and the nucleus(48).This occurred in the absence of cytokine stimulation and even when the RanGTPase active transport system was disrupted by depleting the cells of energy. It seems therefore that two modes of STAT nuclear transport exist, an energy-independent method involving unphosphorylated STATs in which direct interaction with nucleoporins allows constant shuffling between the cytoplasm and nucleus and an energy-dependent system where phosphorylated STATs need to be actively transported into the nucleus(45).Since nuclear translocation of STATs is a relatively fast process (5-10 minutes), a mechanism exists to replenish the cytosolic pool of STATs to allow further ligand induced activation and prolong target gene transcription.

STAT Nuclear Export

Nuclear export is controlled by STAT dephosphorylation and inhibition of tyrosine phosphatases prolongs STAT1 retention in the nucleus. The kinetics of nuclear retention

correlate with the level of STAT-DNA binding, suggesting that STATs are protected from dephosphorylation while bound to DNA(49).How then do nuclear phosphatases gain access to STATs? In the case of STAT1, Darnell and colleagues have proposed an elegant model whereby following dissociation from DNA, the N–terminal domains of both proteins in the dimer interact and undergo rearrangement(30).This forms an antiparallel structure allowing the coiled coil domain of one monomer to bind to the DNA binding domain of the other, thus exposing the phosphate residues to nuclear phosphatases(30),(31).This antiparallel configuration allows the two molecules to remain in association following nuclear export. Thus it seems that a nuclear pool of activated STATs is maintained by constant export and re-import which is controlled by a tightly regulated tyrosine phosphorylation-dephosphorylation cycle(49).

Negative Regulation of STATs by SOCS

The suppressor of cytokine signaling (SOCS) proteins control the negative regulation of cytokine responses. There are seven members of the SOCS family (SOCS1-7) which are all induced by cytokines and therefore they form part of a negative feedback loop of cytokine control, in addition SOCS proteins can be induced by other agonists such as LPS, statins and cAMP. SOCS1 and SOCS3 are potent inhibitors of the JAK/STAT pathway, The SH2 domain of SOCS1 and SOCS3 is necessary to facilitate binding to a site in active JAK1, JAK2 and Tyk2 while the SOCS kinase inhibitory region (KIR) is responsible for suppressing JAK kinase activity(50),(51),The SOCS SH2 domain determines other target selectivity, for example the SH2 domain of SOCS3 binds to phosphorylated tyrosine residues on cytokine receptors such as Tyr757 of gp130 and Tyr800 of IL-12, SOCS1 can bind to both the IFN-α and IFN-• receptors and both the SOCS1 and SOCS3 SH2 domain can bind to the Y1007 residue in the activation loop of JAK2(52),(53).

In addition, SOCS proteins function as E3 ubiquitin ligases and therefore target proteins for proteasomal degradation(37).This is mediated through a region in the C terminus known as the SOCS box which binds a complex containing elongin B/C, cullin-5 and RING-box-2 (RBX2) which recruit E2 ubiquitin transferase, resulting in 20S mediated proeasomal destruction of SOCS-bound proteins(54),(39),Deletion of the SOCS box in SOCS1 led to enhanced levels of phosphorylated STAT1 and increased IFN responses, showing that this region in necessary for the full activity of SOCS1 (41).Initial phosphorylation of JAKs appears to be necessary for SOCS-mediated degradation. In unstimulated cells, JAK2 was found to be mono-ubiquitinated whereas stimulation with IL-3 or IFN led to phosphorylation at Y7001, recruitment of SOCS1 and subsequent polyubiquitination and degradation(55).

The need for correct control of JAK/STAT signaling is highlighted in studies of SOCS1-deficient mice, these mice develop an excessive fatal IFN response which could be rescued by the administration of anti-IFN antibodies(56).Lymphocytes from these mice exhibit accelerated apoptosis with age and SOCS1 MEFs are far more sensitive to TNF-α mediated apoptosis that

their wild type counterparts, showing that tempering of the IFN/STAT1 axis is necessary to restrain exuberant STAT1-mediated apoptosis(57),(58).

The SOCS proteins provide a level of specificity for cytokine signaling through the JAK/STAT pathway. For example, STAT3 is essential for the biological effects both IL-6 and IL-10, however IL-6 is a pro-inflammatory cytokine whereas IL-10 is anti-inflammatory. The differing responses appear to be controlled at the level of SOCS3; IL-6 and IL-10 both upregulateSOCS3, however SOCS3 selectively dampens IL-6 signalling by binding to the IL-6R subunit gp130 without having any effect on IL-10 signalling. IL-6 therefore induces transient STAT3 activation while IL-10 promotes prolonged STAT3 activity; this is evidenced by the prolonged STAT3 phosphorylation seen in SOCS3 deficient cells following IL-6 treatment(42).Prolonged STAT3 activation is therefore instrumental in the anti-inflammatory response and leads to suppression of pro-inflammatory cytokine production by toll-like receptors. Moreover, IL-6 treatment of macrophages deficient in SOCS3 or harboring mutation of the SOCS3 binding site on gp130 produces an anti-inflammatory response, clearly showing that the duration of STAT3 activity determines the differing biological responses to IL-6 and IL-10(59).This was confirmed by studies demonstrating an anti-inflammatory response using modified leptin and erythropoietin receptors which could activate STAT3 but not bind SOCS3(60).and by using a constitutively active STAT3 which also mediates an anti-inflammatory response(61).Thus it seems that regulation of the duration of STAT3 phosphorylation by SOCS3 determines the outcome of anti-inflammatory cytokine signaling.

