Characterization of how interferons (IFNs) mediate their biological response led to identification of the JAK–STAT signaling cascade, where JAKs are receptor-associated kinases and STATs the transcription factors they activate. Today, 4 JAKs and 7 STATs are known to transduce pivotal signals for the over 50 members of the four-helix bundle family of cytokines. This review will provide an overview and historical perspective of the JAK–STAT paradigm.

© 2008 Elsevier Ltd. All rights reserved.
receptors [2–4]. Characterization of the ability of IFN-α to drive ISG expression led to the identification of Signal transducers and activators of transcription (Stat) proteins and their roles. The Janus kinases (JAK) family

Table 1 JAK–STAT signaling by the four-helix bundle cytokines

<table>
<thead>
<tr>
<th>Ligands</th>
<th>JAKs</th>
<th>STATs</th>
</tr>
</thead>
<tbody>
<tr>
<td>IFN-I (type I)</td>
<td>Jak1, Jak2</td>
<td>Stat1, Stat2, Stat3, Stat5 (Stat5b–d)</td>
</tr>
<tr>
<td>IFN-γ (type II)</td>
<td>Jak1, Jak2</td>
<td>Stat1</td>
</tr>
<tr>
<td>IFN-1 (IL-28a,b,-29)</td>
<td>Jak1, Jak2, Stat1, Stat2, Stat3</td>
<td></td>
</tr>
<tr>
<td>IL-10</td>
<td>Jak1, Jak2</td>
<td>Stat1, Stat3</td>
</tr>
<tr>
<td>IL-19</td>
<td>Jak1, Jak2</td>
<td>Stat1, Stat3</td>
</tr>
<tr>
<td>IL-20</td>
<td>Jak1, Jak2</td>
<td>Stat1, Stat3</td>
</tr>
<tr>
<td>IL-22 (IL-TIF)</td>
<td>Jak1, Jak2</td>
<td>Stat1, Stat3 (Stat5a)</td>
</tr>
<tr>
<td>IL-24 (mda7)</td>
<td>Jak1, Jak2</td>
<td>Stat1, Stat3</td>
</tr>
<tr>
<td>IL-26 (AK155)</td>
<td>Jak1, Jak2</td>
<td>Stat1, Stat3</td>
</tr>
<tr>
<td>gp130 family</td>
<td></td>
<td></td>
</tr>
<tr>
<td>IL-6</td>
<td>Jak1, Jak2</td>
<td>Stat3, Stat1</td>
</tr>
<tr>
<td>IL-11</td>
<td>Jak1</td>
<td>Stat3, Stat1</td>
</tr>
<tr>
<td>LIF</td>
<td>Jak1, Jak2</td>
<td>Stat3, Stat1</td>
</tr>
<tr>
<td>CNTF</td>
<td>Jak1, Jak2</td>
<td>Stat3, Stat1</td>
</tr>
<tr>
<td>CLC/CLI§</td>
<td>Jak1, Jak2</td>
<td>Stat3, Stat1</td>
</tr>
<tr>
<td>NP</td>
<td>Jak1, Jak2</td>
<td>Stat3</td>
</tr>
<tr>
<td>CT-1</td>
<td>Jak1, Jak2</td>
<td>Stat3</td>
</tr>
<tr>
<td>OSM</td>
<td>Jak1, Jak2</td>
<td>Stat3, Stat1</td>
</tr>
<tr>
<td>IL-31</td>
<td>Jak1, Jak2</td>
<td>Stat3, Stat5, Stat1</td>
</tr>
<tr>
<td>G-CSF</td>
<td>Jak1, Jak2</td>
<td>Stat3</td>
</tr>
<tr>
<td>Leptin</td>
<td>Jak2</td>
<td>Stat3</td>
</tr>
<tr>
<td>IL-12 (p35 + p40)</td>
<td>Tyk2, Jak2</td>
<td>Stat4</td>
</tr>
<tr>
<td>IL-23 (p19 + p40)</td>
<td>Tyk2, Jak2</td>
<td>Stat3, Stat4, Stat1</td>
</tr>
<tr>
<td>IL-27* (p28 + EB13)</td>
<td>Jak2</td>
<td>Stat1, Stat3, Stat4, Stat5</td>
</tr>
<tr>
<td>IL-35 (p35 + EB13)</td>
<td>Stat3, Stat5</td>
<td></td>
</tr>
<tr>
<td>γC family</td>
<td></td>
<td></td>
</tr>
<tr>
<td>IL-2</td>
<td>Jak1, Jak3</td>
<td>Stat5, Stat3</td>
</tr>
<tr>
<td>IL-7</td>
<td>Jak1, Jak3</td>
<td>Stat5, Stat3</td>
</tr>
<tr>
<td>TSLP*</td>
<td>Stat5</td>
<td></td>
</tr>
<tr>
<td>IL-9</td>
<td>Jak1, Jak3</td>
<td>Stat5, Stat3</td>
</tr>
<tr>
<td>IL-15</td>
<td>Jak1, Jak3</td>
<td>Stat5, Stat3</td>
</tr>
<tr>
<td>IL-21</td>
<td>Jak1, Jak3</td>
<td>Stat5, Stat5a</td>
</tr>
<tr>
<td>IL-4</td>
<td>Jak1, Jak3</td>
<td>Stat6</td>
</tr>
<tr>
<td>IL-13*</td>
<td>Jak1, Jak2</td>
<td>Stat3, Stat5</td>
</tr>
<tr>
<td>IL-3 family</td>
<td></td>
<td></td>
</tr>
<tr>
<td>IL-3</td>
<td>Jak2</td>
<td>Stat5</td>
</tr>
<tr>
<td>IL-5</td>
<td>Jak2</td>
<td>Stat5</td>
</tr>
<tr>
<td>GM-CSF</td>
<td>Jak2</td>
<td>Stat5</td>
</tr>
<tr>
<td>Single chain family</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Epo</td>
<td>Jak2</td>
<td>Stat5</td>
</tr>
<tr>
<td>GH</td>
<td>Jak2</td>
<td>Stat5, Stat3</td>
</tr>
<tr>
<td>Prl</td>
<td>Jak2</td>
<td>Stat5</td>
</tr>
<tr>
<td>Tpo</td>
<td>Jak2</td>
<td>Stat5</td>
</tr>
</tbody>
</table>

