REGULATION OF JAK–STAT SIGNALLING IN THE IMMUNE SYSTEM

Ke Shuai‡ and Bin Liu**

The cytokine-activated Janus kinase (JAK)–signal transducer and activator of transcription (STAT) pathway has an important role in the control of immune responses. Dysregulation of JAK–STAT signalling is associated with various immune disorders. The signalling strength, kinetics and specificity of the JAK–STAT pathway are modulated at many levels by distinct regulatory proteins. Here, we review recent studies on the regulation of the JAK–STAT pathway that will enhance our ability to design rational therapeutic strategies for immune diseases.

Cytokines have essential roles in the control of immune responses. The biological functions of cytokines mainly depend on cytokine-mediated gene activation or repression. Studies on gene induction by interferons (IFNs) led to the discovery of the Janus kinase (JAK)–signal transducer and activator of transcription (STAT) pathway[1], which has since been shown to be a common signalling pathway used by many cytokines. The binding of a cytokine to its cell-surface receptor results in receptor dimerization and the subsequent activation of JAK tyrosine kinases, which are constitutively associated with the receptor. Specific tyrosine residues on the receptor are then phosphorylated by activated JAKs and serve as docking sites for a family of latent cytoplasmic transcription factors known as STATs. STATs are phosphorylated by JAKs, then dimerize and subsequently leave the receptor and translocate to the nucleus, where they activate gene transcription[2,3] (FIG. 1a).

The mammalian JAK family has four members: JAK1, JAK2, JAK3 and tyrosine kinase 2 (TYK2)[4]. Each contains a conserved kinase domain and a related, but catalytically inactivate, pseudo-kinase domain at the carboxyl terminus (FIG. 1b). The pseudo-kinase domain might regulate the kinase activity of JAKs.

There are seven mammalian STATs: STAT1, STAT2, STAT3, STAT4, STAT5A, STAT5B and STAT6 (REF. 2), which are highly homologous in several regions (FIG. 1c), including a SRC homology 2 (SH2) domain, which is involved in the activation and dimerization of STATs[5,6], a DNA-binding domain[7], and a transacivation domain , which is located at the carboxyl terminus[8,9]. The amino-terminal region of STATs is involved in regulating STAT activity, such as the formation of STAT tetramers[10] and tyrosine dephosphorylation[11].

Genetic knockout studies have shown that JAKs and STATs have highly specific functions in the control of various immune responses[12–14] (TABLE 1). Recent studies have shown that JAK–STAT signalling can be regulated at many steps through distinct mechanisms. Key regulators include the suppressor of cytokine signalling (SOCS) proteins and the recently discovered protein inhibitor of activated STAT (PIAS) family, as well as various protein tyrosine phosphatases (PTPs). The modulation of JAKs and STATs by various protein modifications and the cross-talk between different JAK–STAT pathways and other cellular signalling pathways provide additional levels of regulation that might be crucial. This review discusses the latest insights into how these various mechanisms regulate JAK–STAT signalling in the immune system.

The regulation of JAKs

JAKs are mainly regulated at the post-translational level through various mechanisms (FIG. 2).

Regulation of JAKs by the SOCS proteins. SOCS proteins are the most thoroughly studied regulators of JAK–STAT signalling. Biochemical and genetic studies have clearly shown a crucial role for SOCS proteins in

**Division of Hematology-Oncology, Department of Medicine and ‡Department of Biological Chemistry, University of California, Los Angeles, California 90095, USA.*
Correspondence to K. S. e-mail: kshuai@mednet.ucla.edu
doi:10.1038/nri1226

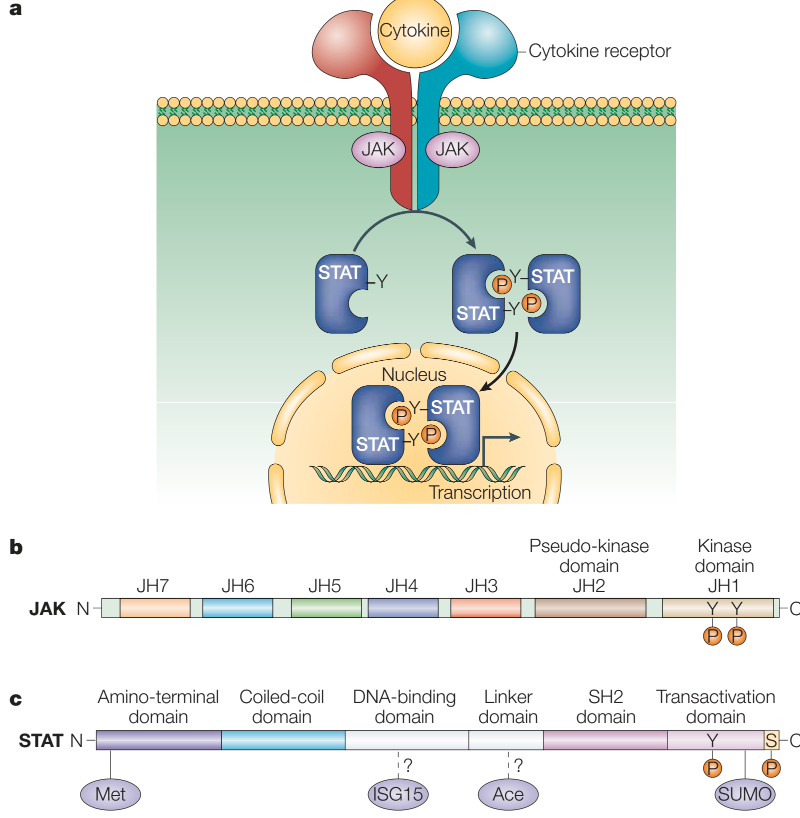


Figure 1 | **The JAK–STAT pathway. a** | A schematic representation of the Janus kinase (JAK)–signal transducer and activator of transcription (STAT) pathway. The activation of JAKs after cytokine stimulation results in the phosphorylation of STATs, which then dimerize and translocate to the nucleus to activate gene transcription. **b** | The domain structure of JAKs. The domains JH1–JH7 are based on sequence similarity of four known JAKs. JH1 is the kinase domain, which contains two tyrosines that can be phosphorylated after ligand stimulation. JH2 is the pseudo-kinase domain. The JH6 and JH7 domains mediate the binding of JAKs to receptors. **c** | The domain structure of STATs. The activity of STATs can be regulated by protein modification, including tyrosine and serine phosphorylation, methylation (Met), sumoylation (SUMO), ISGylation (ISG15) and acetylation (Ace). The modification sites of ISGylation and acetylation have not been identified.

the immune system. The SOCS family of proteins has eight members: CIS (cytokine-inducible SH2 domain protein) and SOCS1–SOCS7 (REFS 15,16). SOCS proteins contain an SH2 domain, which is flanked by a variable amino-terminal domain and a carboxy-terminal SOCS box[17] (FIG. 3a). Among the SOCS family, the roles of SOCS1, SOCS2, SOCS3 and CIS have been well studied in the regulation of JAK–STAT signalling[18]. These SOCS proteins are generally expressed at low levels in unstimulated cells and become rapidly induced by cytokines, thereby inhibiting JAK–STAT signalling and forming a classic negative-feedback loop[19]. SOCS proteins inhibit cytokine signalling through distinct mechanisms (FIG. 3b). The SH2 domain of SOCS1 binds directly to tyrosine phosphorylated JAKs, resulting in the direct inhibition of JAK activity[20–22]. However, the inhibition of JAKs by SOCS3 requires binding of SOCS3 to the activated receptor[23,24]. Instead of acting on JAKs, CIS seems to inhibit STAT activation by competing with STATs for binding to the receptor docking sites[25]. Finally, the involvement of SOCS proteins in the degradation of signalling proteins through the ubiquitin-proteasome pathway (BOX 1) has also been suggested. The SOCS box can bind to elongins B and C, which are known components of a ubiquitin E3 ligase complex[26,27]. So, SOCS proteins might target signalling proteins for degradation.

The regulation of SOCS3 by cytokines can also occur at the post-translational level. It has been documented that SOCS3 becomes rapidly phosphorylated at residues Tyr204 and Tyr221, which are present in the conserved SOCS box, by JAKs and receptor tyrosine kinases in response to certain cytokine and growth-factor stimulation[28,29]. Mutational studies indicate that tyrosine phosphorylation of SOCS3 accelerates the degradation of SOCS3 protein, thereby regulating feedback inhibition of JAK–STAT signalling[30].

Gene-targeting studies indicate that SOCS1 and SOCS3 have essential roles in the regulation of immune functions (TABLE 1). *Socs1*$^{-/-}$ mice die within three weeks of birth, mainly due to dysregulated IFN-γ responses[31–34]. *Socs1*$^{-/-}$ mice show lymphopaenia, increased apoptosis in lymphoid organs and increased levels of IFN-γ in the serum. *Socs3* knockout is embryonic lethal, probably due to placental insufficiency and erythrocytosis[35–37]. Conditional *Socs3* gene-targeting studies have shown an important role for SOCS3 in the negative regulation of interleukin-6 (IL-6) signalling in macrophages[38–40]. Earlier studies indicated that both SOCS1 and SOCS3 are induced by IFN-γ and IL-6, and both can inhibit IFN-γ and IL-6 responses. However, recent genetic studies have shown an unexpected *in vivo* specificity of SOCS1 and SOCS3 in the regulation of cytokine signalling. In *Socs3*$^{-/-}$ macrophages, the activation of STAT1 by IL-6 is prolonged, whereas the activation of STAT1 by IFN-γ is normal[38–40]. By contrast, in *Socs1*$^{-/-}$ macrophages, the opposite is true. In addition, although STAT3 is activated by both IL-6 and IL-10, the tyrosine phosphorylation of STAT3 induced by IL-6, but not IL-10, is prolonged in *Socs3*$^{-/-}$ macrophages. So, SOCS proteins have specificity for cytokines, but not JAKs or STATs.

An interesting property of SOCS proteins is that they specifically affect the kinetics of JAK–STAT-signalling termination, but have no effect on the initial activation process or signalling strength. As a result, prolonged STAT activation induced by cytokines is observed in the absence of SOCS proteins. As discussed later, prolonged STAT activation might lead to altered cytokine responses. In fact, microarray analysis shows that the gene-activation profile induced by IL-6 mimics that induced by IFN-γ in *Socs3*$^{-/-}$ cells, indicating a role for SOCS3 in the control of cytokine-response specificity[38,39]. A similar alteration of the IL-6 response has also been observed in *Stat3*$^{-/-}$ cells, in which STAT1 activation is prolonged[41].

SOCS proteins have also been implicated in cross-talk between different cytokine-signalling pathways, as discussed later.

Regulation of JAKs by protein tyrosine phosphotases. Several PTPs have been indicated to regulate JAKs, including SHP1, SHP2, CD45, PTP1B and T-cell PTP (TCPTP). SHP1 and SHP2 are SH2-domain-containing

PTPs[42]. SHP1 is mainly expressed by haematopoietic cells and has been shown to be physically associated with the IL-3 receptor β chain, the c-KIT receptor, and the erythropoietin receptor (EPOR). Cells expressing a mutant EPOR that is defective in SHP1 binding are hypersensitive to EPO and have prolonged EPO-induced autophosphorylation of JAK2, indicating a role for SHP1 in the dephosphorylation of JAK2 (REF. 43). SHP1 is also involved in the dephosphorylation of JAK1. The IFN-α-induced tyrosine phosphorylation of JAK1, but not TYK2, is enhanced in *SHP1*$^{-/-}$ macrophages[44]. Genetic studies indicate that SHP2 is involved in the negative regulation of JAK1. In *SHP2*$^{-/-}$ fibroblasts, the level of JAK1 tyrosine phosphorylation after IFN-γ stimulation is increased[45].

