Rapid Communication

Receptors for Interleukin-3 (IL-3) and Growth Hormone Mediate an IL-6-Type Transcriptional Induction in the Presence of JAK2 or STAT3

By Yanping Wang, Karen K. Morella, Juergen Ripperger, Chun-Fai Lai, David P. Gearin, Georg H. Fey, Susana P. Campos, and Heinz Baumann

To determine the specificity of signal transducer and activator of transcription (STAT) protein activation by box 3 motif-deficient hematopoietin receptors, expression vectors encoding the receptors for growth hormone, interleukin-3 (IL-3), and IL-4 were transiently transfected into COS-1 cells, together with expression vectors for Janus kinases (JAKs) and STAT proteins. Each receptor mediated a dose-dependent activation of STAT1 and STAT3, and for IL-3R and GHR this process was enhanced by JAK2. The data suggest that a box 3 motif in the cytoplasmic domain of the signal-transducing receptor subunit was not absolutely required for linking the receptor to the JAK/STAT pathway. Transfection of the receptors, in combination with STAT3, into HepG2 cells reconstituted a cytokine-dependent stimulation of gene transcription through IL-6 response elements, providing evidence for a functional role of STAT3 in controlling gene expression.

© 1995 by The American Society of Hematology.

Hematopoietin receptors mediate cell responses that among others include an increased proliferation of hematopoietic cells or enhanced transcription of differentiated genes in various hematopoietic and nonhematopoietic cells. To define the signaling mechanisms controlling gene expression, we reconstituted hematopoietin receptor function in transiently transfected hepatoma cells. Cotransfected reporter gene plasmids, containing specific cytokine-responsive regulatory elements of acute-phase plasma protein (APP) genes, such as the interleukin-6 response element (IL-6RE) of the rat haptoglobin gene or the hematopoietin receptor response element (HRRE) related to the acute phase element of the rat α2-macroglobulin gene, served as indicators for signaling events. The experimental system proved to be applicable not only to the analysis of cytokine receptors intrinsic to hematocytes, ie, receptors for IL-6-type cytokines and growth hormone (GH), but also for various members of the receptor gene family not normally expressed in liver cells such as the granulocyte colony-stimulating factor receptor (G-CSF), c-Mpl, the IL-2R, and the IL-3R.

Structure/function analyses of gp130, leukemia inhibitory factor receptor (LIFR), and G-CSF have indicated that the box 3 motif was not only critical for gene regulation via the IL-6RE but was also needed for the activation of STAT3. Although STAT3 has been implicated in the induction of acute-phase response genes by IL-6, activation of the DNA binding activity of STAT3 in cells per se was not sufficient for transcriptional regulation through the IL-6RE. Only a minor stimulatory effect was observed in cells in which endogenous or ectopically overexpressed STAT3 was activated by cotransfected JAK2. Based on these data, a model for gene regulation by hematopoietin receptor was proposed that involves a STAT3-dependent and a STAT3-independent pathway.

Because the transcription-controlling effect of STAT3 cannot be unequivocally determined by using box 3-containing receptors for IL-6-type cytokines, an alternative approach was needed. The failure of the box 3-deficient receptors to induce regulation through IL-6RE has been attributed to an inefficient engagement of the endogenous JAK/STAT pathway by the receptor complex. We hypothesized that such hematopoietin receptors, which show transcription-regulating activity via HRRE but none via IL-6RE (eg, the IL-3R or the GHR), operate primarily through STAT3-independent pathways of signal transduction. We tested this hypothesis in this study by analyzing the function of the box 3-deficient hematopoietin receptors in the presence of overexpressed STAT proteins and JAK2. A receptor-specific reconstitution of gene regulation through the IL-6RE was achieved that was particularly prominent with the IL-3R. In contrast, the GHR was capable of activating ectopically expressed STAT proteins and mediating JAK2 action similar to the IL-3R and gp130 but was only minimally effective in regulating transcription via the IL-6RE. The data suggest that receptor signaling is, in part, influenced by the combination and relative concentrations of the components of the JAK/STAT pathway and that receptor specific differences in the signal pathways exist that determine the overall transcriptional gene control activity exerted by the STAT proteins.