Genetic and biochemical studies have determined that four-helix bundle cytokines transduce their signals through specific JAKs and STATs. Assignments with the highest level of confidence are shown in bold, those with less confidence are shown in plain lettering, and those with the least confidence are shown in brackets.

1 In humans this family consists of 12 IFN-αs, IFN-β, and Limitin.

§ a.k.a. NNT-1/BSF-3.

* IL-30 is the p28 subunit of IL-27.

‡ Several Interleukins are not members of this family (e.g., IL-1, IL-8, IL-14, IL-16, IL-17, IL-18, IL-25, IL-32, IL-33, IL-34).

2. Discovery of the JAK–STAT signaling paradigm

Shortly after the isolation of the first ISGs, an IFN-I specific enhancer, the ISRE (IFN Stimulated Response Element; AGTTTN3TTTCC), was identified [4,6,15]. Analysis of IFN-α stimulated nuclear extracts revealed three distinct ISRE binding complexes: IFN-I Stimulated Gene Factor 1 (ISGF-1; a.k.a. IRF-2); ISGF-2 (a.k.a. IRF-1); and ISGF-3, whose activation correlated directly with the expression of immediate early ISGs [6,15,16]. Purification of ISGF-3 led to identification of four component proteins of 113 kDa, 91 kDa, 84 kDa and 48 kDa [6,7,16,17]. The 48 kDa protein (p48), previously shown to be the DNA binding component, was recognized as a member of the IRF (IFN-I response factor) family of transcription factors and subsequently named IRF-9 [18]. The 84 kDa (p84) and 91 kDa (p91) proteins were found to be alternative mRNA splice products of a single gene. They also exhibited significant homology with p113, but not other proteins (see Fig. 1). The term STAT was subsequently coined, with p84 becoming Stat1β, p91 Stat1α and p113 Stat2 [5,7].