CD45 is a receptor PTP that is highly expressed by haematopoietic cells and has a crucial role in antigen-receptor signalling in T and B cells[46]. CD45 can directly bind and dephosphorylate all JAKs[47], and enhanced JAK phosphorylation is observed in *CD45*$^{-/-}$ cells. The removal of CD45 increases the formation of erythroid colonies and antiviral activity, which is consistent with a role for CD45 in the negative regulation of EPO and IFN signalling. However, further studies are required to understand fully the importance of CD45 in the regulation of cytokine signalling under physiological conditions.

PTP1B and TCPTP — two highly related PTPs[48] — have also been suggested to dephosphorylate JAKs. JAK2 and TYK2, but not JAK1, can serve as substrates of PTP1B[49], and increased JAK2 phosphorylation has been observed in *Ptp1b*$^{-/-}$ mouse embryo fibroblasts. In addition, PTP1B has been implicated in the negative regulation of LEPTIN signalling, possibly by targeting JAK2 (REFS 50,51). However, no immunological phenotype of PTP1B has been reported. TCPTP can dephosphorylate JAK1 and JAK3 (REF. 52), and in *TCPTP*$^{-/-}$ macrophages, an enhancement of IFN-γ-induced tyrosine phosphorylation of JAK1, but not JAK2, is observed. So, many PTPs participate in the dephosphorylation of JAKs (TABLE 2). Gene-targeting studies support the importance of these PTPs in the regulation of cytokine signalling (TABLE 1).

Regulation of JAKs by ubiquitylation and ISGylation. The ubiquitin–proteasome pathway (BOX 1) has been implicated in regulating JAK–STAT signalling. JAK2 is ubiquitylated *in vivo* and *in vitro*[53], and IL-3 and IFN-γ stimulation enhances the polyubiquitylation of JAK2. Interestingly, tyrosine phosphorylation of JAK2 is found to be required for its efficient ubiquitylation. Polyubiquitylated JAK2 is rapidly degraded. Co-expression of SOCS1, but not SOCS3, promotes the degradation of ubiquitylated JAK2. The SOCS box of SOCS1, which interacts with elongins B and C, is required for the ubiquitylation of JAK2. So, the stability of JAK2 seems to be regulated by a SOCS1-mediated ubiquitin–proteasome pathway. Clearly, further studies are

Table 1 | ***In vivo* immunological functions of the JAK–STAT signalling components and regulators**

Gene	Phenotype of null mice	References
Jak		Reviewed in 12–14
Jak1	Perinatal lethality, defects in lymphoid development	
Jak2	Embryonic lethality, failure of erythropoiesis	
Jak3	SCID caused by cytokine-signalling defects from γ_c-containing receptors	
Tyk2	Hypersensitivity to pathogens due to interferon- and IL-12-signalling defects	
Stat		Reviewed in 12–14
Stat1	Impaired interferon signalling, susceptibility to viral infections	
Stat2	Impaired interferon signalling	
Stat3	Embryonic lethality, impaired responses to pathogens, cell-survival defects	
Stat4	Defects in T_H1-cell differentiation, impaired IL-12 pathway	
Stat5a	Defects in mammary-gland development, impaired prolactin signalling	
Stat5b	Growth-hormone pathway defects, defective NK-cell-mediated proliferation and cytolytic activity.	
Stat5a/5b	No NK cells, impaired IL-2-induced T-cell proliferation	
Stat6	Defects in T_H2-cell differentiation, impaired IL-4/IL-13 pathway	
Socs		Reviewed in 18
Cis	Normal	
Socs1	Perinatal lethality, interferon-γ overproduction, lymphopaenia, increased apoptosis in lymphoid organs, hypersensitivity to LPS	
Socs2	Gigantism, dysregulated growth hormone and Igf1 signalling	
Socs3	Embryonic lethality, placental and haematopoietic defects	
Ptp		
Tcptp	Haematopoietic defects, impaired T- and B-cell functions	137
Ptp1b	Hypersensitivity to insulin, defects in leptin signalling, no immunological phenotype has been reported	50,138
Shp1	Severe immune dysfunction, hyperproliferation of myeloid cells, anaemia	139,140
Shp2	Embryonic lethality, haematopoietic defects	141
Cd45	Defects in thymic development due to enhanced apoptosis and dysfunctional TCR signalling, increased erythroid-colony formation, enhanced antiviral activity	47,142,143

Cis, cytokine-inducible SRC homology 2 (SH2) protein; γ_c, common cytokine receptor γ chain; Igf1, insulin-like growth factor 1; IL, interleukin; Jak, Janus-family kinase; LPS, lipopolysaccharide; NK, natural killer; Ptp, protein tyrosine phosphatase; SCID, severe combined immunodeficiency; Shp, SH2-domain-containing PTP; Socs, suppressor of cytokine signalling; Stat, signal transducer and activator of transcription; Tcptp, T-cell PTP; TCR, T-cell receptor; T_H, T helper; Tyk2, tyrosine kinase 2.

LEPTIN
A hormone that regulates energy homeostasis and body weight. Leptin is mainly produced in white adipose tissue. Leptin binds to its receptor to signal through the JAK–STAT pathway.

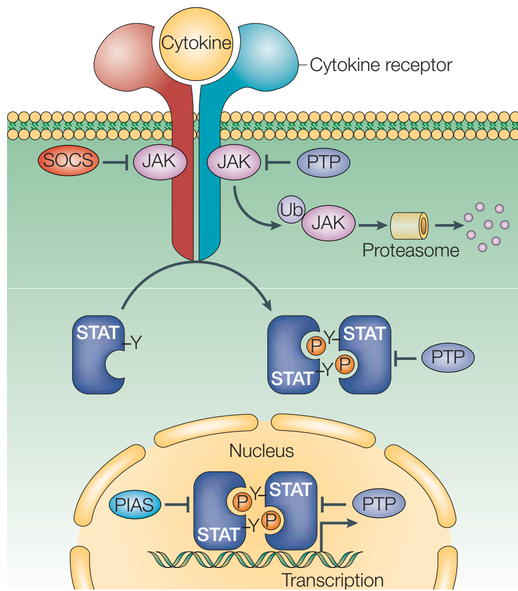


Figure 2 | **Negative regulation of the JAK–STAT pathway.** The Janus kinase (JAK)–signal transducer and activator of transcription (STAT) pathway is regulated at many levels. JAKs can be negatively regulated by suppressor of cytokine signalling (SOCS) proteins, protein tyrosine phosphatases (PTPs), such as SRC homology 2 (SH2)-domain-containing PTP1 (SHP1), SHP2, CD45 and T-cell PTP (TCPTP), and ubiquitin-mediated protein degradation. SOCS proteins, which are induced by cytokines, act as a negative-feedback loop to switch off the activity of JAKs. Many PTPs participate in the regulation of JAKs. The regulation of JAK2 by ubiquitylation (Ub) has been suggested. The physiological significance of protein ubiquitylation in the regulation of JAKs remains to be determined. JAKs might also be regulated by other proteins, such as the SH2-B family of putative adaptor proteins (not shown). STATs can be negatively regulated by PTPs (such as PTP1B and TCPTP) in the cytoplasm, and by PIAS proteins, as well as PTPs (such as TCPTP and SHP2), in the nucleus. Protein inhibitor of activated STAT (PIAS) proteins interact with STATs in response to cytokine stimulation and they inhibit the transcriptional activity of STATs through distinct mechanisms.

required to understand the precise contribution of protein ubiquitylation to the regulation of JAKs under physiological conditions.

Recently, modification of JAKs by conjugation to interferon-stimulated gene 15 (ISG15) — a ubiquitin-like protein group (BOX 1) — has been documented. ISG15 is one of the most strongly induced gene products by type I IFNs, viral infection and lipopolysaccharide (LPS) stimulation[54,55]. However, the identity of ISGylated proteins and the biological role of ISGylation are poorly understood. Using high-throughput immunoblotting screening analysis, several ISGylated proteins have been identified, among which are JAK1 and STAT1 (REF. 56). The biological role of ISGylation in the regulation of JAK–STAT signalling has been shown by gene-targeting studies. UBP43 (also known as ubiquitin-specific protease 18, USP18) — a member of the ubiquitin-protease family — is an important protease that removes ISG15 from ISGylated proteins[57]. Deficiency of UBP43 results in prolonged STAT1 tyrosine phosphorylation, DNA binding and STAT1-dependent gene activation in response to IFN-β stimulation. As a result, *Ubp43*$^{-/-}$ mice are hypersensitive to challenge with type I IFNs[58]. Increased ISGylation of JAK1 and STAT1 has been detected in *Ubp43*$^{-/-}$ cells[56]. The exact ISGylation site(s) of JAK1 or STAT1 has not been identified, nor is it known how the activity of JAK1 or STAT1 is regulated by ISGylation. Nevertheless, ISGylation seems to act as part of a classic positive-feedback loop in the regulation of JAK–STAT pathways.

Additional mechanisms to regulate JAKs might also exist. For example, the SH2-B family of putative adaptor proteins has been implicated in the differential regulation of JAKs[59]. It will be interesting to examine the significance of these adaptor molecules in the regulation of JAKs.

The regulation of STATs

Regulation of STATs by protein modifications. STATs can be post-translationally modified by phosphorylation, methylation, acetylation, ubiquitylation, ISGylation and sumoylation, the most important of which is tyrosine phosphorylation[60,61]. After cytokine-receptor stimulation, STATs are tyrosine phosphorylated on a single conserved residue. The tyrosine phosphorylation of STATs is required for their dimerization, nuclear translocation and DNA binding[8]. So, tyrosine phosphorylation functions as a switching signal to activate STATs. Recently, it has been shown that tyrosine phosphorylated STAT1 needs to be dephosphorylated to leave the nucleus, indicating a role for tyrosine phosphorylation in the nuclear retention of STAT1 (REFS 62–64).

STAT1, STAT3, STAT4, STAT5A and STAT5B are also modified by serine phosphorylation[3]. Serine phosphorylation of STATs seems to be independent of their tyrosine phosphorylation. STAT1 is phosphorylated at Ser727, which is a potential mitogen-activated protein kinase (MAPK) site[65,66]. This serine is constitutively phosphorylated and the level of phosphorylation can be further increased in certain cells. Most importantly, mutational analysis indicates that the serine phosphorylation of STAT1 is required for the maximum induction of IFN-responsive genes. Several serine kinases have been implicated in the phosphorylation of STATs. These include extracellular signal-regulated protein kinase (ERK), p38, JUN N-terminal kinase (JNK), and protein kinase Cδ (PKCδ)[67,68]. It seems that different kinases might be used under different conditions. Recently, calcium/calmodulin-dependent kinase II (CAMK2) has been identified as a potential kinase involved in STAT1 serine phosphorylation in response to IFN-γ[69].