Role of STATs in Treg cell function

Along with TGFβ, IL-2 is a key regulator of differentiation of Treg cells in the thymus and the periphery. As mediators of IL-2 signaling, STAT5A/B are critical for the differentiation of Treg cells. Their effect is very direct in that STAT5/A directly bind the Foxp3 gene and drive expression of this key gene(69-72).In addition, STAT5A/B regulate IL2ra, expression of which is also a critical for Treg cells. Surprisingly, STAT3 also has an important role in Treg cell function (73).Deletion of STAT3 in Treg cells results in lethal gastrointestinal disease, but the effect is selective and does not globally impairTreg cell function. Treg cells retain the ability to limit T cell proliferation but have impaired ability to block Th17- mediated pathology. Of interest, STAT3 physically associates with Foxp3.

Roles of STATs in T helper cell subsets

With the recognition of a multiplicity of fates for T cells, it has become clear that STATs are also key elements for these “new” subsets. We now know that STAT3 is critical for Th17 differentiation both in mouse and humans, mediating signals by IL-23 and IL-6(74-76),STAT3 regulates Th17differentiation by directly binding Il17a/f, Rorc and Il23r, as well as other genes involved inTh17 differentiation(77).In this case, the action of STAT5A/B action is verydirect – they compete with STAT3 binding to the Il17a/f locus(79).Intriguingly, by sequestering IL-2,

regulatory T cells promote Th17 differentiation(80),(81). One of the newest "lineages" of CD4 T cells is the follicular helper T cell, which provideshelp to B cells in germinal centers. Cytokines like IL-6 and IL-21 act on STAT3 andpromote expression of Bcl6 and other molecules that contribute to the phenotype andfunction of this subset(82-84).
However, IL-12 and STAT4 also turn out to be drivers of Tfh cells(85),(86).STAT4 directly binds many genes involved in Tfh differentiation, including Bcl6 and Il21. Conversely, IL-2 inhibits Tfh differentiation and once again, the action of STAT5 appears to be very direct. It competes with STAT3 binding to the Bcl6 locus and also promotes expression of Prdm1, which encodes Blimp1(87-89).Perhaps less surprising given its role in transmitting IL-4 signals, STAT6 is an important regulator of Th9 cells(90).

STATs and CD8 memory

STATs and CD8 memory(88)IL-7 and IL-15 are important for CD8 memory and accordingly STAT5A/B are also important(91),(92). STAT5A/Bis essential for the survival of viral-specific CD8 T cells and expression of Bcl-2. In contrast though, in the setting of viral infection, the numbers of CD4 effector T cells are unaffected by the absence of STAT5A/B. However, STAT5A/B are not the only family members important for CD8 cell function; STAT3 is also important, mediating signals by IL-10 and IL-21 (93).Expression of such key molecules as Eomes, Bcl-6, Blimp-1, and Socs-3 are all reduced in STAT3-deficient CD8 T cells. A similar defect in CD8 T cell memory was seen in patients with hyperimmunoglobulin E syndrome and dominant-negative STAT3 mutations(94).

STAT5 in B cells

IL-7, acting via STAT5A/B, is important in B lymphopoiesis, controlling survival and development (95).Conversely, the B cell adapter, BLNK, antagonizes IL-7 signaling via inhibition of JAK3, and absence of BLNK leads to constitutive JAK-Stat activation and leukomogenesis(96).

STATs and Innate Immunity

STATs also have numerous functions in innate immunity—too many to review in detail here, but summarized in detail elsewhere(7),(64).The importance of STAT1 in mediating IFN effects has long been recognized, as has the role of STAT3 in IL-6 signaling and the acute phase response. Colony-stimulating factors and cytokines like granulocyemacrophage-CSF, granulocyte-CSF, and IL-5, which regulate myeloid development, also signal via STATs. Consequently, STATs have key functions for neutrophils and macrophages (97-99).GM-CSF inhibits Flt3L-mediated plasmacytoidDC production and conventional DC growth and STAT5