Antibodies developed against Stat1 and Stat2 revealed that both proteins were localized to the cytoplasm in resting cells. Upon IFN-α stimulation, however, Stat1 (both isoforms) and Stat2 were rapidly phosphorylated on a single conserved tyrosine. This led to the formation of a stable Stat1:Stat2 heterodimer and nuclear translocation (see Fig. 1; [8]). Exploiting these antibodies, it was determined that IFN-γ stimulated the rapid activation of just Stat1 [19]. Moreover, the IFN-γ stimulated Stat1 homodimers were found to directly bind to a distinct palindromic sequence, the Gamma-IFN activated site (GAS; TTTCNCGGAAA; [20–23]). Consistent with their ability to activate Stat1, type I IFNs (IFN-Is) were also subsequently determined to direct the formation of Stat1 homodimers and drive expression of GAS target genes, albeit more transiently. Ensuing biochemical and structural studies determined that the stable interaction between the phosphotyrosine of one STAT with the SH2 domain of the corresponding STAT was responsible for dimerization [24–27].

During the same period, founding members of the unique JAK family (i.e., Tyk2, Jak1 and Jak2) were identified through tyrosine kinase homology screens (see Fig. 1; [28,29]). Subsequent elegant genetic and biochemical studies linked Tyk2 with the IFN-I response, and then Jak1 and Jak2 with a number of other cytokines, providing important insight into how cytokine receptors stimulate tyrosine phosphorylation [10,30–33]. The identification of four additional STATs and one JAK provided the tools to determine that all ~50 members of the four-helix bundle family of cytokines transduce their biological responses through this pathway (see Table 1 and Fig. 2; [34–43]). Intriguingly, except for the ~20 type I IFNs (and 3 recently identified type III IFNs [44,45]), all other members of this family transduce their signals through the simpler JAK–STAT pathway associated with GAS target genes (see Fig. 2; [46]).

3. The Janus kinases (JAK) family

The four JAK family members, Jak1, Jak2, Jak3 and Tyk2, range in size from 120 kDa to 140 kDa, and except for Jak3 (leukocyte-JAK [36]), are expressed in most tissues (reviewed in Refs. [46,47]). This kinase family features seven conserved JAK homology (JH) domains (see Fig. 1), notably including a tandem set of carboxy terminal kinase domains, where only JH1 has bona fide catalytic activity (Ki). JH2 is referred to as the pseudo kinase (Psi1) domain. Ruminant of other kinases, activation is driven by phosphorylation of critical tyrosines in the inactivation loop, which releases its blockade of the catalytic site. Although no function has been assigned to the SH2-related domain (“SH2“; JH5 and half of JH4),
the amino terminal domains (JH1-3 and half of JH4) constitute a FERM (four point one, ezrin, radixin, moesin) domain, which directs stable association with membrane proximal receptor motifs. As illustrated in Fig. 2, Jak1 stably associates with IFNAR2 and IFNGR1; Jak2 with IFNGR2; and Tyk2 with IFNAR1.

Gene targeting studies have underscored the critical role JAKs play in the biological response to cytokines. Jak1 knockout mice die perinatally due to a failure to nurse (ascribed to a LIF defect). Their tissues are defective in response to cytokines from the IL-2, IL-6, IFN and IL-10 families ([48]; see also Table 1). Jak2 knockout mice exhibit an earlier lethality (i.e., E12.5), reflecting the critical role this kinase plays in definitive erythropoiesis [49,50]. Ex vivo studies on Jak2−/− tissues have highlighted the important role this kinase plays in directing signals stimulated by the IFN-γ, as well as the single-chain, IL-2 and IL-3 receptor families (see Table 1). Notably, several myeloproliferative disorders, including the majority of cases of polycythemia vera, essential thrombocytopenia and primary myelofibrosis have been attributed to a single Stat5-activating point mutation in the JH2 domain of Jak2, V617F, underscoring a potential therapeutic target (see [51,156–158]).