STAT1 can be methylated on Arg31 by protein arginine methyl-transferase 1 (PRMT1), which has also been found to be associated with the IFN-α/β receptor[70–72]. The arginine methylation of STAT1 occurs constitutively, independent of tyrosine or serine phosphorylation. Methylation of STAT1 increases its DNA-binding activity, possibly due to inhibition of the interaction of PIAS1 with non-methylated STAT1 (REF. 70). Whether other STATs are also regulated by protein methylation remains to be determined.

STATs cooperate with the histone acetyltransferase cAMP response element-binding protein (CREB)-binding protein (CBP)/p300 for gene activation. Acetylation of STAT6 by CBP/p300 has been reported, but the site of such acetylation has not been determined[73,74]. In addition to CBP/p300, STAT2 recruits the acetyltransferase general control non-repressed 5 (GCN5) to regulate transcription. It remains to be determined whether other STATs are modified by acetylation.

STATs can be post-translationally modified by ubiquitin and ubiquitin-related molecules. Polyubiquitylation of STAT1 has been described[75], although it seems that this does not have an important role in regulating STAT1 activity[2]. However, certain viruses evade the immune system by targeting STATs for degradation through the polyubiquitin–proteasome pathway. Members of the *Rubulavirus* genus of the Paramyxovirus family of RNA viruses encode a protein known as V that induces polyubiquitylation and proteasomal degradation of STATs. Interestingly, simian virus 5 targets STAT1 for degradation, whereas type II human parainfluenza virus targets STAT2 for degradation. In addition, mumps virus induces the degradation of STAT1 and STAT3. The V proteins function by promoting the formation of STAT-directed ubiquitin E3 ligase complexes[76–79].

As discussed earlier, modification of STAT1 by ISGylation has been reported[56]. Genetic studies have shown a positive regulatory role for protein ISGylation in the regulation of JAK–STAT signalling[58], but the exact role of STAT1 ISGylation in the regulation of STAT1 activity remains to be determined. Based on the finding that PIAS proteins have SUMO (small ubiquitin-related modifier) E3 ligase activity (discussed later), studies have been carried out to examine whether STATs are sumoylated. SUMO is a ubiquitin-related molecule and protein–SUMO conjugation (sumoylation) has been suggested to have various functions, including regulating the activity of transcription factors (BOX 1). Recently, it has been shown that STAT1 can be sumoylated on Lys703, which can be strongly enhanced by PIAS proteins[80,81]. In addition, treatment with IFN-γ seems to induce STAT1 sumoylation[81]. However, contradictory results have been reported on the potential role of STAT1 sumoylation. Rogers *et al.*[80] showed that the mutation of Lys703 to Arg703 did not affect the activation of STAT1 or the ability of PIAS1 to repress STAT1-mediated gene activation, whereas Ungureanu *et al.*[81] showed that the same mutation resulted in increased STAT1-dependent gene activation in response to IFN-γ[81]. Further studies are required to clarify whether sumoylation has a role in regulating STAT1 function under physiological conditions.

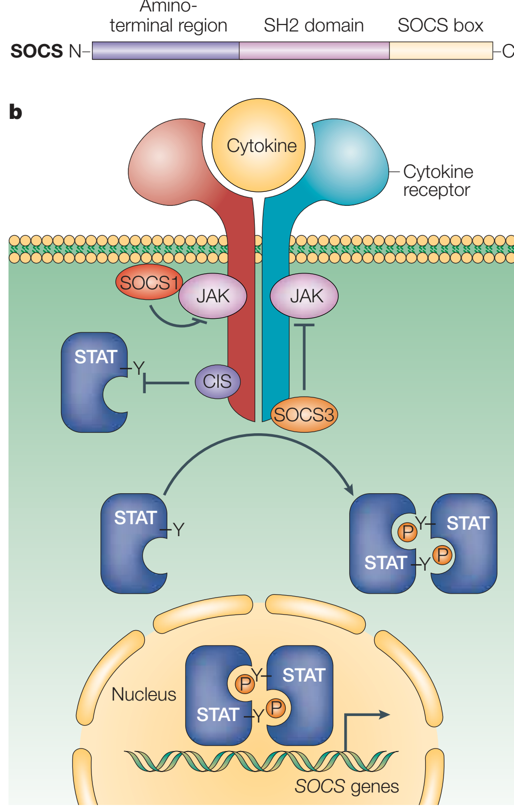
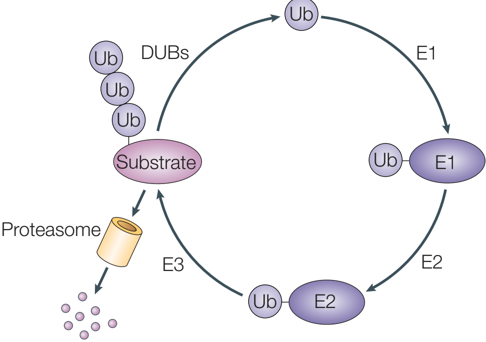


Figure 3 | **The SOCS family of proteins. a** | Domain structure of suppressor of cytokine signalling (SOCS) proteins. The SOCS family of proteins has eight members: cytokine-inducible SRC homology 2 (SH2) domain protein (CIS) and SOCS1–SOCS7. SOCS proteins contain an SH2 domain that is flanked by a variable amino-terminal domain and a carboxy-terminal SOCS box. The SOCS box can bind to elongins B and C, which are known components of a ubiquitin E3 ligase complex. **b** | Inhibition of the Janus kinase (JAK)–signal transducer and activator of transcription (STAT)-signalling pathway by SOCS proteins through distinct mechanisms. SOCS1 binds directly to tyrosine-phosphorylated JAKs through the SH2 domain, resulting in the inhibition of kinase activity. SOCS3 inhibits JAKs through binding to the receptor. By contrast, CIS does not affect the activity of JAKs. Instead, CIS inhibits STATs by competing with STATs for docking sites on the receptor.

Regulation of STATs by the PIAS family. PIAS1 (also known as Gu-binding protein, GBP)[82,83] was identified by yeast two-hybrid assays using STAT1β as the 'bait'. Other members of the PIAS family were subsequently identified through searching the expressed sequence tag (EST) database and complementary DNA screening. The mammalian PIAS family consists of four members: PIAS1, PIAS3, PIASX and PIASY[84]. Different splicing variants of PIAS proteins exist. PIAS3β (otherwise known as potassium-channel-associated protein, KChAP) contains a small insertion of 39 amino acids that is absent from the original isolated PIAS3 clone[85]. PIASXα (androgen receptor interaction protein 3, ARIP3) and PIASXβ (Msx-interacting-zinc finger protein 1, MIZ1) are identical, except for their carboxy-terminal regions[82,86,87]. The most highly conserved domain of the PIAS family is a RING-finger-like zinc-binding domain (RLD) in the central part of PIAS (BOX 2). In addition, a putative domain known as SAP (scaffold attachment factor A/B (SAF-A/B), acinus and PIAS)[88] is localized at the amino-terminus of PIAS. The SAP domain of SAF-A/B has been shown to recognize and bind specifically to scaffold/matrix attachment regions (S/MARs) — the chromatin regions that bind the nuclear matrix[89].

Box 1 | **The ubiquitin–proteasome degradation pathway**



The covalent conjugation of ubiquitin (Ub) — a 76-amino-acid polypeptide[134] — to substrate proteins is known as protein ubiquitylation. Ubiquitin is attached to lysine residues of substrates. Protein ubiquitylation is an ATP-dependent process that requires the sequential actions of three enzymes: an activating enzyme (E1), a conjugating enzyme (E2) and a ligase (E3). E3 ligases have high substrate specificity. Substrates marked with a polymer of ubiquitins (a polyubiquitin chain) are selectively targeted to a multisubunit ATP-dependent protease known as the 26S proteasome, resulting in degradation of the substrates and recycling of ubiquitin. Ubiquitylation is reversible and ubiquitin is removed from substrates by deconjugating enzymes (DUBs). Ubiquitin-dependent proteolysis has important roles in many cellular processes, including cell-cycle regulation, transcription, antigen presentation and signal transduction. Suppressor of cytokine signalling (SOCS) proteins can bind to a ubiquitin E3 ligase to target signalling proteins for degradation.

Several ubiquitin-like molecules have been identified, including small ubiquitin-related modifier (SUMO) and interferon-stimulated gene 15 (ISG15). The conjugation of SUMO (sumoylation) or ISG15 (ISGylation) to substrate proteins occurs through a pathway that is analogous to ubiquitin conjugation, but distinct enzymes are involved[135]. Recent studies indicate that protein ISGylation has a positive role in the regulation of Janus kinase (JAK)–signal transducer and activator of transcription (STAT) signalling[58]. The function of protein sumoylation is poorly understood, but has been suggested to regulate a wide variety of cellular processes, including nuclear-protein targeting, protein–protein interactions, protein stability, formation of subnuclear structures and modulation of transcription factors. Protein inhibitor of activated STAT (PIAS) proteins have SUMO E3 ligase activity[136]. The role of PIAS SUMO ligase activity in the regulation of STAT activity remains to be clarified.

This interaction might be involved in anchoring independent chromatin loops to the nuclear scaffold, and presumably, affecting the expression of adjacent genes. The functional significance of the PIAS SAP domain in regulating STAT activity remains to be established.

In vivo co-immunoprecipitation studies using antibodies specific for PIAS proteins have identified specific PIAS–STAT interactions in cultured mammalian cells. After cytokine stimulation, PIAS1, PIAS3 and PIASX interact with STAT1, STAT3 and STAT4, respectively[82,90,91]. In addition, PIASY has also been shown to be associated with STAT1 (REF. 92) (TABLE 2). The PIAS–STAT interaction is cytokine dependent and PIAS proteins do not interact with STATs in unstimulated cells. The cytokine dependency of the interaction might be explained by the finding that PIAS1 can bind to the dimeric, but not the monomeric, form of STAT1 (REF. 93). When overexpressed, PIAS3 can interact with STAT5 to regulate prolactin-induced STAT5-mediated gene expression[94].

Each member of the PIAS family has been shown to inhibit STAT-mediated gene activation. Distinct mechanisms for PIAS-mediated inhibition of STATs have been indicated (FIG. 4). PIAS1 and PIAS3 can inhibit the DNA-binding activity of STAT1 and STAT3, respectively[82,90]. By contrast, PIASX and PIASY can inhibit STAT4- and STAT1-dependent transcription without affecting the DNA-binding activity of STAT4 and STAT1 (REFS 91,92). The interaction of PIAS proteins with histone deactylases (HDACs) has been described. PIASX has been shown to interact with HDAX3 (REF. 95). In addition, the ability of PIASX to inhibit IL-12-induced STAT4-dependent gene activation is abolished by TSA — a HDAC inhibitor[91]. PIASY has also been found to interact with HDAC1 (REF. 96). So, it is probable that PIASX and PIASY function as transcriptional co-repressors of STATs, possibly by recruiting HDACs and other co-repressor molecules. Interestingly, PIAS proteins have been shown to have SUMO E3 ligase activity[97,98]. It has been suggested that PIAS proteins might regulate transcription by promoting SUMO conjugation of transcription factors. As discussed earlier, recent studies indicate that STAT1 can be sumoylated by PIAS proteins, but the role of sumoylation in the regulation of STAT1 activity remains to be clarified[80,81]. PIAS proteins have also been shown to regulate other transcription factors through similar molecular mechanisms. These transcription factors include the tumour suppressor p53, the androgen receptor and the transforming growth factor-β (TGF-β) signalling protein SMAD. In addition, an interesting mechanism has been proposed for the inhibition of lymphoid enhancer factor 1 (LEF1) — the Wnt-responsive transcription factor. It has been proposed that PIASY might repress the transcriptional activity of LEF1 by sequestering LEF1 in distinct subnuclear localizations through the PIASY SAP domain[99]. However, this mechanism of action has not been shown for the inhibition of STATs by PIAS proteins. Interestingly, members of the PIAS family have also been shown to enhance the transcriptional activity of some transcription factors, such as the androgen receptor, under certain conditions[100]. How PIAS proteins can activate transcription is not understood.