Materials and Methods

Cells. Human hepatoma HepG2 and COS-1 cells were cultured in minimal essential medium (MEM) containing 10% and 5% fetal calf serum, respectively, and penicillin, streptomycin, and gentamicin. Cytokine treatments were performed in serum-free MEM. Unless noted otherwise, the concentration was 100 ng/mL for the human recombinant cytokines IL-3 and granulocyte-macrophage colony-stimulating factor (GM-CSF) (provided by Dr F. Meyer [Sandoz, Basel, Switzerland], G-CSF, and IL-4 [Genentech, Seattle, WA], GH [Genentech, South San Francisco, CA], and IL-6 [Genetics Institute, Cambridge, MA]). To enhance cytokine effect on chloramphenicol-resistant expression vectors, co-transfection with expression vectors for JAKs and STATs was performed.

From the Department of Molecular and Cellular Biology, Roswell Park Cancer Institute; the Division of Endocrinology, Children's Hospital, Buffalo, NY; Chair of Genetics, Universitaet Erlangen-Nuernberg, Erlangen, Germany; and SyStemix, Palo Alto, CA.

Submitted May 9, 1995; accepted June 2, 1995.

Supported by National Institutes of Health Grants No. DK33886 and CA26122 to H.B.; DFG: 291/5-4 to G.H.F.; and Buswell Fellowship of the SUNY at Buffalo to S.P.C.

Address reprint requests to Heinz Baumann, PhD, Department of Molecular and Cellular Biology, Roswell Park Cancer Institute, Elm and Carlton Sts, Buffalo, NY 14263.

The publication costs of this article were defrayed in part by page charge payment. This article must therefore be hereby marked “advertisement” in accordance with 18 U.S.C. section 1734 solely to indicate this fact.

© 1995 by The American Society of Hematology.

phenolic acetyl transferase (CAT) gene regulation in HepG2 cells,15 1 μmol/L dexamethasone was included in the treatment medium.

Expression vectors. The expression vectors for the following receptors have been described previously58 and include: human IL-3Ra,16 IL-3Rb,17 IL-3Rc,18 IL-2Rγ,19 IL-4Rα,20 the chimeric construct G-CSFR-gp130(277),9 and rabbit GHR.21 Expression vector composed of mouse JAK322 in pCD2 and rat STAT1 and STAT3 in pSV-Sport1 (GIBCO, Grand Island, NY) have been recently described.23 Human STAT6 (IL-4STAT)24 cDNA provided by Dr S.L. McKnight (Tularik, South San Francisco, CA) was inserted as Not 1 fragment in pCD. Expression vector pEF-BOS-JAK225 was provided by Dr D.M. Wojchowki (Pennsylvania State University, University Park).

CAT reporter gene constructs. Regulation of transcriptional activity was determined by transfecting the CAT gene contained in the vector pCAT-promoter (Promega, Madison, WI). These vectors also carried inserted at its Bgl 2 site either 8 tandem copies of the 27 bp HRRE sequence (=pHRRE-CAT) or 5 tandem copies of the 23-bp IL-6RE sequence from the rat haptoglobin gene (=pIL-6RE-CAT)5,10

Cell transfection and analysis. For analysis of CAT gene regulation, HepG2 cells were transfected with DNA-calcium phosphate precipitates26 containing a total of 20 μg DNA/mL. The DNA mixtures consisted of CAT gene plasmid (10 μg), expression vector for receptors (0.5 to 1 μg), STATs (0 to 3 μg), and JAK2 or JAK3 (0 to 0.1 μg), pIE-MUP (2 μg) served as internal marker for transfection efficiency.27 After a recovery period for 16 hours, the cultures were subdivided into 6-well cluster plates and 24 hours later the subcultures were treated for an additional 24 hours with cytokines. CAT activities were determined in serially diluted cell extracts and normalized to the amounts of major urinary protein derived from the plasmid pIE-MUP and secreted into the medium by the same cell cultures. The values were then calculated relative to the untreated control cultures (defined as 1.0).

Expression of STAT protein and activation by receptors were determined in COS-1 cells that had been transiently transfected with DNA-DEAE dextran.28 The DNA standard mixture contained 10 μg/mL DNA consisting of expression vectors for receptor (0.75 to 1.5 μg), JAKs (0.1 μg), and STATs (0 to 3 μg), pIE-MUP (0.5 μg), and empty vector as filler DNA. The transfected cell cultures were subdivided. After a recovery period of 24 hours, the cells were maintained for 16 hours in serum-free medium followed by 15-minute treatment with and without cytokines.