Jak3 expression is limited to lymphoid tissues. Biochemical and genetic studies have genetically and physically linked Jak3 to the common gamma chain (γC), which is associated with members of the lymphoid predominant IL-2 family of cytokine receptors (e.g., receptors for IL-2, IL-4, IL-7, IL-9, IL-15, and IL-21; see Table 1). Consistent with this, Jak3 and γC knockout mice both exhibit Severe Combined Immunodeficiency (SCID)-like defects, highlighting Jak3 as an appealing therapeutic target [51–54].

As outlined above, Tyk2 was initially associated with IFN-I response. However, subsequent biochemical and genetic studies implicated this kinase in the response to IL-12 and IL-23, as well as several members of the IL-6 and IL-10 receptor families. Intriguingly, loss of Tyk2 has been associated with distinct phenotypes in humans and mice. Whereas Tyk2 knockout mice feature modest cytokine defects and a proclivity towards type 2 (i.e., allergic) T-cell responses [55–57], Tyk2 deficient humans exhibit a severe allergic phenotype that has been attributed to an impaired antimicrobial response [58]. In mice, Tyk2 may play a more important role in integrating the response to multiple cytokines [59].

4. The STAT family of transcription factors

The seven mammals STAT (Stats1–6, 5a and 5b) range in size from 750 and 900 amino acids (see Fig. 1). Both their chromosomal distribution and homologues in model eukaryotes, suggest this family arose from a single primordial gene, as the need for cell-to-cell communication increased [60,61]. Stat3 and Stat5 are most closely related to those homologues found in model eukaryotes, like Dictyostelium, C. elegans and Drosophilia (see article number 4; [60]). Notably, the single Drosophilia STAT transduces signals through a “classic” JAK–STAT pathway, whereas homologues in Dictyostelium and C. elegans appear to signal through alternative pathway(s).

STATs can be divided into 7 structurally and/or functionally conserved domains (see Fig. 1: [24,25,62,63]): (1) The Amino Terminal Domain (NH2; ~125 amino acids) is well conserved and promotes the formation of homotypic dimers among unphosphorylated STATs [63–66]. This not only assures that STATs remain integrated in an “off” conformation in the resting state, but also facilitates delivery and subsequent activation of STAT pairs at the receptor.
(2) The Coiled-Coil Domain (amino acids ∼135 to ∼315) consists of a potentially dynamic four-helix bundle that protrudes laterally (∼80 Å) from the core. This domain associates with regulatory proteins and has also been implicated in controlling the process of nuclear import and export (see article number 3; [46,67]). (3) The DNA Binding Domain (DBD; amino acids ∼320 to ∼480) is also well conserved and mediates a robust binding to GAS palindromes. All activated STAT homodimers, except Stat2, directly bind GAS elements. The DBD has also been implicated in the regulation of nuclear import and export (see also article number 3; [24,25,67,68]). (4) The Linker Domain (amino acids ∼480 to ∼575) structurally translates active dimerization to the DNA binding motif. Studies also suggest that it regulates a process of continual basal (i.e., in resting cells) nuclear export [69]. (5) The SH2 Domain (amino acids ∼575 to ∼680) is the most highly conserved motif. It mediates specific recruitment to receptor chains, as well as the formation of active STAT dimers [26,27,46]. It has been argued that this domain may represent the primordial SH2 domain [25]. (6) The Tyrosine Activation Motif consists of a conserved tyrosine along with 5–7 specific carboxy terminal amino acids, usually near residue 700. Like the corresponding SH2 domain, this motif resides on the exposed surface of the inactive homodimer, facilitating its JAK-dependent phosphorylation during receptor recruitment [63,64]. Upon phosphorylation, this motif is recognized and bound by the corresponding SH2 domain of the partner STAT, directing the critical structural changes required for an active conformation [62–64]. (7) The Transcriptional Activation Domain (TAD) resides at the carboxy terminus and is highly variable in length and sequence between STAT family members. However, for each specific STAT, except Stat2, this sequence is conserved in humans and mice [46,70]. Many TADs include conserved serine phosphorylation sites that facilitate the recruitment of coactivators (e.g., CBP, p300 and the MCM complex; see below [71,72]). STAT TADs also recruit pol II, HATs (e.g., PCAF, GCNS and NcoA-1 [73–75]), chromatin modifying complexes (e.g., BAF and SWI2-SNF2 [76–79]) and HDACs [80,81]. The STAT TAD also appears to regulate protein stability. Specifically, Stat4, Stat5 and Stat6 can be targeted for ubiquitin-dependent destruction, whereas Stat1, Stat2 and Stat3 are more stable [82,83]. Finally, a number of native carboxy terminally truncated STAT isoforms have been shown to direct unique programs of gene expression through their association with other transcription factors (e.g., Stat1β with Stat2 in ISGF-3 and Stat3β with c-jun [5,84,85]).