Genetic studies indicate that the *Drosophila* PIAS (dPIAS; otherwise known as Zimp) negatively regulates the JAK–STAT pathway in *Drosophila*[101]. Biochemical studies indicate that there is specificity as well as redundancy in PIAS-mediated inhibition of STATs (TABLE 2). Genetic studies are required to understand the physiological roles of mammalian PIAS proteins in the regulation of STAT signalling.

Regulation of STATs by PTPs. STATs can also be inactivated by PTPs in both the cytoplasm and the nucleus. SHP2 is involved in the dephosphorylation of STAT5 in the cytoplasm[102,103]. SHP2 interacts with and can directly dephosphorylate STAT5, and dephosphorylation of STAT5 in the cytoplasm is inhibited in *Shp2*$^{-/-}$ cells[102]. Interestingly, it has been indicated that SHP2 is involved in the dephosphorylation of STAT1 at both tyrosine and serine residues. PTP1B has also been implicated in the dephosphorylation of STAT5 under overexpression conditions[104]. However, whether STAT5 is a physiological substrate of PTP1B remains to be established.

Earlier studies indicated the existence of a PTP activity in the nucleus to inactivate STAT1 (REFS 105,106). Through biochemical purification, TC45 — the nuclear isoform of TCPTP — has been identified as a STAT1

Table 2 | **Specificity in the negative regulation of JAK–STAT signalling**

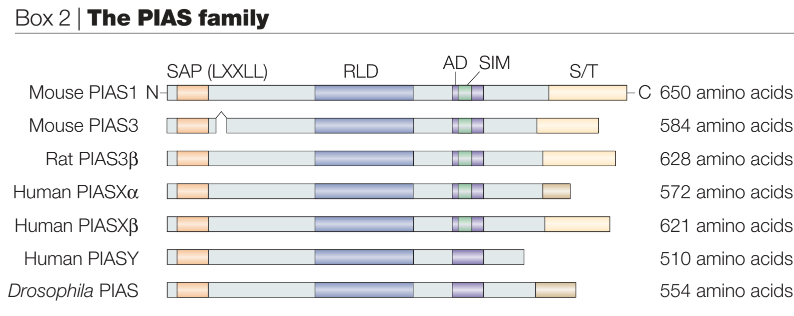
Inhibitor	Target	References
JAK PTPs	***JAKs***	
SHP1	JAK2, JAK1	43,44
SHP2	JAK1	45
CD45	JAK1, JAK2, JAK3, TYK2	46,47
PTP1B	JAK2, TYK2	49
TCPTP	JAK1, JAK3	52
Cytoplasmic STAT PTPs	***STATs***	
SHP2	STAT5	102,103
PTP1B	STAT5	104
TCPTP	STAT1, STAT3	107
Nuclear STAT PTPs	***STATs***	
SHP2	STAT1	108
TCPTP	STAT1, STAT3	107
PIAS proteins	***STATs***	
PIAS1	STAT1	82
PIAS3	STAT3	90
PIASX	STAT4	91
PIASY	STAT1	92

JAK, Janus-family kinase; PIAS, protein inhibitor of activated STAT; PTP, protein tyrosine phosphatase; SHP, SH2-domain-containing PTP; STAT, signal transducer and activator of transcription; TCPTP, T-cell PTP; TYK, tyrosine kinase 2.

PTP[107]. TC45 can directly dephosphorylate STAT1, and in *Tcptp*$^{-/-}$ cells, the nuclear dephosphorylation of STAT1 is defective. In addition to TC45, SHP2 is also involved in the nuclear dephosphorylation of STAT1 (REF. 108). How other STATs become dephosphorylated remains unknown, but recent studies have shown that there is specificity in the dephosphorylation of STATs by PTPs. For example, using *Tcptp*$^{-/-}$ cells, it has been shown that TCPTP is involved in the dephosphorylation of both STAT1 and STAT3, but not STAT5 or STAT6 (REF. 107). The identification of additional PTPs and the understanding of how specificity is achieved in STAT dephosphorylation will be of great interest.

Cross-regulation among the STAT family. The activity of a STAT protein can be regulated by other members of the STAT family. STATs function as dimers and different STAT dimers (homo or hetero) have distinct DNA-binding activity[2]. Recent studies indicate that cross-regulation among the STAT-family members has an important role in the maintenance of cytokine-signalling specificity. For example, STAT1 and STAT3 are both activated by IL-6 stimulation and form three distinct dimers: STAT1–STAT1, STAT1–STAT3 and STAT3–STAT3. The removal of STAT3 in mouse embryonic fibroblasts results in prolonged STAT1 activation by IL-6. As a result, IL-6 triggers an IFN-γ-like response in *Stat3*$^{-/-}$ cells[41]. So, the signalling specificity of IL-6 is modulated by the activation of STAT3 and the cross-talk between STAT1 and STAT3. Another example of STAT cross-regulation is the finding that certain naturally occurring STAT splice variants act as dominant-negative STATs[109,110].

Box 2 | **The PIAS family**



Four members of the mammalian PIAS (protein inhibitor of activated signal transducer and activator of transcription, STAT) family have been identified: PIAS1 (also known as Gu-binding protein, GBP), PIAS3 (PIAS3β is also known as potassium-channel-associated protein, KChAP), PIASX — PIASXα (also known as androgen receptor interaction protein 3, ARIP3) and PIASXβ (Msx-interacting-zinc finger protein 1, MIZ1) as two variants — and PIASY[84]. PIAS homologues are found in *Drosophila* (dPIAS/ZimP), *Caenorhabditis elegans*, yeast (SIZ1 and SIZ2) and plants[97,101]. The mammalian PIAS proteins have marked sequence homology (>40%) and have several conserved domains. The most striking domain is the central RING-finger-like zinc-binding domain (RLD). This C3HC4 RLD shows marked similarity to genuine RING domains, but it lacks two of the conserved cysteine residues that are involved in zinc chelation. PIAS proteins also contain a putative domain known as SAP (scaffold attachment factor A and B (SAF-A/B), acinus and PIAS), which is evolutionarily conserved in proteins ranging from yeast to humans and shared by other chromatin-binding proteins, such as SAF-A and SAF-B[88]. In the SAP domain, a Lys-Xaa-Xaa-Lys-Lys signature motif is present in all PIAS proteins, which has been shown to mediate interactions between nuclear receptors and their co-regulators. A highly acidic region (AD) is also conserved in the PIAS family. In the AD, a putative small ubiquitin-related modifier 1 (SUMO1) interaction motif (SIM) is present in all PIAS proteins except PIASY and dPIAS. The carboxy-terminal regions of PIAS proteins are the least conserved. A serine/threonine rich (S/T) region is found in all PIAS proteins except PIASY. *Drosophila* contain a single PIAS gene, *dPIAS*. At least two splice variants exist.

Regulation through signalling cross-talk

Under physiological conditions, immune cells are generally regulated by the action of many cytokines and it has become clear that cross-talk between different cytokine-signalling pathways is involved in the regulation of the JAK–STAT pathway.

Cross-talk among the JAK–STAT pathways. Prior exposure of cells to one cytokine followed by stimulation with the same or a different cytokine can cause antagonistic or synergistic effects, depending on the cellular context and/or the cytokines involved. Certain genes downstream of STATs have an important role in signalling cross-talk. A classic example is the cross-talk between type I and type II IFNs (FIG. 5a). Pretreatment with IFN-γ markedly sensitizes cells to IFN-α, owing largely to the increased expression of STAT1 and IRF9 induced by IFN-γ[1]. STAT1 and IRF9 are two key components of the transcription factor complex ISGF3, which activates IFN-α-responsive genes. Similarly, pretreatment with low concentrations of IFN-γ, which increases the level of STAT1 protein, can enhance the subsequent IFN-γ response during macrophage activation[111]. In these two cases, STAT1 acts in a positive-feedback loop to increase subsequent stimulation by the same or a different cytokine. Similarly, ISG15 — a downstream target of the IFN-α-signalling pathway — can modify components of the JAK–STAT pathway through protein ISGylation[58], resulting in an enhanced IFN-α response.

A role for SOCS proteins in the cross-talk between opposing cytokines has been shown in several cases. IFNs inhibit the IL-4 response in human monocytes. The inhibitory activity of IFN on IL-4 signalling is

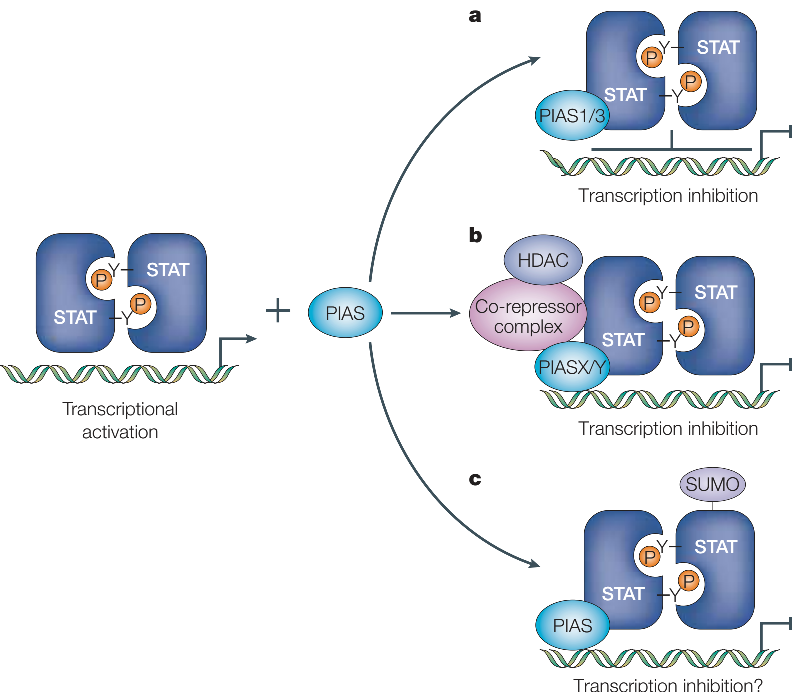


Figure 4 | **Proposed mechanisms for inhibiting the JAK–STAT pathway by PIAS proteins.** Different PIAS (protein inhibitor of activated STAT) proteins can inhibit the Janus kinase (JAK)–signal transducer and activator of transcription (STAT) pathway through distinct mechanisms. **a** | PIAS1 and PIAS3 block the DNA-binding activity of STAT dimers. **b** | PIASX and PIASY might act as transcriptional co-repressors of STAT by recruiting other co-repressor proteins such as histone deacetylase (HDAC). **c** | PIAS proteins can promote the conjugation of small ubiquitin-related modifier (SUMO) to STAT1. The significance of STAT1 sumoylation in regulating STAT1 activity is controversial and needs to be clarified.

largely mediated through the induction of SOCS1 expression by IFN, which inhibits IL-4-induced STAT6 activation[112]. IL-10 has anti-inflammatory activity in immune cells, partially through the inhibition of the activity of pro-inflammatory cytokines such as IFNs. IL-10 can block IFN signalling by inducing the expression of SOCS3 (REF. 113). Similarly, the induction of SOCS3 expression by IL-3 has been implicated in the inhibition of IL-11 signalling as well as IL-11-mediated B-cell development[114].