is important in this process(100).In contrast, STAT3 is important for the expansion of DC progenitors. The importance of IL-22, acting via STAT3, in regulating the barrier function of epithelial cells and wound repair is a topic of considerable interest(101)Like IL-10, IL-22 is produced by and acts on innate immune cells and has critical anti-inflammatory properties. Precisely how STAT3
promotes inflammation in some circumstances and inhibits in others is an important but challenging question(60).STAT3 can negatively regulate IFN responses and has been proposed to inhibit TLR signaling either by inducing anti-inflammatory molecules or by a direct suppression of NF-kB(102).Nonetheless, a clear understanding of the pro- and anti-inflammatory actions of STAT3 remains elusive.
Recently, the role of innate immune cells in promoting Th2 cell responses has become increasingly apparent. Thymic stromal lymphopoetin (TSLP) in particular is an important type I cytokine that promotes allergic responses. It acts on multiple cells, especially
basophils, which are major producers of IL-4(103),(104).The identity of the JAKsresponsible for signaling had been enigmatic, but we nowknow that TSLP signals via JAK1 and JAK2 to activate STAT5(105).In addition to the classical mode of activating macrophages via IFN-g, the appreciation of the importance of Th2 cytokines in generating alternatively activated macrophages (AAMs) isnow recognized. AAMs appear to be important in a range of processes including host defense, fibrosis, metabolic regulation, obesity, and cancer. As IL-4 and IL-13 are major drivers of theAAM, STAT6 is a key player for these cells. STAT6 is important in regulating insulin action, lipid metabolism, and expression of proliferation-activated receptor isoforms(106),(107).
Very recently, AAMs and STAT6 have been implicated in the mammalian thermogenicresponse(108).Intriguingly, AAMs secrete catacholamines in a STAT6-dependent manner and induce thermogenic gene expression in brown adipose tissue and lipolysis in white adipose tissue. Beyond their role as transcription factors, a direct role of STATs in mitochondrial function makes the argument for key roles in metabolism even more compelling(109-111).Although it has long been recognized that viruses can disrupt IFN signaling by disrupting STAT signaling(112),recent work shows that T. gondiialters hostresponse by injecting the kinase ROP16 and activating both STAT3 and STAT6(113),(94).In macrophages, the effect is downregulation of proinflammatory cytokine signaling and deviation to an alternatively activated phenotype. Viruses can also activate STAT6 and can do so apparently in a JAK-independent manner(114).In this case though, Stat6 activation is protective in terms of host response.

Conclusions

JAK-STAT signaling is one of the most important pathways determining gliogenic cell fates. JAKs and STATs remain central players in all of the key cells, ranging from the “newest” CD4

helper cell subset to alternatively activated macrophages. It is now clear that STATs activate and repress gene expression and serve to organize the epigenetic landscape of immune cells. The bias of neuroepithelial cells towards gliogenesis also indicates dysregulation of JAK-STAT signaling during brain development. The Notch signaling pathway coincides with the JAK-STAT pathway to bring about the gliogenic shift. Without JAK-STAT signaling, the Notch pathway instead represses gliogenicgenes.Defective JAK-STAT signaling may contribute to the overproduction of glial cells. Therefore, it is crucial to understand the role of JAK-STAT signaling pathways in regulation of B cells, CD4, CD8T cells, and gene expressions in Cancer and Autoimmunity as a potential therapeutic target

Reference

1. Horvath CM. STAT proteins and transcriptional responses to extracellular signals. Trends in biochemical sciences. 2000;25(10):496-502.
2. Ihle JN. The Stat family in cytokine signaling. Current opinion in cell biology. 2001;13(2):211-7.
3. Boulay J-L, O'Shea JJ, Paul WE. Molecular phylogeny within type I cytokines and their cognate receptors. Immunity. 2003;19(2):159-63.
4. Minegishi Y, Saito M, Tsuchiya S, Tsuge I, Takada H, Hara T, et al. Dominant-negative mutations in the DNA-binding domain of STAT3 cause hyper-IgE syndrome. Nature. 2007;448(7157):1058-62.
5. Notarangelo LD, Mella P, Jones A, de Saint Basile G, Savoldi G, Cranston T, et al. Mutations in severe combined immune deficiency (SCID) due to JAK3 deficiency. Human mutation. 2001;18(4):255-63.
6. Watford WT, O'Shea JJ. Human tyk2 kinase deficiency: another primary immunodeficiency syndrome. Immunity. 2006;25(5):695-7.
7. Murray PJ. The JAK-STAT signaling pathway: input and output integration. The Journal of Immunology. 2007;178(5):2623-9.
8. O'Shea JJ, Pesu M, Borie DC, Changelian PS. A new modality for immunosuppression: targeting the JAK/STAT pathway. Nature reviews Drug discovery. 2004;3(7):555-64.
9. Shuai K, Liu B. Regulation of JAK–STAT signalling in the immune system. Nature Reviews Immunology. 2003;3(11):900-11.
10. McBride KM, Banninger G, McDonald C, Reich NC. Regulated nuclear import of the STAT1 transcription factor by direct binding of importin-α. The EMBO journal. 2002;21(7):1754-63.
11. Begitt A, Meyer T, van Rossum M, Vinkemeier U. Nucleocytoplasmic translocation of Stat1 is regulated by a leucine-rich export signal in the coiled-coil domain. Proceedings of the National Academy of Sciences. 2000;97(19):10418-23.
12. Melen K, Kinnunen L, Julkunen I. Arginine/lysine-rich structural element is involved in interferon-induced nuclear import of STATs. Journal of Biological Chemistry. 2001;276(19):16447-55.
13. Meyer T, Begitt A, Lödige I, van Rossum M, Vinkemeier U. Constitutive and IFN-γ-induced nuclear import of STAT1 proceed through independent pathways. The EMBO journal. 2002;21(3):344-54.