4.1. Stat1

Consistent with biochemical studies linking Stat1 activation with the biological response to IFN-α (i.e., ISGF-3 [71]) and IFN-γ (i.e., a Stat1 homodimer; see Fig. 2; [9]), Stat1 knockout mice exhibit profound defects in their biological response to type I and type II IFNs [86,87]. However, defects in the biological response to other STAT1 activating ligands (e.g., IL-6 and EGF) are considerably more modest. In humans, defects in IFN-γ—Stat1 axis have been intimately linked with increased susceptibility to mycobacterial infection [88,89]. In addition to their role in directing an effective innate response to intracellular bacteria, Stat1 target genes have been associated with suppression of cellular proliferation [46]. This contrasts the pro-proliferative and anti-inflammatory activities linked to Stat3 (see below; see also article numbers 4, 11 and 12), and raises the possibility that Stat1 and Stat3 serve to functionally antagonize each other (e.g., [90]). Finally, Stat1β, which arises as an alternate splice isoform, is missing the 39 amino acid carboxy terminal TAD [7]. Although Stat1β appears to be fully functional in the response to IFN-1s, it is defective in the response to IFN-γ, where it may actually antagonize Stat1α (i.e., full length) activity [91].

4.2. Stat2

Most divergent in sequence and function, Stat2 neither appears to homodimerize nor bind DNA directly. Rather, in an exclusive response to type I (and type III [44,45]) IFNs, Stat2 forms an active heterodimer with either Stat1α or Stat1β. This Stat1-Stat2 dimer associates with a unique DNA binding protein, IRF-9, to drive a Stat2-TAD-dependent expression of target genes [5,92,93]. This includes the expression of microRNAs [94]. Curiously, the Stat2 TAD is not conserved between humans and mice [70]. Consistent with these biochemical studies, Stat2 knockout mice exhibit profound defects in their biological response to type I IFNs and likely type III IFNs [95]. More detailed analysis of IFN-1 response in Stat2−/− tissues has revealed a loss in IFN-I autocrine activity, abnormal DC maturation and a loss in SOCS-1 expression [95–97]. This latter response appears to assure that the response to IFN-Is is considerably more transient than the response to IFN-γ [97,154].