Electrophoretic mobility shift assay (EMSA). COS-1 cells were washed three times with cold phosphate-buffered saline (PBS), scraped off in PBS containing 1 mmol/L NaVO4, 10 mmol/L NaF, 10 μg/mL leupeptin and aprotinin, and 1 mmol/L phenylmethylsulfonyl fluoride (PMSF). Whole-cell extracts were prepared as described by Sadowski et al29 and directly used for DNA binding reaction. The high-affinity form of the sis-inducible element (SIE) served as a substrate for STAT1 and STAT3.26 The IL-4- and interferon-γ (IFN-
G protein response sequence of the FcyR1 gene, generically termed gamma activator site (GAS), has low affinity to STAT1 and none to STAT3 and was used as a probe for STAT6 (see Figs 3 and 6). The oligonucleotides were end-labeled by kinase reaction. Whole-cell extracts (0.5 to 5 μL) were incubated in 20 μL reaction buffer with 2.5 μg poly(dI-dC) for 15 minutes on ice followed by addition of the probe (20,000 cpm). After 15 minutes at room temperature, 10 μL of the reaction mixture was applied to a 4% polyacrylamide gel in 0.5× TRIS borate EDTA buffer. In all separations, a reaction mixture with extracts from nontransfected rat hepatoma H-35 or COS-1 cells treated with IL-6 served as a marker for the relative mobilities of the DNA-STAT complexes. The SIF-bound protein complexes are referred to as SIF-A (STAT3 homodimer), SIF-B (STAT1-STAT3 heterodimer), and SIF-C (STAT1 homodimer).

Western blot analysis. Equal amounts of whole-cell extract proteins were separated on 6% sodium dodecyl sulfate (SDS)-polyacrylamide gels. The proteins were transferred to Immobilon membrane (Millipore, Bedford, MA), incubated with either rabbit-antihuman STAT1, or rabbit-antimouse STAT3 (Transduction Laboratories), and processed for chemiluminescent (ECL) reaction according to the instructions of the supplier (Amersham, Arlington Heights, IL).

RESULTS AND DISCUSSION

STAT protein activation by box 3-deficient GHR and IL-3R. The GHR and the IL-3R failed to regulate and to activate transcription of IL-6RE–containing gene constructs. Therefore, we determined whether these receptors were inefficient in activating DNA binding activity of STAT proteins or differed from the box 3-containing gp130 in their specificity for STAT proteins. Transiently transfected COS-1 cells served as an assay system for receptor signaling. A representative experiment with transfected GHR is shown in Fig 1. GHR was introduced together with increasing concentrations of expression vectors for rat STAT1, STAT3, or a combination of both. After 15 minutes of treatment with GHR, the profile of activated STAT proteins was visualized by EMSA (Fig 1A). The enhanced level of activated STAT6, a property that we could not detect for the other receptors in our system (data not shown). The activation of STAT6 appeared to be the preferred process of the IL-6R as judged from the almost complete prevention of STAT6 (Fig 3) or STAT1 (data not shown) activation in the presence of equal amounts of STAT6 expression vector. However, the activated STAT6 did not form detectable heterodimers with either STAT3 (Fig 3) or STAT1 identifiable by either EMSA or antibody-mediated supershift EMSA (data not shown).

The results from Figs 1 through 3 indicate that the pattern of STAT proteins activated by a given hematopoietin receptor is, to a large extent, a function of the relative composition of the cellular STAT proteins and, to a lesser extent, a function of the receptor type. These receptor promiscuity for STAT proteins may explain the numerous publications which reported the link to different efficiency of the receptors in engaging the STAT pathway. Therefore, the data allowed us to make only a semi-quantitative assessment of the efficiency of the receptors to activate STAT proteins. Based on data from reconstitution experiments in which equal amounts of expression vector for IL-3R, GHR, and G-CSFR-gp130 were coexpressed in COS-1 cells, we observed a magnitude of STAT activation by the receptors that followed the order G-CSFR-gp130 > IL-3R > GHR. The relatively high activity of gp130 was intuitively attributed to the presence of the box 3 motif that facilitates the receptor-proximal interaction with the STAT pathway.

The COS-1 cell assay system permitted a more precise statement regarding the STAT protein preferences. Four independent reconstitution experiments, as shown in Figs 1 and 2, consistently indicated a more prominent activation of STAT3 than STAT1 by gp130, and a roughly equal activation of STAT3 and STAT1 by the IL-3R.