14. Lillemeier BF, Köster M, Kerr IM. STAT1 from the cell membrane to the DNA. The EMBO journal. 2001;20(10):2508-17.
15. Levy DE, Darnell J. Stats: transcriptional control and biological impact. Nature reviews Molecular cell biology. 2002;3(9):651-62.
16. Hou T, Ray S, Lee C, Brasier AR. The STAT3 NH2-terminal domain stabilizes enhanceosome assembly by interacting with the p300 bromodomain. Journal of Biological Chemistry. 2008;283(45):30725-34.
17. Murray PJ. The primary mechanism of the IL-10-regulated antiinflammatory response is to selectively inhibit transcription. Proceedings of the National Academy of Sciences of the United States of America. 2005;102(24):8686-91.
18. Pelletier S, Duhamel F, Coulombe P, Popoff MR, Meloche S. Rho family GTPases are required for activation of Jak/STAT signaling by G protein-coupled receptors. Molecular and cellular biology. 2003;23(4):1316-33.
19. Yu C-L, Meyer DJ, Campbell GS, Larner AC, Carter-Su C, Schwartz J, et al. Enhanced DNA-binding activity of a Stat3-related protein in cells transformed by the Src oncoprotein. Science. 1995;269(5220):81-3.
20. Lund TC, Coleman C, Horvath E, Sefton BM, Jove R, Medveczky MM, et al. The Src-family kinase Lck can induce STAT3 phosphorylation and DNA binding activity. Cellular signalling. 1999;11(11):789-96.
21. Wen X, Lin HH, Shih H-M, Kung H-J, Ann DK. Kinase activation of the non-receptor tyrosine kinase Etk/BMX alone is sufficient to transactivate STAT-mediated gene expression in salivary and lung epithelial cells. Journal of Biological Chemistry. 1999;274(53):38204-10.
22. Priel-Halachmi S, Ben-Dor I, Shpungin S, Tennenbaum T, Molavani H, Bachrach M, et al. FER kinase activation of Stat3 is determined by the N-terminal sequence. Journal of Biological Chemistry. 2000;275(37):28902-10.
23. Fischer P, Hilfiker-Kleiner D. Survival pathways in hypertrophy and heart failure: the gp130-STAT3 axis. Basic research in cardiology. 2007;102(5):393-411.
24. Roig E, Orús J, Paré C, Azqueta M, Filella X, Perez-Villa F, et al. Serum interleukin-6 in congestive heart failure secondary to idiopathic dilated cardiomyopathy. The American journal of cardiology. 1998;82(5):688-90.
25. Hirota H, Chen J, Betz UA, Rajewsky K, Gu Y, Ross J, et al. Loss of a gp130 cardiac muscle cell survival pathway is a critical event in the onset of heart failure during biomechanical stress. Cell. 1999;97(2):189-98.
26. Hirota H, Izumi M, Hamaguchi T, Sugiyama S, Murakami E, Kunisada K, et al. Circulating interleukin-6 family cytokines and their receptors in patients with congestive heart failure. Heart and vessels. 2004;19(5):237-41.
27. Torre-Amione G, Kapadia S, Benedict C, Oral H, Young JB, Mann DL. Proinflammatory cytokine levels in patients with depressed left ventricular ejection fraction: a report from the Studies of Left Ventricular Dysfunction (SOLVD). Journal of the American College of Cardiology. 1996;27(5):1201-6.
28. Khan SQ, Kelly D, Quinn P, Davies JE, Ng LL. Cardiotrophin-1 predicts death or heart failure following acute myocardial infarction. Journal of cardiac failure. 2006;12(8):635-40.
29. Ndubuisi MI, Guo GG, Fried VA, Etlinger JD, Sehgal PB. Cellular physiology of STAT3: where's the cytoplasmic monomer? Journal of Biological Chemistry. 1999;274(36):25499-509.
30. Zhong M, Henriksen MA, Takeuchi K, Schaefer O, Liu B, Ten Hoeve J, et al. Implications of an antiparallel dimeric structure of nonphosphorylated STAT1 for the activation–inactivation