4.3. Stat3

Initially identified as an IL-6-dependent transcription factor [98], two alternate and functionally distinct splice isoforms have been rigorously characterized, Stat3α (full length) and Stat3β (missing the carboxy terminal TAD [84,99]). Reflecting Stat3’s ancient lineage [61], biochemical and genetic studies have underscored the important role this transcription factor plays in transducing signals for the IL-6 family (IL-6, IL-11, IL-31, LIF, CNTF, CLC/CLF, NP, CT1, OSM), the IL-10 family (IL-10, IL-19, IL-20, IL-22, IL-24, IL-26), as well as G-CSF, Leptin, IL-21, IL-27 and potentially IFN-I [see Table 1; see also article numbers 4 and 12; [47,60,100]]. Consistent with a broad range in activity, Stat3 knockout mice exhibit an early embryonic lethal phenotype (at E6.5–7.5) [101]. Tissue specific Stat3 knockout mice have been associated with an increased inflammatory response, altered energy homeostasis, developmental defects and a decreased oncogenic potential [102–111]. The inflammatory phenotype associated with Stat3 deficiency likely reflects its role in directing the response to anti-inflammatory cytokines (e.g., IL-10 family and IL-27), as well as Th17 and regulatory T-cells activity (see article number 10; [100,112–114]). In contrast, Stat3 hyper-activation has been associated with immune suppression and transformation [115,116]. Thus, Stat3’s role in transformation is likely to be complex [110,117,156].

4.4. Stat4

Identified in a search for Stat1 homologues [36,37], Stat4 was mapped adjacent to Stat1 on murine chromosome 2 [118]. Subsequently, Stat4 was found to transduce signals for IL-12 (consisting of p40 + p35 subunits) and more recently IL-23 (consisting of p19 + p35 subunits [119,120]). Specifically, Stat4 directs the IL-12-dependent polarization of naïve CD4+ T-cells towards IFN-γ secreting Th1 cells, as well as the activation of IFN-γ secreting NK cells [121–123]. Stat4 also plays an important role in the IL-23-dependent polarization of naïve CD4+ T-cells into Th17 cells (see article number 10; [100,113]). Finally, studies have highlighted the ability of other cytokines to synergize with IL-12 in stimulating potent Stat4 activation through their capacity to promote Stat4 serine phosphorylation [124].

4.5. Stat5

Initially identified as prolactin and IL-3 stimulated transcription factor [40–42], Stat5a and Stat5b arise from a set of tandemly duplicated genes adjacent to Stat3 on murine chromosome 17 [61,118]. Like Stat3, these two STATs exhibit the highest degree of
homology with invertebrate STATs and are functionally pleiotropic (see article number 4; [46,47,61]). Biochemical and genetic studies have revealed that Stat5a and Stat5b direct the biological response for the IL-3 family (IL-3, IL-5 and GM-CSF), single chain family (e.g., GH, Prl, Tpo and Epo) and γc family (i.e., the IL-2, IL-7, IL-9, IL-15 and IL-21) of cytokine receptors (see Table 1; [46,47]). At 96% amino acid identity, these two STATs appear to be functionally redundant, excepting the response to Prl, which favors Stat5a, and GH, which favors Stat5b (see article number 6; [40,125–127]). Deletion of the entire Stat5a + Stat5b locus has underscored the critical role Stat5 plays in driving both erythropoiesis and lymphopoiesis [128].

4.6. Stat6

Initially identified as IL-4Stat, Stat6 was subsequently shown to transduce signals for IL-13, which shares a receptor chain with IL-4 [38,39,46,47,121]. Reflecting its evolutionary juxta-position with Stat2 on murine chromosome 12 [118], Stat6 is divergent in sequence and features a large (~150 residue), functionally unique TAD [118,129]. Intriguingly, Stat6 homodimers bind to a GAS element that features an additional central nucleotide, providing an opportunity to activate a distinct subset of GAS-driven genes. Stat6 knockout mice have underscored the critical role this STAT plays in directing IL-4/IL-13 dependent: TH2-cell polarization; B-cell function (e.g., proliferation, maturation, MHC-II and IgE expression); and mast cell activity [121,130–132].