Cross-talk between JAK–STAT and other pathways. The NUCLEAR FACTOR-κB (NF-κB) family is a family of latent cytoplasmic transcription factors activated by various signals, including tumour-necrosis factor (TNF), IL-1 and LPS. The NF-κB-signalling pathway has a crucial role in immune regulation[115], and the activation of several genes that have antiviral or immunoregulatory functions requires the cooperation of STATs and NF-κB. Early studies indicated that there might be cross-talk between these two main cytokine-signalling pathways. For example, although STAT1 is not directly activated by TNF, STAT1 seems to be required for TNF-induced apoptosis[116]. Recent studies indicate that SOCS1 might mediate the cross-talk between the JAK–STAT and NF-κB-signalling pathways. SOCS proteins can be induced by cytokines that use the JAK–STAT or the NF-κB pathway[20] (FIG. 5b). In macrophages, SOCS1 is rapidly induced by LPS, which in turn inhibits LPS-induced activation of NF-κB and STAT1 (REFS 117,118). Consistent with these observations, *Socs1*$^{-/-}$ mice are hypersensitive to LPS-induced endotoxic shock. Interestingly, SOCS1 is found to interact with IL-1R-associated kinase (IRAK) — a signalling component in the LPS-induced NF-κB pathway. The SOCS1–IRAK interaction might account for the inhibitory effect of SOCS1 on LPS-induced activation of NF-κB[118]. In addition, the involvement of SOCS1 in TNF signalling has been indicated by the finding that *Socs1*$^{-/-}$ embryonic fibroblasts are more sensitive to TNF-induced apoptosis[119]. So, the STAT and NF-κB pathways might interact through SOCS proteins.

NUCLEAR FACTOR-κB (NF-κB). A family of transcription factors important for pro-inflammatory and anti-apoptotic responses. They are activated by the phosphorylation and subsequent ubiquitin-dependent proteolytic degradation of their respective inhibitors, known as inhibitor of κB (IκB). Phosphorylation of IκB occurs through tissue-specific kinases, IκB kinase 1 (IKK1) and IKK2.

Cross-talk between the JAK–STAT pathway and the TGF-β-activated SMAD pathway has also been documented. The IFN-γ-activated STAT pathway negatively regulates the TGF-β-triggered SMAD-signalling pathway through the induction of SMAD7, an inhibitory SMAD[120]. Leukaemia inhibitory factor (LIF) and bone morphogenetic protein 2 (BMP2), which activate STAT- and SMAD-signalling pathways, respectively, have a synergistic effect on the induction of astrocytes from neural progenitors. The cooperative signalling of LIF and BMP2 involves the formation of a STAT3–SMAD1 complex bridged by the transcriptional co-activator p300 (REF. 121).

Recently, the regulation of the JAK–STAT pathway by integrin signalling has been reported[122]. It was observed that the detachment of cells from matrix markedly attenuated IFN-γ-induced activation of STAT1 in human embryonic kidney 293 cells and mouse embryonic fibroblasts, indicating a role for cell adhesion in the regulation of STAT signalling. Integrin engagement modulates the activity of protein kinase Cε (PKCε). There is a markedly attenuated response to IFN-γ in *PKCε*$^{-/-}$ macrophages. In the absence of PKCε, although there is no change in JAK1 or JAK2 activation, the IFN-γ-induced STAT1 tyrosine phosphorylation is inhibited. Although the detailed mechanism is not understood, these results indicate that PKCε might mediate the cross-talk between integrin and IFN-γ signalling through regulating the activation of STAT1 by JAKs (FIG. 5c).

Dysregulation of JAK–STAT signalling

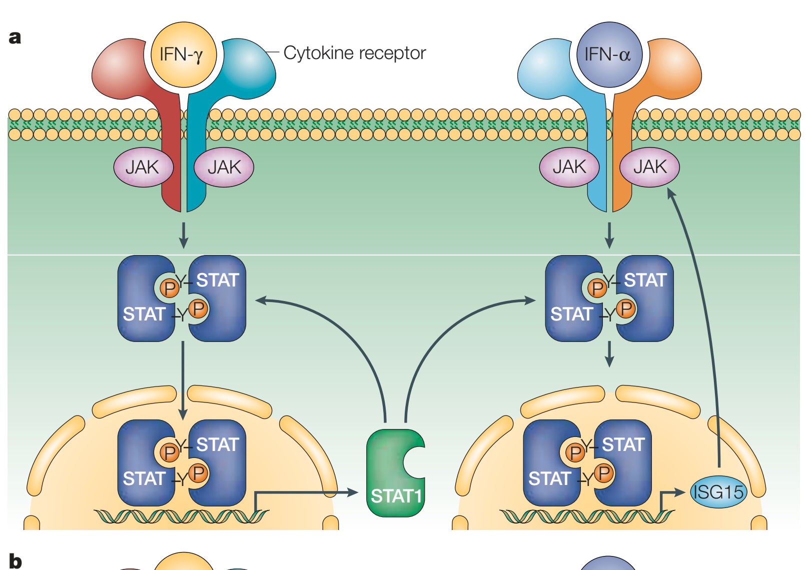
Dysregulation of JAK–STAT signalling is associated with several immune diseases. JAK3 is highly expressed by haematopoietic cells and is required for signalling by cytokines that use the cytokine receptor common γ chain (γ_c), such as IL-2, IL-4, IL-7, IL-9, IL-15 and IL-21 (REF. 123). Various mutations that cause JAK3 deficiency have been detected in patients with severe combined immunodeficiency (T cell$^-$B cell$^+$)[124].

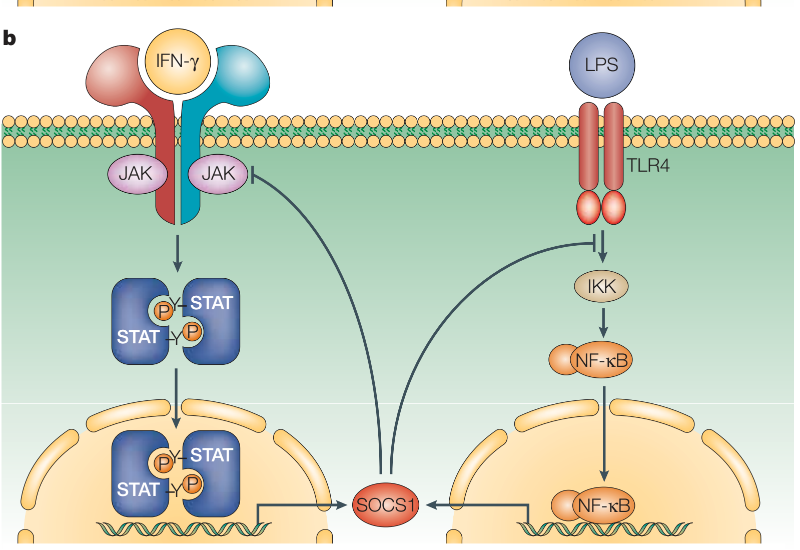
Markedly increased airway levels of STAT6, which is crucial for IL-4 signalling and T helper 2 (T_H2)-cell responses, have been detected in asthmatic patients[125]. But the functional significance of the observed increase in STAT6 expression in asthmatic patients is not clear. Recently, a role for SOCS3 in regulating the onset and maintenance of T_H2-mediated allergic immune disease has been described[126]. SOCS3 is mainly expressed by

T_H2 cells. There is a strong correlation between the expression of SOC3 and the pathology of T_H2-mediated allergic immune diseases such as atopic dermatitis and asthma. Furthermore, SOCS3 transgenic mice showed increased airway hypersensitivity and enhanced T_H2-cell responses, partly due to the preferential inhibition of IL-12-induced T_H1-cell differentiation by SOCS3. These results indicate that targeting dysregulated SOCS3 under pathological conditions might be a potential therapeutic strategy for the development of anti-allergy drugs.

Viruses can evade the host immune system by inactivating different components of the IFN-activated JAK–STAT pathway. As described earlier, members of the Paramyxovirus family of RNA viruses target STATs for degradation. Epstein–Barr virus (EBV) inhibits the expression of IFN-γ receptor through the action of the EBV immediate-early protein, BZLF1 (REF. 127). Human cytomegalovirus inhibits IFN-γ-induced expression of MHC class II molecules by selectively targeting JAK1 for degradation[128]. By contrast, infection with varicella-zoster virus inhibits the expression of STAT1 and JAK2, but not JAK1 (REF. 129). Individuals with defects in the IFN–JAK–STAT pathway show increased susceptibility to viruses and intracellular bacteria. Patients with mutations in the IFN-γ receptor chains are susceptible to infection with mycobacteria[130]. Recently, patients with STAT1 deficiency have been reported[131]. These individuals suffered from mycobacterial infection and died of lethal viral disease.

The aetiopathology of Crohn's disease — a chronic inflammatory bowel disease — is poorly understood. Mice with tissue-specific disruption of *Stat3* during haematopoiesis show Crohn's disease-like pathogenesis[132]. In addition, constitutively tyrosine phosphorylated STAT3 is found in intestinal T cells from patients with Crohn's disease[133]. These results indicate that the dysregulation of STAT3 signalling might be involved in the pathogenesis of Crohn's disease. However, the exact role of STAT3 in the pathogenesis of Crohn's disease is not understood.





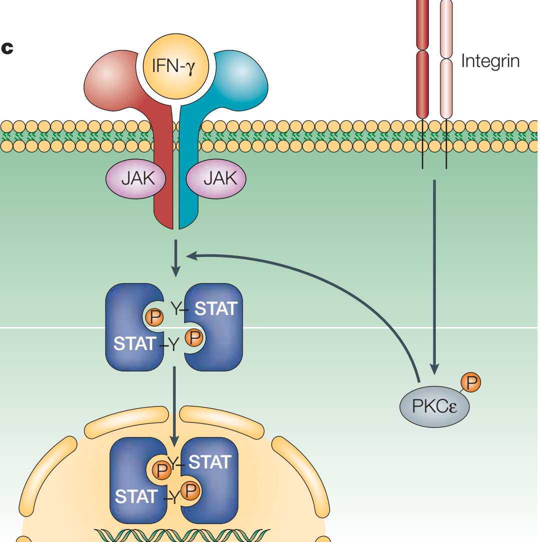


Figure 5 | **The cross-talk between cytokine-signalling pathways. a** | Cross-talk between two Janus kinase (JAK)–signal transducer and activator of transcription (STAT) pathways. The interferon-γ (IFN-γ)-activated JAK–STAT pathway can induce the transcription of STAT1, which then positively regulates the JAK–STAT pathways triggered by subsequent stimulation with IFN-γ or IFN-α. Similarly, IFN-α treatment can induce the production of ISG15, which can sensitize the subsequent IFN-α-activated JAK–STAT pathway. **b** | Cross-talk between IFN and lipopolysaccharide (LPS) pathways. Both IFN and LPS can induce the expression of suppressor of cytokine signalling 1 (SOCS1) through the JAK–STAT and nuclear factor-κB (NF-κB) pathways, respectively. SOCS1 is a negative regulator of both IFN and LPS pathways. **c** | Cross-talk between IFN-γ and integrin pathways. Activation of the integrin pathway leads to the phosphorylation of protein kinase Cε (PKCε), which can facilitate the phosphorylation of STAT1. The exact mechanism involved remains to be elucidated. IKK, inhibitor of NF-κB kinase; TLR4, Toll-like receptor 4.