cycle. Proceedings of the National Academy of Sciences of the United States of America. 2005;102(11):3966-71.
31. Mao X, Ren Z, Parker GN, Sondermann H, Pastorello MA, Wang W, et al. Structural bases of unphosphorylated STAT1 association and receptor binding. Molecular cell. 2005;17(6):761-71.
32. Wenta N, Strauss H, Meyer S, Vinkemeier U. Tyrosine phosphorylation regulates the partitioning of STAT1 between different dimer conformations. Proceedings of the National Academy of Sciences. 2008;105(27):9238-43.
33. Wang Y, Wu TR, Cai S, Welte T, Chin YE. Stat1 as a component of tumor necrosis factor alpha receptor 1-TRADD signaling complex to inhibit NF-κB activation. Molecular and cellular biology. 2000;20(13):4505-12.
34. Decker T, Kovarik P. Serine phosphorylation of STATs. Oncogene. 2000;19(21).
35. Kovarik P, Mangold M, Ramsauer K, Heidari H, Steinborn R, Zotter A, et al. Specificity of signaling by STAT1 depends on SH2 and C-terminal domains that regulate Ser727 phosphorylation, differentially affecting specific target gene expression. The EMBO journal. 2001;20(1-2):91-100.
36. Baetz A, Frey M, Heeg K, Dalpke AH. Suppressor of cytokine signaling (SOCS) proteins indirectly regulate toll-like receptor signaling in innate immune cells. Journal of Biological Chemistry. 2004;279(52):54708-15.
37. Yoshimura A, Naka T, Kubo M. SOCS proteins, cytokine signalling and immune regulation. Nature Reviews Immunology. 2007;7(6):454-65.
38. Kile BT, Schulman BA, Alexander WS, Nicola NA, Martin HM, Hilton DJ. The SOCS box: a tale of destruction and degradation. Trends in biochemical sciences. 2002;27(5):235-41.
39. Zhang J-G, Farley A, Nicholson SE, Willson TA, Zugaro LM, Simpson RJ, et al. The conserved SOCS box motif in suppressors of cytokine signaling binds to elongins B and C and may couple bound proteins to proteasomal degradation. Proceedings of the National Academy of Sciences. 1999;96(5):2071-6.
40. Boyle K, Egan P, Rakar S, Willson TA, Wicks IP, Metcalf D, et al. The SOCS box of suppressor of cytokine signaling-3 contributes to the control of G-CSF responsiveness in vivo. Blood. 2007;110(5):1466-74.
41. Zhang J-G, Metcalf D, Rakar S, Asimakis M, Greenhalgh CJ, Willson TA, et al. The SOCS box of suppressor of cytokine signaling-1 is important for inhibition of cytokine action in vivo. Proceedings of the National Academy of Sciences. 2001;98(23):13261-5.
42. Lang R, Pauleau A-L, Parganas E, Takahashi Y, Mages J, Ihle JN, et al. SOCS3 regulates the plasticity of gp130 signaling. Nature immunology. 2003;4(6):546-50.
43. Kamizono S, Hanada T, Yasukawa H, Minoguchi S, Kato R, Minoguchi M, et al. The SOCS box of SOCS-1 accelerates ubiquitin-dependent proteolysis of TEL-JAK2. Journal of Biological Chemistry. 2001;276(16):12530-8.
44. Stross C, Radtke S, Clahsen T, Gerlach C, Volkmer-Engert R, Schaper F, et al. Oncostatin M receptor-mediated signal transduction is negatively regulated by SOCS3 through a receptor tyrosine-independent mechanism. Journal of Biological Chemistry. 2006;281(13):8458-68.
45. Meyer T, Hendry L, Begitt A, John S, Vinkemeier U. A single residue modulates tyrosine dephosphorylation, oligomerization, and nuclear accumulation of stat transcription factors. Journal of Biological Chemistry. 2004;279(18):18998-9007.
46. Ma J, Zhang T, Novotny-Diermayr V, Tan AL, Cao X. A novel sequence in the coiled-coil domain of Stat3 essential for its nuclear translocation. Journal of Biological Chemistry. 2003;278(31):29252-60.