It appears that hematopoietin receptors, including members of the IL-2R group, generally have the ability to activate both STAT1 and STAT3. Recently, we reported that the IL4R had a relatively minor transcription-controlling effect in the hepatic reconstitution systems but that it can be converted to an IL-6–like receptor by coexpression of JAK3. This finding suggested that the IL-4R may use an alternative STAT activation program via JAK3. Nevertheless, this program converges with the IL-6R pathways directed toward the same genetic target. A STAT activation assay in COS-1 cells with transfected IL-4R (Fig 3) showed a similar STAT1 and STAT3 activation as noted with GHR, IL-3R, and gp130. However, as predicted, the IL-4R also efficiently used STAT6, a property that we could not detect for the other receptors in our system (data not shown). The activation of STAT6 appeared to be the preferred process of the IL-4R as judged from the almost complete prevention of STAT3 (Fig 3) or STAT1 (data not shown) activation in the presence of equal amounts of STAT6 expression vector.

JAKs enhance activation of STAT proteins. The current model of hematopoietin receptor action proposes that receptor-associated members of the JAK family are involved in the recruitment of STAT proteins to the receptors. The STAT proteins are activated to function as mobile messengers towards the target DNA sequence.
A

STAT1

STAT3

SIF-A

SIF-B

SIF-C

IL-3

G-CSF

B

Anti STAT1

Anti STAT3

0 0.1 0.3 1 3 pSV-STAT1 (μg/ml)

0 0.1 0.3 1 3 pSV-STAT3 (μg/ml)

Fig 2. Activation of STAT proteins by IL-3R. COS-1 cell cultures in 16 10-cm dishes were transfected with the expression vector for IL-3Ra and -p or G-CSFR-gp130 (1 μg/mL), and STAT1 and STAT3 (gradient from 0.1 to 3 μg/mL, as schematically indicated at the top). The cells cultures were divided and treated for 15 minutes with IL-3 or G-CSF. (A) Same amount of cell extract from each series was reacted with SIE and separated in parallel on two gels. IL-6-treated H-35 cells served as marker for rat SIF-A, -B and -C complexes. After 16 hours of exposure, the autoradiograms of the gel section showing the DNA-protein complexes are reproduced. (B) Selected series of the cell extracts from (A) are analyzed in duplicate by Western blotting for expression of STAT1 or STAT3.

Fig 3. STAT activation by IL-4R. COS-1 cells in 24 6-cm dishes were transfected with expression vectors for IL-2Rγ and IL-4Rα (1 μg/mL) and combinations of STAT1, STAT3, and STAT6 (gradient from 0.1 to 3 μg/mL or constant 3 μg/mL). As schematically indicated, all cell cultures were treated for 15 minutes with IL-4. Each cell extract was reacted with SIE and all those containing STAT6 also with GAS. The standard (Std) represents extract of IL-6-treated H-35 cells. The complexes were electrophoresed in parallel on two separate gels. The autoradiograms show the section with the DNA-protein complexes after a 16-hour exposure.

was used to assess the efficiency and "specificity" of JAK2 and JAK3 to modulate the STAT signaling by the receptors used in Figs 1 through 3. The combination of JAK2 and GHR showed two important features (Fig 4A): (1) by increasing the concentration of intracellular JAK2, GHR gained the ability to activate more efficiently the endogenous STATs (STAT1 predominates in COS-1 cells [see Fig 1B]), as well as ectopically expressed rat STAT1 and STAT3; and (2) the STAT protein activation depended on the relative amount of JAK2 expression vector used, was either in part or completely independent of ligand activation, and correlated with the amount of overexpressed GHR. By Western blot analysis (Fig 4B), we verified that the JAK2 effect in the transfected cell cultures was not caused by an enhanced expression of STAT proteins. Essentially the same JAK2 action was observed in combination with IL-3R (Fig 5). This experiment also illustrated the activation of both endogenous and transfected STAT proteins, which led to the appearance of an SIF-B-like complex most likely representing a heterodimer of rat STAT3 and primate STAT1.