Conclusion

JAKs and STATs are the two main components of JAK–STAT signalling pathways. The use of the same type of factor (STAT) to bind directly to the cell-surface receptor as well as the DNA-response element in the nucleus allows for optimal preservation of signalling specificity. Indeed, STATs have highly specific functions in the immune system. Studies in the past few years have shown that JAK–STAT signalling is regulated at various steps, allowing control of signalling strength, duration and specificity. The study of the regulation of JAK–STAT signalling is clearly an important research area, as unbalanced JAK–STAT signalling contributes to immune diseases. Although progress has been made in understanding the regulation of the JAK–STAT pathway, many important questions remain to be answered. The dephosphorylation of STATs in the nucleus is still poorly understood. Specifically, the PTPs that are responsible for the nuclear dephosphorylation of STAT2, STAT4 and STAT6 have not been identified. Further studies are required to understand the regulation and substrate specificity of nuclear STAT PTPs. In addition, the molecular basis for the recently discovered *in vivo* specificity of SOCS1 and SOCS3 needs to be investigated. The physiological role of mammalian PIAS proteins in the regulation of cytokine signalling has not been defined. An interesting question that remains to be answered is how PIAS proteins are regulated. Furthermore, more work is required to understand fully the physiological roles of protein sumoylation and ISGylation in the regulation of JAK–STAT signalling. Another important area of research is to continue investigating the possible involvement of various JAK–STAT regulators in immune diseases and the molecular mechanisms that are involved. Such studies will provide useful information for the design of therapeutic drugs. As many JAK–STAT regulators are essential for normal cellular functions, a potential strategy is to develop drugs that can specifically target these regulators only under pathological conditions. Clearly, studies on the regulation of JAK–STAT signalling will remain both challenging and exciting in years to come.

1. Darnell, J. E., Jr, Kerr, I. M. & Stark, G. R. Jak–STAT pathways and transcriptional activation in response to IFNs and other extracellular signaling proteins. *Science* **264**, 1415–1421 (1994).
2. Darnell, J. E., Jr. STATs and gene regulation. *Science* **277**, 1630–1635 (1997).
3. Levy, D. E. & Darnell, J. E. Signalling: Stats: transcriptional control and biological impact. *Nature Rev. Mol. Cell Biol.* **3**, 651–662 (2002).
4. Stark, G. R., Kerr, I. M., Williams, B. R., Silverman, R. H. & Schreiber, R. D. How cells respond to interferons. *Annu. Rev. Biochem.* **67**, 227–264 (1998).
5. Fu, X. Y. & Zhang, J. J. Transcription factor p91 interacts with the epidermal growth factor receptor and mediates activation of the c-fos gene promoter. *Cell* **74**, 1135–1145 (1993).
6. Shuai, K. *et al.* Interferon activation of the transcription factor Stat91 involves dimerization through SH2-phosphotyrosyl peptide interactions. *Cell* **76**, 821–828 (1994).
7. Horvath, C. M., Wen, Z. & Darnell, J. E., Jr. A STAT protein domain that determines DNA sequence recognition suggests a novel DNA-binding domain. *Genes Dev.* **9**, 984–994 (1995).
8. Shuai, K., Stark, G. R., Kerr, I. M. & Darnell, J. E., Jr. A single phosphotyrosine residue of Stat91 required for gene activation by interferon-γ. *Science* **261**, 1744–1746 (1993).
9. Muller, M. *et al.* Complementation of a mutant cell line: central role of the 91 kDa polypeptide of ISGF3 in the interferon-α and -γ signal transduction pathways. *EMBO J.* **12**, 4221–4228 (1993).
10. Xu, X., Sun, Y. L. & Hoey, T. Cooperative DNA binding and sequence-selective recognition conferred by the STAT amino-terminal domain. *Science* **273**, 794–797 (1996).
11. Shuai, K., Liao, J. & Song, M. M. Enhancement of antiproliferative activity of γ-interferon by the specific inhibition of tyrosine dephosphorylation of Stat1. *Mol. Cell. Biol.* **16**, 4932–4941 (1996).
12. Igaz, P., Toth, S. & Falus, A. Biological and clinical significance of the JAK–STAT pathway; lessons from knockout mice. *Inflamm. Res.* **50**, 435–441 (2001).
13. O'Shea, J. J. Jaks, STATs, cytokine signal transduction, and immunoregulation: are we there yet? *Immunity* **7**, 1–11 (1997).
14. Ihle, J. N. *et al.* The roles of Jaks and Stats in cytokine signaling. *Cancer. J. Sci. Am.* **4 Suppl 1**, S84–S91 (1998).
15. Hilton, D. J. *et al.* Twenty proteins containing a C-terminal SOCS box form five structural classes. *Proc. Natl Acad. Sci. USA* **95**, 114–119 (1998).
16. Hilton, D. J. Negative regulators of cytokine signal transduction. *Cell. Mol. Life. Sci.* **55**, 1568–1577 (1999).
17. Kile, B. T. *et al.* The SOCS box: a tale of destruction and degradation. *Trends. Biochem. Sci.* **27**, 235–241 (2002).
18. Alexander, W. S. Suppressors of cytokine signalling (SOCS) in the immune system. *Nature Rev. Immunol.* **2**, 410–416 (2002).
19. Greenhalgh, C. J. & Hilton, D. J. Negative regulation of cytokine signaling. *J. Leukoc. Biol.* **70**, 348–356 (2001).
20. Starr, R. *et al.* A family of cytokine-inducible inhibitors of signalling. *Nature* **387**, 917–921 (1997).
21. Endo, T. A. *et al.* A new protein containing an SH2 domain that inhibits JAK kinases. *Nature* **387**, 921–924 (1997).
22. Naka, T. *et al.* Structure and function of a new STAT-induced STAT inhibitor. *Nature* **387**, 924–929 (1997).
References 20–22 report the identification of the suppressors of cytokine signalling (SOCS) family of proteins.
23. Nicholson, S. E. *et al.* Mutational analyses of the SOCS proteins suggest a dual domain requirement but distinct mechanisms for inhibition of LIF and IL-6 signal transduction. *EMBO J.* **18**, 375–385 (1999).
24. Sasaki, A. *et al.* CIS3/SOCS-3 suppresses erythropoietin (EPO) signaling by binding the EPO receptor and JAK2. *J. Biol. Chem.* **275**, 29338–29347 (2000).
25. Yoshimura, A. The CIS family: negative regulators of JAK–STAT signaling. *Cytokine Growth Factor Rev.* **9**, 197–204 (1998).
26. Kamura, T. *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 Dev.* **12**, 3872–3881 (1998).
27. Zhang, J. G. *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. *Proc. Natl Acad. Sci. USA* **96**, 2071–2076 (1999).
28. Cohney, S. J. *et al.* SOCS-3 is tyrosine phosphorylated in response to interleukin-2 and suppresses STAT5 phosphorylation and lymphocyte proliferation. *Mol. Cell. Biol.* **19**, 4980–4988 (1999).
29. Cacalano, N. A., Sanden, D. & Johnston, J. A. Tyrosine-phosphorylated SOCS-3 inhibits STAT activation but binds to p120 RasGAP and activates Ras. *Nature Cell Biol.* **3**, 460–465 (2001).
30. Haan, S. *et al.* Tyrosine phosphorylation disrupts elongin interaction and accelerates SOCS3 degradation. *J. Biol. Chem.* **278**, 31972–31979 (2003).
31. Starr, R. *et al.* Liver degeneration and lymphoid deficiencies in mice lacking suppressor of cytokine signaling-1. *Proc. Natl Acad. Sci. USA* **95**, 14395–14399 (1998).
32. Naka, T. *et al.* Accelerated apoptosis of lymphocytes by augmented induction of Bax in SSI-1 (STAT-induced STAT inhibitor-1) deficient mice. *Proc. Natl Acad. Sci. USA* **95**, 15577–15582 (1998).
33. Alexander, W. S. *et al.* SOCS1 is a critical inhibitor of interferon-γ signaling and prevents the potentially fatal neonatal actions of this cytokine. *Cell* **98**, 597–608 (1999).
34. Marine, J. C. *et al.* SOCS1 deficiency causes a lymphocyte-dependent perinatal lethality. *Cell* **98**, 609–616 (1999).
References 33 and 34 show an essential role of SOCS1 in the negative regulation of interferon-γ (IFN-γ) signalling.
35. Marine, J. C. *et al.* SOCS3 is essential in the regulation of fetal liver erythropoiesis. *Cell* **98**, 617–627 (1999).
36. Roberts, A. W. *et al.* Placental defects and embryonic lethality in mice lacking suppressor of cytokine signaling 3. *Proc. Natl Acad. Sci. USA* **98**, 9324–9329 (2001).
37. Takahashi, Y. *et al.* SOCS3: an essential regulator of LIF receptor signaling in trophoblast giant cell differentiation. *EMBO J.* **22**, 372–384 (2003).
38. Croker, B. A. *et al.* SOCS3 negatively regulates IL-6 signaling *in vivo*. *Nature Immunol.* **4**, 540–545 (2003).
39. Lang, R. *et al.* SOCS3 regulates the plasticity of gp130 signaling. *Nature Immunol.* **4**, 546–550 (2003).
40. Yasukawa, H. *et al.* IL-6 induces an anti-inflammatory response in the absence of SOCS3 in macrophages. *Nature Immunol.* **4**, 551–556 (2003).
References 38–40 show the *in vivo* specificity of SOCS3 in the negative regulation of interleukin-6 (IL-6) signalling.
41. Costa-Pereira, A. P. *et al.* Mutational switch of an IL-6 response to an interferon-γ-like response. *Proc. Natl Acad. Sci. USA* **99**, 8043–8047 (2002).
42. Neel, B. G. Structure and function of SH2-domain containing tyrosine phosphatases. *Semin. Cell Biol.* **4**, 419–432 (1993).
43. Klingmuller, U., Lorenz, U., Cantley, L. C., Neel, B. G. & Lodish, H. F. Specific recruitment of SH-PTP1 to the erythropoietin receptor causes inactivation of JAK2 and termination of proliferative signals. *Cell* **80**, 729–738 (1995).
44. David, M., Chen, H. E., Goelz, S., Larner, A. C. & Neel, B. G. Differential regulation of the α/β interferon-stimulated Jak/Stat pathway by the SH2 domain-containing tyrosine phosphatase SHPTP1. *Mol. Cell. Biol.* **15**, 7050–7058 (1995).
45. You, M., Yu, D. H. & Feng, G. S. Shp-2 tyrosine phosphatase functions as a negative regulator of the interferon-stimulated Jak/STAT pathway. *Mol. Cell. Biol.* **19**, 2416–2424 (1999).
46. Penninger, J. M., Irie-Sasaki, J., Sasaki, T. & Oliveira-dos-Santos, A. J. CD45: new jobs for an old acquaintance. *Naure. Immunol.* **2**, 389–396 (2001).
47. Irie-Sasaki, J. *et al.* CD45 is a JAK phosphatase and negatively regulates cytokine receptor signalling. *Nature* **409**, 349–354 (2001).
48. Neel, B. G. & Tonks, N. K. Protein tyrosine phosphatases in signal transduction. *Curr. Opin. Cell Biol.* **9**, 193–204 (1997).
49. Myers, M. P. *et al.* TYK2 and JAK2 are substrates of protein-tyrosine phosphatase 1B. *J. Biol. Chem.* **276**, 47771–47774 (2001).
50. Cheng, A. *et al.* Attenuation of leptin action and regulation of obesity by protein tyrosine phosphatase 1B. *Dev. Cell* **2**, 497–503 (2002).
51. Zabolotny, J. M. *et al.* PTP1B regulates leptin signal transduction *in vivo*. *Dev. Cell* **2**, 489–495 (2002).
52. Simoncic, P. D., Lee-Loy, A., Barber, D. L., Tremblay, M. L. & McGlade, C. J. The T cell protein tyrosine phosphatase is a negative regulator of janus family kinases 1 and 3. *Curr. Biol.* **12**, 446–453 (2002).