47. McBride KM, McDonald C, Reich NC. Nuclear export signal located within the DNA-binding domain of the STAT1transcription factor. The EMBO journal. 2000;19(22):6196-206.
48. Marg A, Shan Y, Meyer T, Meissner T, Brandenburg M, Vinkemeier U. Nucleocytoplasmic shuttling by nucleoporins Nup153 and Nup214 and CRM1-dependent nuclear export control the subcellular distribution of latent Stat1. The Journal of cell biology. 2004;165(6):823-33.
49. Meyer T, Marg A, Lemke P, Wiesner B, Vinkemeier U. DNA binding controls inactivation and nuclear accumulation of the transcription factor Stat1. Genes & development. 2003;17(16):1992-2005.
50. Narazaki M, Fujimoto M, Matsumoto T, Morita Y, Saito H, Kajita T, et al. Three distinct domains of SSI-1/SOCS-1/JAB protein are required for its suppression of interleukin 6 signaling. Proceedings of the National Academy of Sciences. 1998;95(22):13130-4.
51. Sasaki A, Yasukawa H, Suzuki A, Kamizono S, Syoda T, Kinjyo I, et al. Cytokine-inducible SH2 protein-3 (CIS3/SOCS3) inhibits Janus tyrosine kinase by binding through the N-terminal kinase inhibitory region as well as SH2 domain. Genes to Cells. 1999;4(6):339-51.
52. Yasukawa H, Misawa H, Sakamoto H, Masuhara M, Sasaki A, Wakioka T, et al. The JAK-binding protein JAB inhibits Janus tyrosine kinase activity through binding in the activation loop. The EMBO journal. 1999;18(5):1309-20.
53. Yu C-L, Jove R, Burakoff S. Constitutive activation of the Janus kinase-STAT pathway in T lymphoma overexpressing the Lck protein tyrosine kinase. The Journal of Immunology. 1997;159(11):5206-10.
54. Kamura T, Sato S, Haque D, Liu L, Kaelin WG, Conaway RC, et al. The Elongin BC complex interacts with the conserved SOCS-box motif present in members of the SOCS, ras, WD-40 repeat, and ankyrin repeat families. Genes & development. 1998;12(24):3872-81.
55. Ungureanu D, Saharinen P, Junttila I, Hilton DJ, Silvennoinen O. Regulation of Jak2 through the ubiquitin-proteasome pathway involves phosphorylation of Jak2 on Y1007 and interaction with SOCS-1. Molecular and cellular biology. 2002;22(10):3316-26.
56. Alexander WS, Starr R, Fenner JE, Scott CL, Handman E, Sprigg NS, et al. SOCS1 is a critical inhibitor of interferon γ signaling and prevents the potentially fatal neonatal actions of this cytokine. Cell. 1999;98(5):597-608.
57. Naka T, Matsumoto T, Narazaki M, Fujimoto M, Morita Y, Ohsawa Y, et al. Accelerated apoptosis of lymphocytes by augmented induction of Bax in SSI-1 (STAT-induced STAT inhibitor-1) deficient mice. Proceedings of the National Academy of Sciences. 1998;95(26):15577-82.
58. Morita Y, Naka T, Kawazoe Y, Fujimoto M, Narazaki M, Nakagawa R, et al. Signals transducers and activators of transcription (STAT)-induced STAT inhibitor-1 (SSI-1)/suppressor of cytokine signaling-1 (SOCS-1) suppresses tumor necrosis factor α-induced cell death in fibroblasts. Proceedings of the National Academy of Sciences. 2000;97(10):5405-10.
59. Yasukawa H, Ohishi M, Mori H, Murakami M, Chinen T, Aki D, et al. IL-6 induces an anti-inflammatory response in the absence of SOCS3 in macrophages. Nature immunology. 2003;4(6):551-6.
60. El Kasmi KC, Holst J, Coffre M, Mielke L, de Pauw A, Lhocine N, et al. General nature of the STAT3-activated anti-inflammatory response. The Journal of Immunology. 2006;177(11):7880-8.

61. Williams LM, Sarma U, Willets K, Smallie T, Brennan F, Foxwell BM. Expression of constitutively active STAT3 can replicate the cytokine-suppressive activity of interleukin-10 in human primary macrophages. Journal of Biological Chemistry. 2007;282(10):6965-75.
62. Darnell JE, Kerr IM, Stark GR. Jak-STAT pathways and transcriptional activation in response to IFNs and other extracellular signaling proteins. Science. 1994;264(5164):1415-21.
63. Leonard WJ, O'Shea JJ. Jaks and STATs: biological implications*. Annual review of immunology. 1998;16(1):293-322.
64. O'Shea JJ, Murray PJ. Cytokine signaling modules in inflammatory responses. Immunity. 2008;28(4):477-87.
65. Paul WE. What determines Th2 differentiation, in vitro and in vivo&quest. Immunology and cell biology. 2010;88(3):236-9.
66. Liao W, Schones DE, Oh J, Cui Y, Cui K, Roh T-Y, et al. Priming for T helper type 2 differentiation by interleukin 2–mediated induction of interleukin 4 receptor α-chain expression. Nature immunology. 2008;9(11):1288-96.
67. Liao W, Lin J-X, Wang L, Li P, Leonard WJ. Modulation of cytokine receptors by IL-2 broadly regulates differentiation into helper T cell lineages. Nature immunology. 2011;12(6):551-9.
68. Stritesky GL, Muthukrishnan R, Sehra S, Goswami R, Pham D, Travers J, et al. The transcription factor STAT3 is required for T helper 2 cell development. Immunity. 2011;34(1):39-49.
69. Burchill MA, Yang J, Vogtenhuber C, Blazar BR, Farrar MA. IL-2 receptor β-dependent STAT5 activation is required for the development of Foxp3+ regulatory T cells. The Journal of Immunology. 2007;178(1):280-90.
70. Yao Z, Cui Y, Watford WT, Bream JH, Yamaoka K, Hissong BD, et al. Stat5a/b are essential for normal lymphoid development and differentiation. Proceedings of the National academy of Sciences of the United States of America. 2006;103(4):1000-5.
71. Yao Z, Kanno Y, Kerenyi M, Stephens G, Durant L, Watford WT, et al. Nonredundant roles for Stat5a/b in directly regulating Foxp3. Blood. 2007;109(10):4368-75.
72. Zorn E, Nelson EA, Mohseni M, Porcheray F, Kim H, Litsa D, et al. IL-2 regulates FOXP3 expression in human CD4+ CD25+ regulatory T cells through a STAT-dependent mechanism and induces the expansion of these cells in vivo. Blood. 2006;108(5):1571-9.
73. Chaudhry A, Rudra D, Treuting P, Samstein RM, Liang Y, Kas A, et al. CD4+ regulatory T cells control TH17 responses in a Stat3-dependent manner. Science. 2009;326(5955):986-91.
74. Chen Z, Laurence A, Kanno Y, Pacher-Zavisin M, Zhu B-M, Tato C, et al. Selective regulatory function of Socs3 in the formation of IL-17-secreting T cells. Proceedings of the National Academy of Sciences. 2006;103(21):8137-42.
75. Mathur AN, Chang H-C, Zisoulis DG, Stritesky GL, Yu Q, O'Malley JT, et al. Stat3 and Stat4 direct development of IL-17-secreting Th cells. The Journal of Immunology. 2007;178(8):4901-7.
76. Milner JD, Brenchley JM, Laurence A, Freeman AF, Hill BJ, Elias KM, et al. Impaired TH17 cell differentiation in subjects with autosomal dominant hyper-IgE syndrome. Nature. 2008;452(7188):773-6.
77. Durant L, Watford WT, Ramos HL, Laurence A, Vahedi G, Wei L, et al. Diverse targets of the transcription factor STAT3 contribute to T cell pathogenicity and homeostasis. Immunity. 2010;32(5):605-15.
78. Laurence A, Tato CM, Davidson TS, Kanno Y, Chen Z, Yao Z, et al. Interleukin-2 signaling via STAT5 constrains T helper 17 cell generation. Immunity. 2007;26(3):371-81.