In contrast to GHR and IL-3R, the signaling action of the IL-4R was minimally affected by JAK2 (data not shown). When provided excess JAK3, however, a drastic increase in the activation of STAT1 and STAT3, but not STAT6, was evident (Fig 6). The effects of JAK3 were comparable to those induced by JAK2 with GHR, or IL-3R. The data from Figs 4 through 6 indicate that JAKs perform the predicted function as an intermediary between the receptor and STAT
Fig 4. Effect of JAK2 on STAT protein activation by GHR. COS-1 cells in 6-cm dishes were transfected with the expression vector for GHR (1 μg/mL), and combinations of STAT1, STAT3 (3 μg/mL), and JAK2 (0.1 μg/mL) as indicated. Each culture was subdivided. The subcultures were treated for 15 minutes with medium alone or with GH, extracted, and subjected to EMSA (A). Selected extracts were also used for Western blot analysis of STAT1 and STAT3 (B). The data indicate that coexpression of JAK2 does not modify the level of STAT proteins. Moreover, the analysis did not show a cytokine-induced shift in STAT protein mobility.

pathways. The function was not specific for either the receptors (with the exceptions of the JAK3 for IL-2Rγ-containing cytokine receptor) or to the STAT proteins. It appears that the cellular concentration of the JAKs is an important determinant of the level of active STAT proteins attainable by a given receptor system. Under conditions of excess JAK expression, the receptor gained ligand-independent STAT signaling, which can exceed that achieved by ligand-stimulated receptor in the absence of cotransfected JAKs and STATs by several hundred-fold. These results also suggest that enhancement of the relative concentration of the signaling protein has the potential to introduce a receptor response that was not triggered by ligand nor mimicked by receptor mutation.

JAKs and STATs contribute to transcriptional induction of target genes. The observation that JAK3 together with the IL-4R appreciably enhanced activation of various STAT isoforms provided a potential explanation for the prominent stimulation of transcription achieved in HepG2 cells. Through the transfected IL-4R, JAK3 enhanced the activation of the HepG2 cell-resident STAT proteins, in particular STAT3, and via a still undefined mechanism of the induction of transcription via the IL-6RE. We hypothesized that receptors capable of interacting with the signaling machinery of the host hepatic cells, but lacking the STAT interaction motif (ie, box 3), were unable to recruit sufficient STAT3 necessary to mediate transcriptional activation via the IL-6RE. A separate mechanism, not apparently dependent on STAT3, was sufficient for activation via the HRRE gene regulation.

Taking into consideration the results of the COS-1 cell assays (Figs 1 through 6), we predicted that a reconstitution of the GHR, IL-3R, and IL-4R in HepG2 cells by complementation with STATs will introduce an IL-6RE–specific transcriptional induction. Moreover, the combination of JAK2 with GHR or IL-3R should yield a similar transcription-controlling effect, and this effect should be comparable to that found with the combination of JAK3 with IL-4R. If the predicted two-signal model of hematopoietin receptors indeed applies, then the enhanced JAK, but not STAT3, level may also increase transcription via the HRRE. This is expected, especially for those receptors that display low activity in transfected hepatic cells.

Fig 5. JAK2 enhanced STAT activation by IL-3R. COS-1 cells were transfected with expression vectors for IL-3Rα and β (1 μg/mL each). Some cultures also received expression vectors for JAK2 (0.1 μg/mL) or STAT3 (5 μg/mL) as indicated at the top. Extracts were subjected to EMSA using SIE as a probe.
As shown in the representative examples (Fig 7), transcriptional stimulation through the IL-6RE was achieved with STAT3 and JAK2. IL-3R, together with STAT3 but not STAT1, produced an IL-6R-like action on the IL-6RE (Fig 7A). The signaling event was shown to depend on the IL-3Rβ subunit, which was shared with GM-CSFR and IL-3R. Therefore, a similar STAT3 action could also be reconstituted by transfecting the combination of GM-CSFRα and IL-3Rβ (Fig 7B). As anticipated, supplementation of the IL-4R with STAT3 was equally effective (Fig 7B). Surprisingly, STAT6 proved to be inactive in transcriptional control.

Dose-response analysis (Fig 8A, right panel) indicated that maximal receptor action was attained when a ratio of receptor expression vector to STAT3 expression vector of approximately 10:1 was applied. In several experiments, reconstitution of the GHR response was substantially lower than that of the IL-3R or the IL-4R. At present, we do not know whether this is due to low GHR expression in HepG2 cells and/or to a low STAT activating action of the transfected GHR.