53. Ungureanu, D., Saharinen, P., Junttila, I., Hilton, D. J. & Silvennoinen, O. Regulation of Jak2 through the ubiquitin–proteasome pathway involves phosphorylation of Jak2 on Y1007 and interaction with SOCS-1. *Mol. Cell. Biol.* **22**, 3316–3326 (2002).
54. Blomstrom, D. C., Fahey, D., Kutny, R., Korant, B. D. & Knight, E., Jr. Molecular characterization of the interferon-induced 15-kDa protein. Molecular cloning and nucleotide and amino acid sequence. *J. Biol. Chem.* **261**, 8811–8816 (1986).
55. Daly, C. & Reich, N. C. Characterization of specific DNA-binding factors activated by double-stranded RNA as positive regulators of interferon α/β-stimulated genes. *J. Biol. Chem*. **270**, 23739–23746 (1995).
56. Malakhov, M. P. *et al.* High-throughput Immunoblotting. Ubiquitin-like protein is g15 modifies key regulators of signal transduction. *J. Biol. Chem*. **278**, 16608–16613 (2003).
57. Malakhov, M. P., Malakhova, O. A., Kim, K. I., Ritchie, K. J. & Zhang, D. E. UBP43 (USP18) specifically removes ISG15 from conjugated proteins. *J. Biol. Chem.* **277**, 9976–9981 (2002).
58. Malakhova, O. A. *et al.* Protein ISGylation modulates the JAK-STAT signaling pathway. *Genes Dev.* **17**, 455–460 (2003). **Together with reference 56, this study shows an important role of protein ISGylation in the positive regulation of the Janus kinase (JAK)–signal transducer and activator of transcription (STAT)-signalling pathway.**
59. O'Brien, K. B., O'Shea, J. J. & Carter-Su, C. SH2-B family members differentially regulate JAK family tyrosine kinases. *J. Biol. Chem.* **277**, 8673–8681 (2002).
60. Schindler, C., Shuai, K., Prezioso, V. R. & Darnell, J. E., Jr. Interferon-dependent tyrosine phosphorylation of a latent cytoplasmic transcription factor. *Science* **257**, 809–813 (1992).
61. Shuai, K., Schindler, C., Prezioso, V. R. & Darnell, J. E., Jr. Activation of transcription by IFN-γ: tyrosine phosphorylation of a 91-kD DNA binding protein. *Science* **258**, 1808–1812 (1992).
62. Meyer, T., Marg, A., Lemke, P., Wiesner, B. & Vinkemeier, U. DNA binding controls inactivation and nuclear accumulation of the transcription factor Stat1. *Genes Dev.* **17**, 1992–2005 (2003).
63. McBride, K. M., McDonald, C. & Reich, N. C. Nuclear export signal located within the DNA-binding domain of the STAT1transcription factor. *EMBO J.* **19**, 6196–6206 (2000).
64. McBride, K. M., Banninger, G., McDonald, C. & Reich, N. C. Regulated nuclear import of the STAT1 transcription factor by direct binding of importin-α. *EMBO J.* **21**, 1754–1763 (2002).
65. Wen, Z. & Darnell, J. E., Jr. Mapping of Stat3 serine phosphorylation to a single residue (727) and evidence that serine phosphorylation has no influence on DNA binding of Stat1 and Stat3. *Nucleic Acids Res.* **25**, 2062–2067 (1997).
66. Wen, Z., Zhong, Z. & Darnell, J. E., Jr. Maximal activation of transcription by Stat1 and Stat3 requires both tyrosine and serine phosphorylation. *Cell* **82**, 241–250 (1995).
67. Decker, T. & Kovarik, P. Serine phosphorylation of STATs. *Oncogene* **19**, 2628–2637 (2000).
68. Platanias, L. C. The p38 mitogen-activated protein kinase pathway and its role in interferon signaling. *Pharmacol. Ther.* **98**, 129–142 (2003).
69. Nair, J. S. *et al.* Requirement of Ca^{2+} and CaMKII for Stat1 Ser-727 phosphorylation in response to IFN-γ. *Proc. Natl Acad. Sci. USA* **99**, 5971–5976 (2002).
70. Mowen, K. A. *et al.* Arginine methylation of STAT1 modulates IFNα/β induced transcription. *Cell* **104**, 731–741 (2001). **This study indicates that the activity of STAT1 is regulated by protein arginine methylation.**
71. Altschuler, L., Wook, J. O., Gurari, D., Chebath, J. & Revel, M. Involvement of receptor-bound protein methyltransferase PRMT1 in antiviral and antiproliferative effects of type I interferons. *J. Interterfon Cytokine Res.* **19**, 189–195 (1999).
72. Abramovich, C., Yakobson, B., Chebath, J. & Revel, M. A protein-arginine methyltransferase binds to the intracytoplasmic domain of the IFNAR1 chain in the type I interferon receptor. *EMBO J.* **16**, 260–266 (1997).
73. McDonald, C. & Reich, N. C. Cooperation of the transcriptional co-activators CBP and p300 with Stat6. *J. Interterfon Cytokine Res.* **19**, 711–722 (1999).
74. Shankaranarayanan, P., Chaitidis, P., Kuhn, H. & Nigam, S. Acetylation by histone acetyltransferase CREB-binding protein/p300 of STAT6 is required for transcriptional activation of the 15-lipoxygenase-1 gene. *J. Biol. Chem.* **276**, 42753–42760 (2001).
75. Kim, T. K. & Maniatis, T. Regulation of interferon-γ-activated STAT1 by the ubiquitin-proteasome pathway. *Science* **273**, 1717–1719 (1996).
76. Parisien, J. P. *et al.* The V protein of human parainfluenza virus 2 antagonizes type I interferon responses by destabilizing signal transducer and activator of transcription 2. *Virology* **283**, 230–239 (2001).
77. Parisien, J. P., Lau, J. F., Rodriguez, J. J., Ulane, C. M. & Horvath, C. M. Selective STAT protein degradation induced by paramyxoviruses requires both STAT1 and STAT2 but is independent of α/β interferon signal transduction. *J. Virol.* **76**, 4190–4198 (2002).
78. Ulane, C. M. & Horvath, C. M. Paramyxoviruses SV5 and HPIV2 assemble STAT protein ubiquitin ligase complexes from cellular components. *Virology* **304**, 160–166 (2002).
79. Ulane, C. M., Rodriguez, J. J., Parisien, J. P. & Horvath, C. M. STAT3 ubiquitylation and degradation by mumps virus suppress cytokine and oncogene signaling. *J. Virol.* **77**, 6385–6393 (2003).
80. Rogers, R. S., Horvath, C. M. & Matunis, M. J. SUMO modification of STAT1 and its role in PIAS-mediated inhibition of gene activation. *J. Biol. Chem*. **278**, 30091–30097 (2003).
81. Ungureanu, D. *et al.* PIAS proteins promote SUMO-1 conjugation to STAT1. *Blood* (in the press).
82. Liu, B. *et al.* Inhibition of Stat1-mediated gene activation by PIAS1. *Proc. Natl Acad. Sci. USA* **95**, 10626–10631 (1998).
83. Valdez, B. C., Henning, D., Perlaky, L., Busch, R. K. & Busch, H. Cloning and characterization of Gu/RH-II binding protein. *Biochem. Biophy. Res. Com.* **234**, 335–340 (1997).
84. Shuai, K. Modulation of STAT signaling by STAT-interacting proteins. *Oncogene* **19**, 2638–2644 (2000).
85. Wible, B. A. *et al.* Increased K+ efflux and apoptosis induced by the potassium channel modulatory protein KChAP/PIAS3β in prostate cancer cells. *J. Biol. Chem.* **277**, 17852–17862 (2002).
86. Moilanen, A. M. *et al.* A testis-specific androgen receptor coregulator that belongs to a novel family of nuclear proteins. *J. Biol. Chem.* **274**, 3700–3704 (1999).
87. Wu, L. *et al.* Miz1, a novel zinc finger transcription factor that interacts with Msx2 and enhances its affinity for DNA. *Mech. Dev.* **65**, 3–17 (1997).
88. Aravind, L. & Koonin, E. V. SAP — a putative DNA-binding motif involved in chromosomal organization. *Trends Biochem. Sci.* **25**, 112–114 (2000).
89. Kipp, M. *et al.* SAF *Cell. Biol.* **20**, 7480–7489 (2000).
90. Chung, C. D. *et al.* Specific inhibition of Stat3 signal transduction by PIAS3. *Science* **278**, 1803–1805 (1997). **This paper reports the first identification of protein inhibitor of activated STAT (PIAS) proteins in the negative regulation of STATs.**
91. Arora, T. *et al.* PIASx is a transcriptional co-repressor of signal transducer and activator of transcription 4. *J. Biol. Chem.* **278**, 21327–21330 (2003).
92. Liu, B., Gross, M., ten Hoeve, J. & Shuai, K. A transcriptional co-repressor of Stat1 with an essential LXXLL signature motif. *Proc. Natl Acad. Sci. USA* **98**, 3203–3207 (2001).
93. Liao, J., Fu, Y. & Shuai, K. Distinct roles of the NH2- and COOH-terminal domains of the protein inhibitor of activated signal transducer and activator of transcription (STAT)1 (PIAS1) in cytokine-induced PIAS1–Stat1 interaction. *Proc. Natl Acad. Sci. USA* **97**, 5267–5272 (2000).
94. Rycyzyn, M. A. & Clevenger, C. V. The intranuclear prolactin/cyclophilin B complex as a transcriptional inducer. *Proc. Natl Acad. Sci. USA* **99**, 6790–6795 (2002).
95. Tussie-Luna, M. I., Bayarsaihan, D., Seto, E., Ruddle, F. H. & Roy, A. L. Physical and functional interactions of histone deacetylase 3 with TFII-I family proteins and PIASxβ. *Proc. Natl Acad. Sci. USA* **99**, 12807–12812 (2002).
96. Long, J., Matsuura, I., He, D., Wang, G., Shuai, K., and Liu, F. Repression of Smad transcriptional activity by PIASy. *Proc. Natl Acad. Sci. USA* **100**, 9791–9796 (2003).
97. Johnson, E. S. & Gupta, A. A. An E3-like factor that promotes SUMO conjugation to the yeast septins. *Cell* **106**, 735–744 (2001).
98. Kahyo, T., Nishida, T. & Yasuda, H. Involvement of PIAS1 in the sumoylation of tumor suppressor p53. *Mol. Cell* **8**, 713–718 (2001).
99. Sachdev, S. *et al.* PIASy, a nuclear matrix-associated SUMO E3 ligase, represses LEF1 activity by sequestration into nuclear bodies. *Genes Dev.* **15**, 3088–3103 (2001).
100. Gross, M. *et al.* Distinct effects of PIAS proteins on androgen-mediated gene activation in prostate cancer cells. *Oncogene* **20**, 3880–3887 (2001).
101. Betz, A., Lampen, N., Martinek, S., Young, M. W. & Darnell, J. E., Jr. A Drosophila PIAS homologue negatively regulates stat92E. *Proc. Natl Acad. Sci. USA* **98**, 9563–9568 (2001). **This paper provides genetic evidence that *Drosophila* PIAS might negatively regulate the *Drosophila* JAK–STAT pathway.**
102. Chen, Y. *et al.* Identification of Shp-2 as a Stat5A phosphatase. *J. Biol. Chem.* **278**, 16520–16527 (2003).
103. Chughtai, N., Schimchowitsch, S., Lebrun, J. J. & Ali, S. Prolactin induces SHP-2 association with Stat5, nuclear translocation, and binding to the β-casein gene promoter in mammary cells. *J. Biol. Chem.* **277**, 31107–31114 (2002).
104. Aoki, N. & Matsuda, T. A cytosolic protein-tyrosine phosphatase PTP1B specifically dephosphorylates and deactivates prolactin-activated STAT5a and STAT5b. *J. Biol. Chem.* **275**, 39718–39726 (2000).
105. David, M., Grimley, P. M., Finbloom, D. S. & Larner, A. C. A nuclear tyrosine phosphatase downregulates interferon-induced gene expression. *Mol. Cell. Biol.* **13**, 7515–7521 (1993).
106. Haspel, R. L. & Darnell, J. E., Jr. A nuclear protein tyrosine phosphatase is required for the inactivation of Stat1. *Proc. Natl Acad. Sci. USA* **96**, 10188–10193 (1999).
107. ten Hoeve, J. *et al.* Identification of a nuclear Stat1 protein tyrosine phosphatase. *Mol. Cell. Biol.* **22**, 5662–5668 (2002).
108. Wu, T. R. *et al.* SHP-2 is a dual-specificity phosphatase involved in Stat1 dephosphorylation at both tyrosine and serine residues in nuclei. *J. Biol. Chem.* **277**, 47572–47580 (2002). **References 107 and 108 report the identification of a STAT1 protein tyrosine phosphatase. In addition, the data indicate the existence of substrate specificity in the dephosphorylation of STATs in the nucleus.**
109. Yoo, J. Y., Huso, D. L., Nathans, D. & Desiderio, S. Specific ablation of Stat3β distorts the pattern of Stat3-responsive gene expression and impairs recovery from endotoxic shock. *Cell* **108**, 331–344 (2002).
110. Henriksen, M. A., Betz, A., Fuccillo, M. V. & Darnell, J. E., Jr. Negative regulation of STAT92E by an N-terminally truncated STAT protein derived from an alternative promoter site. *Genes Dev.* **16**, 2379–2389 (2002).
111. Hu, X. *et al.* Sensitization of IFN-γ Jak-STAT signaling during macrophage activation. *Nature Immunol.* **3**, 859–866 (2002).
112. Dickensheets, H. L., Venkataraman, C., Schindler, U. & Donnelly, R. P. Interferons inhibit activation of STAT6 by interleukin 4 in human monocytes by inducing SOCS-1 gene expression. *Proc. Natl Acad. Sci. USA* **96**, 10800–10805 (1999).
113. Ito, S. *et al.* Interleukin-10 inhibits expression of both interferon α- and interferon γ-induced genes by suppressing tyrosine phosphorylation of STAT1. *Blood* **93**, 1456–1463 (1999).
114. Magrangeas, F., Boisteau, O., Denis, S., Jacques, Y. & Minvielle, S. Negative cross-talk between interleukin-3 and interleukin-11 is mediated by suppressor of cytokine signalling-3 (SOCS-3). *Biochem. J.* **353**, 223–230 (2001).
115. Li, Q. & Verma, I. M. NF-κB regulation in the immune system. *Nature Rev. Immunol.* **2**, 725–734 (2002).
116. Kumar, A., Commane, M., Flickinger, T. W., Horvath, C. M. & Stark, G. R. Defective TNF-α-induced apoptosis in STAT1-null cells due to low constitutive levels of caspases. *Science* **278**, 1630–1632 (1997).
117. Kinjyo, I. *et al.* SOCS1/JAB is a negative regulator of LPS-induced macrophage activation. *Immunity* **17**, 583–591 (2002).
118. Nakagawa, R. *et al.* SOCS-1 participates in negative regulation of LPS responses. *Immunity* **17**, 677–687 (2002). **References 117 and 118 uncover a role of SOCS1 in lipopolysaccharide signalling.**
119. Morita, Y. *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. *Proc. Natl Acad. Sci. USA* **97**, 5405–5410 (2000).
120. Ulloa, L., Doody, J. & Massaguae, J. Inhibition of transforming growth factor-β/SMAD signalling by the interferon-γ/STAT pathway. *Nature* **397**, 710–713 (1999).
121. Nakashima, K. *et al.* Synergistic signaling in fetal brain by STAT3-Smad1 complex bridged by p300. *Science* **284**, 479–482 (1999).
122. Ivaska, J., Bosca, L. & Parker, P. J. PKCε is a permissive link in integrin-dependent IFN-γ signalling that facilitates JAK phosphorylation of STAT1. *Nature Cell Biol.* **5**, 363–369 (2003). **This paper reports cross-talk between IFN- and integrin-signalling pathways.**
123. Leonard, W. J. & O'Shea, J. J. Jaks and STATs: biological implications. *Annu. Rev. Immu.* **16**, 293–322 (1998).
124. Notarangelo, L. D. *et al.* Mutations in severe combined immune deficiency (SCID) due to JAK3 deficiency. *Hum. Mutat.* **18**, 255–263 (2001).
125. Mullings, R. E. *et al.* Signal transducer and activator of transcription 6 (STAT-6) expression and function in asthmatic bronchial epithelium. *J. Allergy Clin. Immunol.* **108**, 832–838 (2001).
126. Seki, Y. I. *et al.* SOCS-3 regulates onset and maintenance of T_H2-mediated allergic responses. *Nature Med.* **9**, 1047–1054 (2003). **This paper provides evidence that increased SOCS3 expression might contribute to the pathophysiology of T-helper-2-cell-mediated immune diseases.**
127. Morrison, T. E., Mauser, A., Wong, A., Ting, J. P. & Kenney, S. C. Inhibition of IFN-γ signaling by an Epstein–Barr virus immediate-early protein. *Immunity* **15**, 787–799 (2001).
128. Miller, D. M. *et al.* Human cytomegalovirus inhibits major histocompatibility complex class II expression by disruption of the Jak/Stat pathway. *J. Exp. Med.* **187**, 675–683 (1998).
129. Abendroth, A. *et al.* Modulation of major histocompatibility class II protein expression by varicella-zoster virus. *J. Virol.* **74**, 1900–1907 (2000).