79. Yang X-P, Ghoreschi K, Steward-Tharp SM, Rodriguez-Canales J, Zhu J, Grainger JR, et al. Opposing regulation of the locus encoding IL-17 through direct, reciprocal actions of STAT3 and STAT5. Nature immunology. 2011;12(3):247-54.
80. Chen Y, Haines CJ, Gutcher I, Hochweller K, Blumenschein WM, McClanahan T, et al. Foxp3+ regulatory T cells promote T helper 17 cell development in vivo through regulation of interleukin-2. Immunity. 2011;34(3):409-21.
81. Pandiyan P, Conti HR, Zheng L, Peterson AC, Mathern DR, Hernández-Santos N, et al. CD4+ CD25+ Foxp3+ regulatory T cells promote Th17 cells in vitro and enhance host resistance in mouse Candida albicans Th17 cell infection model. Immunity. 2011;34(3):422-34.
82. Batten M, Ramamoorthi N, Kljavin NM, Ma CS, Cox JH, Dengler HS, et al. IL-27 supports germinal center function by enhancing IL-21 production and the function of T follicular helper cells. The Journal of experimental medicine. 2010;207(13):2895-906.
83. Eddahri F, Denanglaire S, Bureau F, Spolski R, Leonard WJ, Leo O, et al. Interleukin-6/STAT3 signaling regulates the ability of naive T cells to acquire B-cell help capacities. Blood. 2009;113(11):2426-33.
84. Nurieva RI, Chung Y, Hwang D, Yang XO, Kang HS, Ma L, et al. Generation of T follicular helper cells is mediated by interleukin-21 but independent of T helper 1, 2, or 17 cell lineages. Immunity. 2008;29(1):138-49.
85. Nakayamada S, Kanno Y, Takahashi H, Jankovic D, Lu KT, Johnson TA, et al. Early Th1 cell differentiation is marked by a Tfh cell-like transition. Immunity. 2011;35(6):919-31.
86. Schmitt N, Morita R, Bourdery L, Bentebibel SE, Zurawski SM, Banchereau J, et al. Human dendritic cells induce the differentiation of interleukin-21-producing T follicular helper-like cells through interleukin-12. Immunity. 2009;31(1):158-69.
87. Johnston RJ, Choi YS, Diamond JA, Yang JA, Crotty S. STAT5 is a potent negative regulator of TFH cell differentiation. The Journal of experimental medicine. 2012;209(2):243-50.
88. Nurieva RI, Podd A, Chen Y, Alekseev AM, Yu M, Qi X, et al. STAT5 protein negatively regulates T follicular helper (Tfh) cell generation and function. Journal of Biological Chemistry. 2012;287(14):11234-9.
89. Olson MR, Verdan FF, Hufford MM, Dent AL, Kaplan MH. STAT3 Impairs STAT5 Activation in the Development of IL-9–Secreting T Cells. The Journal of Immunology. 2016:1501801.
90. Goswami R, Jabeen R, Yagi R, Pham D, Zhu J, Goenka S, et al. STAT6-dependent regulation of Th9 development. The Journal of Immunology. 2012;188(3):968-75.
91. Hand TW, Cui W, Jung YW, Sefik E, Joshi NS, Chandele A, et al. Differential effects of STAT5 and PI3K/AKT signaling on effector and memory CD8 T-cell survival. Proceedings of the National Academy of Sciences. 2010;107(38):16601-6.
92. Tripathi P, Kurtulus S, Wojciechowski S, Sholl A, Hoebe K, Morris SC, et al. STAT5 is critical to maintain effector CD8+ T cell responses. The Journal of Immunology. 2010;185(4):2116-24.
93. Cui W, Liu Y, Weinstein JS, Craft J, Kaech SM. An interleukin-21-interleukin-10-STAT3 pathway is critical for functional maturation of memory CD8+ T cells. Immunity. 2011;35(5):792-805.
94. Siegel AM, Heimall J, Freeman AF, Hsu AP, Brittain E, Brenchley JM, et al. A critical role for STAT3 transcription factor signaling in the development and maintenance of human T cell memory. Immunity. 2011;35(5):806-18.