Although STAT overexpression enabled the transfected receptors to stimulate transcription via the IL-6RE, it did not enhance the signaling via the endogenous IL-6R (Figs 7 and 8A) or transfected G-CSFR-gp130 (data not shown). Similarly, transfection of either STAT1 or STAT3 could not significantly modulate the signaling by the box 3-containing receptors. Transfection of IL-3R or GHR with JAK2 mediated a transcriptional induction via the IL-6RE that was similar in magnitude to the ones achieved by STAT3 (Fig 7A and Fig 8A, left panel). Expression of JAK2 was accompanied by a significant increase of basal expression of the reporter gene constructs. This effect became particularly prominent when the concentration of transfected JAK2 vector exceeded 1 μg/mL. The receptor specificity of JAK2 action was shown by the failure of the kinase to increase gene expression above that of control cells in cells transfected with IL-4R (Fig 8A).

Both the changes in basal activity and the cytokine response mediated by JAK2 were interpreted to be the results of elevated activity of the endogenous STAT proteins (Fig 4). This interpretation is supported by the observation of an additive...
action of transfected JAK2 and STAT3 (Figs 7 and 9, upper panel). As noted with STAT3, the cells transfected with JAK2 did not show an improved IL-6R signaling (Fig 8A), suggesting that the signal transduction by the endogenous IL-6R or transfected gp130 constructs was already maximally activated by the pre-existing transcription control mechanisms.

The reconstitution experiments with IL-3R, GHR, and IL-4R have yielded an assay for transcriptional gene expression by STAT3. This regulatory mechanism was not caused by a change in binding activity of the receptor α subunit as shown by the cytokine dose response (Fig 8B). The half-maximal stimulation of the transcription through the IL-6RE was achieved with cytokine concentrations between 0.1 and 1 ng/mL and is in agreement with concentrations needed for half-maximal proliferation of cell responses.27

The transcriptional control through the HRRE differed from that through IL-6RE in that it was not affected by STAT3 overexpression (Fig 9). In contrast, JAK most notably increased the HRRE regulation with GHR. The action of IL-3R without additional JAK2 was already at a high level, thus not producing any prominent increase. These results were interpreted to indicate that the transcriptional induction via the HRRE was mediated by JAK or other receptor-recruited kinases but that the substrates of these kinases do not detectably involve STAT3. Possible substrates may include other STAT isoforms or constituents of signaling pathways believed to mediate the stimulation of immediate growth response genes. Likely candidates of such non-STAT pathways include signaling route from Shc (or IRS-1) to Grb-2, Ras, and MAPK.30 Association of the hematopoietin receptors, such as GHR, IL-3R, IL-4R with signaling molecules of these pathways, has been detected.30-45 The molecules that interact with the transcriptional control element, eg, HRRE, and cause the transcriptional activation of the gene linked in cis remain to be identified.

In this study, the successful reconstitution of the transcriptional control of several hematopoietin receptors using STAT3 as a mediator was shown. The data clearly support the notion that separate receptors use common, apparently ubiquitous, signaling pathways. The biochemical link of the receptor to the JAK/STAT pathway does not appear to be as specific as was suspected.46 Important determinants for the signaling specificity have emerged: the combinations and the relative concentration of the constituents of the JAK/STAT pathway expressed in the host cells and the relative activity and preference of the receptor subunits to recruit and activate the signal initiation molecules.

ACKNOWLEDGMENT

We thank Dr S.L. McKnight for providing STAT6 cDNA; Drs B.A. Witthuhn and J.N. Ihle for JAK3 cDNA; Dr A. Lopez for the
IL-3/β receptor expression vector; Dr D.M. Wojchowski for the JAK2 expression vector; Immunex Corp., Genentech, and Genetics Institute for generous supply of cytokines; Dr F. Meyer for IL-3 and GM-CSF; and Marcia Held for secretarial assistance.

REFERENCES


34. Thomas MJ, Gronowski AM, Berry SA, Bergad PL, Rotwein P: Growth hormone rapidly activate rat serine protease inhibitor 2.1 gene transcription and induces a DNA binding activity distinct from those of STAT1, -3 and -4. Mol Cell Biol 15:12, 1995


44. Welham MJ, Duronio V, Leslie KB, Bowtell D, Schrader JW: Multiple hemopoietins, with the exception of interleukin-4, induce modification of Shc and mSos1, but not their translocation. J Biol Chem 269:21165, 1994


Receptors for interleukin-3 (IL-3) and growth hormone mediate an IL-6-type transcriptional induction in the presence of JAK2 or STAT3

Y Wang, KK Morella, J Ripperger, CF Lai, DP Gearing, GH Fey, SP Campos and H Baumann