130. Dupuis, S. *et al.* Human interferon-γ-mediated immunity is a genetically controlled continuous trait that determines the outcome of mycobacterial invasion. *Immunol. Rev.* **178**, 129–137 (2000).
131. Dupuis, S. *et al.* Impaired response to interferon-α/β and lethal viral disease in human STAT1 deficiency. *Nature Genet.* **33**, 388–391 (2003).
132. Welte, T. *et al.* STAT3 deletion during hematopoiesis causes Crohn's disease-like pathogenesis and lethality: a critical role of STAT3 in innate immunity. *Proc. Natl Acad. Sci. USA* **100**, 1879–1884 (2003).
133. Lovato, P. *et al.* Constitutive STAT3 activation in intestinal T cells from patients with Crohn's disease. *J. Biol. Chem.* **278**, 16777–16781 (2003).
134. Pickart, C. M. Mechanisms underlying ubiquitination. *Annu. Rev. Biochem.* **70**, 503–533 (2001).
135. Melchior, F. SUMO — nonclassical ubiquitin. *Annu. Rev. Cell. Dev. Biol.* **16**, 591–626 (2000).
136. Jackson, P. K. A new RING for SUMO: wrestling transcriptional responses into nuclear bodies with PIAS family E3 SUMO ligases. *Genes Dev.* **15**, 3053–3058 (2001).
137. You-Ten, K. E. *et al.* Impaired bone marrow microenvironment and immune function in T cell protein tyrosine phosphatase-deficient mice. *J. Exp. Med.* **186**, 683–693 (1997).
138. Elchebly, M. *et al.* Increased insulin sensitivity and obesity resistance in mice lacking the protein tyrosine phosphatase-1B gene. *Science* **283**, 1544–1548 (1999).
139. Shultz, L. D., Coman, D. R., Bailey, C. L., Beamer, W. G. & Sidman, C. L. 'Viable motheaten,' a new allele at the motheaten locus. I. Pathology. *Am. J. Pathol.* **116**, 179–192 (1984).
140. Shultz, L. D., Rajan, T. V. & Greiner, D. L. Severe defects in immunity and hematopoiesis caused by SHP-1 protein-tyrosine-phosphatase deficiency. *Trends Biotechnol.* **15**, 302–307 (1997).
141. Qu, C. K., Nguyen, S., Chen, J. & Feng, G. S. Requirement of Shp-2 tyrosine phosphatase in lymphoid and hematopoietic cell development. *Blood* **97**, 911–914 (2001).
142. Byth, K. F. *et al.* CD45-null transgenic mice reveal a positive regulatory role for CD45 in early thymocyte development, in the selection of $CD4^+CD8^+$ thymocytes, and B cell maturation. *J. Exp. Med.* **183**, 1707–1718 (1996).
143. Kishihara, K. *et al.* Normal B lymphocyte development but impaired T cell maturation in CD45-exon6 protein tyrosine phosphatase-deficient mice. *Cell* **74**, 143–156 (1993).

Acknowledgements

This work is supported by the National Institutes of Health, American Cancer Society and United States Army Medical Research and Materiel Command (K.S.). B.L. is a Leukaemia and Lymphoma Special Fellow.

Online links

DATABASES

The following terms in this article are linked online to:

LocusLink: http://www.ncbi.nlm.nih.gov/LocusLink/
BMP2 | CAMK2 | CD45 | CIS | EPOR | JAK1 | JAK2 | JAK3 | LEF1 | LIF | PIAS1 | PIAS3 | PIASX | PIASY | PRMT1 | PTP1B | SHP1 | SHP2 | SOCS1 | SOCS2 | SOCS3 | STAT1 | STAT2 | STAT3 | STAT4 | STAT5A | STAT5B | STAT6 | TC-PTP | TYK2 | UBP43

FURTHER INFORMATION

Ke Shuai's homepage:
http://www.uclaaccess.ucla.edu/cfm/access_faculty.cfm?FacultyKey=112

Access to this interactive links box is free online.