95. Malin S, McManus S, Cobaleda C, Novatchkova M, Delogu A, Bouillet P, et al. Role of STAT5 in controlling cell survival and immunoglobulin gene recombination during pro-B cell development. Nature immunology. 2010;11(2):171-9.
96. Nakayama J, Yamamoto M, Hayashi K, Satoh H, Bundo K, Kubo M, et al. BLNK suppresses pre–B-cell leukemogenesis through inhibition of JAK3. Blood. 2009;113(7):1483-92.
97. Nguyen-Jackson H, Panopoulos AD, Zhang H, Li HS, Watowich SS. STAT3 controls the neutrophil migratory response to CXCR2 ligands by direct activation of G-CSF–induced CXCR2 expression and via modulation of CXCR2 signal transduction. Blood. 2010;115(16):3354-63.
98. Panopoulos AD, Zhang L, Snow JW, Jones DM, Smith AM, El Kasmi KC, et al. STAT3 governs distinct pathways in emergency granulopoiesis and mature neutrophils. Blood. 2006;108(12):3682-90.
99. Zhang H, Nguyen-Jackson H, Panopoulos AD, Li HS, Murray PJ, Watowich SS. STAT3 controls myeloid progenitor growth during emergency granulopoiesis. Blood. 2010;116(14):2462-71.
100. Esashi E, Wang Y-H, Perng O, Qin X-F, Liu Y-J, Watowich SS. The signal transducer STAT5 inhibits plasmacytoid dendritic cell development by suppressing transcription factor IRF8. Immunity. 2008;28(4):509-20.
101. Sonnenberg GF, Fouser LA, Artis D. Border patrol: regulation of immunity, inflammation and tissue homeostasis at barrier surfaces by IL-22. Nature immunology. 2011;12(5):383-90.
102. Wang W-B, Levy DE, Lee C-K. STAT3 negatively regulates type I IFN-mediated antiviral response. The Journal of immunology. 2011;187(5):2578-85.
103. Siracusa MC, Saenz SA, Hill DA, Kim BS, Headley MB, Doering TA, et al. TSLP promotes interleukin-3-independent basophil haematopoiesis and type 2 inflammation. Nature. 2011;477(7363):229-33.
104. van Panhuys N, Prout M, Forbes E, Min B, Paul WE, Le Gros G. Basophils are the major producers of IL-4 during primary helminth infection. The Journal of Immunology. 2011;186(5):2719-28.
105. Rochman Y, Kashyap M, Robinson GW, Sakamoto K, Gomez-Rodriguez J, Wagner K-U, et al. Thymic stromal lymphopoietin-mediated STAT5 phosphorylation via kinases JAK1 and JAK2 reveals a key difference from IL-7–induced signaling. Proceedings of the National Academy of Sciences. 2010;107(45):19455-60.
106. Ricardo-Gonzalez RR, Eagle AR, Odegaard JI, Jouihan H, Morel CR, Heredia JE, et al. IL-4/STAT6 immune axis regulates peripheral nutrient metabolism and insulin sensitivity. Proceedings of the National Academy of Sciences. 2010;107(52):22617-22.
107. Szanto A, Balint BL, Nagy ZS, Barta E, Dezso B, Pap A, et al. STAT6 transcription factor is a facilitator of the nuclear receptor PPARγ-regulated gene expression in macrophages and dendritic cells. Immunity. 2010;33(5):699-712.
108. Nguyen KD, Qiu Y, Cui X, Goh YS, Mwangi J, David T, et al. Alternatively activated macrophages produce catecholamines to sustain adaptive thermogenesis. Nature. 2011;480(7375):104-8.
109. Gough DJ, Corlett A, Schlessinger K, Wegrzyn J, Larner AC, Levy DE. Mitochondrial STAT3 supports Ras-dependent oncogenic transformation. Science. 2009;324(5935):1713-6.
110. Potla R, Koeck T, Wegrzyn J, Cherukuri S, Shimoda K, Baker DP, et al. Tyk2 tyrosine kinase expression is required for the maintenance of mitochondrial respiration in primary pro-B lymphocytes. Molecular and cellular biology. 2006;26(22):8562-71.

111. Wegrzyn J, Potla R, Chwae Y-J, Sepuri NB, Zhang Q, Koeck T, et al. Function of mitochondrial Stat3 in cellular respiration. Science. 2009;323(5915):793-7.
112. Ramachandran A, Horvath CM. Paramyxovirus disruption of interferon signal transduction: STATus report. Journal of Interferon & Cytokine Research. 2009;29(9):531-7.
113. Butcher BA, Fox BA, Rommereim LM, Kim SG, Maurer KJ, Yarovinsky F, et al. Toxoplasma gondii rhoptry kinase ROP16 activates STAT3 and STAT6 resulting in cytokine inhibition and arginase-1-dependent growth control. PLoS Pathog. 2011;7(9):e1002236.
114. Chen H, Sun H, You F, Sun W, Zhou X, Chen L, et al. Activation of STAT6 by STING is critical for antiviral innate immunity. Cell. 2011;147(2):436-46.