5. Regulating STAT activity

A characteristic feature of JAK–STAT signaling is its rapid onset and decay. Consistent with this, STATs associate with several classes of regulators, including those that promote covalent modifications in addition to canonical tyrosine phosphorylation. The best-characterized negative regulators include phosphatases, nuclear import/export machinery and members of the SOCS family. However, other negative regulators like PIAS and Nmi have been reported [133,134].

5.1. Covalent STAT modifications

STATs appear to undergo covalent modifications in addition to canonical tyrosine phosphorylation, most notably serine phosphorylation (see below). However, there are also several reports of acetylation and O-glycosylation [135–138]. Intriguingly, there is biochemical and genetic evidence for the ubiquitin-directed decay of Stat4, Stat5 and Stat6 [82,83]. However, evidence supporting a role for R-methylation (Stat1) and SUMOylation (Stat1) in controlling STAT activity remains more controversial [139–141].

With the potential exception of Stat2, all STATs are phosphorylated on at least one serine residue in their TAD, a modification that promotes transcriptional activity (see above [71,72,124,142,143]). However, it is not clear where this modification occurs. Conserved phosphorylation sites include, a PMS*P motif (S727 in Stat1 and Stat3; S721 in Stat4), a PS*P motif (S725 in Stat5a; S730 in Stat5b) and a SS*PD motif (S756 in Stat6 [82]). Stat1 and Stat5 feature at least one additional serine phosphorylation site in their TAD, S708 and S779, respectively. Biochemical studies have implicated a number of kinases in STAT serine phosphorylation, including MAP kinases (e.g., p38: STAT1, 3 and 4; ERK: Stat3 and Stat5; JNK: Stat3), PKCθ (Stat1 and Stat3), mTOR (Stat3), NLK (Stat3), CaMKII and IKKζ (Stat1 [71,144,145]). However, genetic evidence supporting a role for these kinases in regulating STAT activity is considerably more limited.

5.2. Phosphatases

Since kinases play an important role in cytokine response, it is not surprising that phosphatases, including SHP-1, SHP-2 and CD45 have been implicated in returning cytokine receptors and JAKs back to their basal unphosphorylated state ([60,146]; see also article number 12). Likewise, SHP-2, PTP1B, TC-PTP and PTP-1B have been implicated in restoring STATs to basal unphosphorylated state [146–151]. However, only two of these phosphatases, SHP-2 and TC-PTP, appear to exhibit robust activity in the nucleus, where STAT dephosphorylation has been linked to STAT nuclear export [67,152,153].

5.3. Nuclear import–export

The dramatic nuclear accumulation of activated STATs belie the complex process regulating STAT localization (see article number 3; [67,152]). The predominately cytosolic localization of inactive STATs reflects a steady state, where continuous basal nuclear import is balanced by continuous basal export. Upon stimulation, this balance is shifted towards STAT nuclear accumulation, and then in the opposite direction during the process of signal decay. Of note, multiple nuclear export sequence (NES) and nuclear localization sequence (NLS) elements have been implicated in this dynamic process [67,152].

5.3.1. The SOCS family

A subset of the SOCS proteins constitute a classic negative “feed-back loop” [14,154]. In the basal state SOCS proteins are expressed at low levels. However, upon stimulation the expression of these STAT target genes is rapidly induced, whereupon they function to antagonize further STAT activation. Gene targeting studies have underscored important roles for SOCS-1, SOCS-2 and SOCS-3 in antagonizing the IFN-γ–Stat1, IL-12–Stat4, IL-4–Stat6, GH–Stat5 and IL-6–Stat3 axes.

6. A bright future

Characterization of the ability of IFNs to direct an antiviral response led to the identification of the JAK–STAT signaling cascade, and provided insight into how the more than 50 members of the four-helix bundle cytokine family transduce their biological response (see Table 1). Future studies are likely to exploit conditional gene targeting, as well as improving pharmaceutical agents to explore how these pathways regulate immune homeostasis in vivo. This is not only likely to include the discovery of additional regulators, ligands and receptors, but also provide new insight into “crosstalk” with other signaling cascades.

References


315


