



## SOCS negative regulation of the JAK-STAT pathway

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### Abstract

The Janus kinase (JAK)-signal transducer and activator of transcription (STAT) canonical signal transduction pathway is activated primarily by cytokines, hormones, and growth factors and has been shown to play a role in many intracellular processes including cell differentiation, adaptive and innate immune responses, and cell growth. The JAK-STAT pathway has also been implicated to affect a wide variety of hematologic and non-hematologic diseases such as cancer and renal disease. JAK-STAT pathway activation is achieved through extracellular ligand binding resulting in transcription factor and receptor interactions and subsequent gene expression. Given the importance of the JAK-STAT pathway in human cellular functions, the regulation of this signal transduction pathway is vitally important. The current review focuses on the JAK-STAT pathway as well as the structure and function of the primary negative regulatory proteins of the JAK-STAT pathway, the suppressors of cytokine signaling (SOCS) proteins. SOCS proteins facilitate the negative regulation of signal transduction pathways by targeting specific signaling components for proteosomal destruction. Understanding the role of SOCS proteins in disease progression is of great importance to microbiologists and immunologists. Much research is directed at identifying and developing specific JAK-STAT inhibitors and SOCS inhibitors that may prove useful in counteracting the cellular effects observed in many carcinomas and infectious diseases.

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## Introduction

Cytokines are important regulators of the immune system. These cell-to-cell chemical messengers are small molecular weight proteins secreted by leukocytes and other immune cells that bind to extracellular receptors on the surface of target cells to initiate signal transduction pathways (Taniguchi, 1995). Signal transduction pathways lead to the modulation of gene expression in the nucleus. Cytokine-specific proteins produced as a result of gene expression mediate critical biological effects in response to the stimulatory signal. Generally, cytokines exert a multitude of specific effects on the cells of the immune system such as promoting cell proliferation, cell differentiation, hematopoiesis, cell death, and initiating host defense mechanisms (Ishihara and Hirano, 2002).

## JAK-STAT pathway

The Janus kinase/signal transducers and activators of transcription (JAK/STAT) pathway is the major pathway for cytokine signaling and immune system development (Liongue, O'Sullivan, Trengove, Ward, 2012). Intracellular signaling events in the JAK/STAT pathway led to the observed cellular functions associated with specific ligands. The Janus kinase family of nonreceptor tyrosine kinase proteins are tyrosine kinases that associate with cytokine receptor subunits. In the case of the IFN- $\gamma$  signaling pathway, activation involves two members of the JAK tyrosine family, JAK1 and JAK2 (Kotenko and Pestka, 2000). Upon ligand binding dimerization of the receptor subunits occur, bringing the two JAK molecules in close proximity allowing for their autophosphorylation and subsequent IFN- $\gamma$  receptor activation. Once activated, JAK molecules phosphorylate the receptor subunit. JAK-mediated phosphorylation of specific residues on the receptor subunit provides unique docking sites for the STAT1 monomers, which bind to a phosphotyrosine on the receptor subunit through src homology domain 2 (SH2), a highly conserved domain located on STAT.

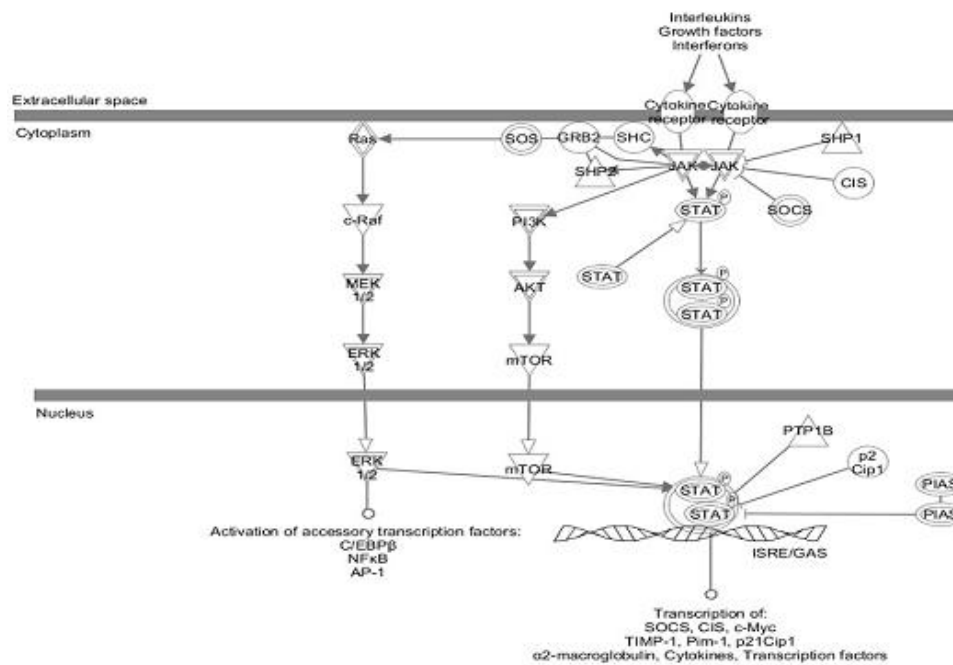
proteins. JAK proteins then phosphorylate STAT1 at specific tyrosine residues (Horvath, 2000; Kisseleva *et al.*, 2002). Additional phosphorylation of STAT1 at serine residue 727 is required for transcriptional activity. Phosphorylation of STAT1 causes the molecule to be translocated to the nucleus by as yet unknown mechanisms (Fig. 1). Following translocation to the nucleus, STAT1 bind to gamma-activating sequences (GAS) and activates transcription of IFN- $\gamma$  cellular response genes (Johnson *et al.*, 1994; Samuel, 2001). Dysregulation of the JAK-STAT pathway was recently shown to contribute to renal fibrosis and excessive proliferation and growth of glomerular mesangial cells, contributing to diabetic nephropathy (Chuang and He, 2010; Marrero *et al.*, 2006). Extensive research has also generated interesting data on the role of the JAK-STAT pathway in the progression and survival of several human carcinomas including prostate cancer, gliomas, and oesophageal squamous cell carcinoma (Liu *et al.*, 2012; Verma *et al.*, 2003; You *et al.*, 2012).

## Janus kinase

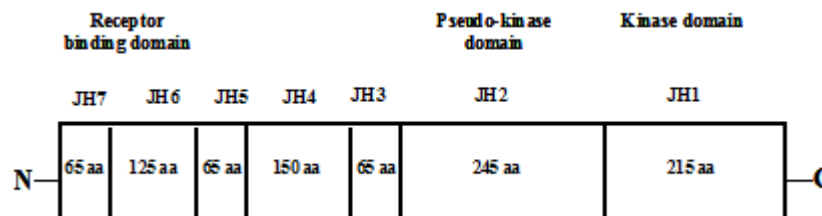
The mammalian family of JAK nonreceptor tyrosine kinase proteins contains four members: JAK1, JAK2, JAK3, and Tyk2. JAK proteins (>1000 amino acids) are approximately 120 to 130 kDa cytosolic proteins expressed in many types of tissue with the exception of JAK3 whose expression is restricted to natural killer cells and thymocytes (Leonard and O'Shea, 1998; Stark and Darnell, 2012). Members of the JAK protein family contain highly conserved structural domains designated JAK homology domains (JH). There are currently seven known JH domains (JH1-JH7). JH1 is the functional catalytic kinase domain based on sequence homology with other known tyrosine kinases. This domain consists of approximately 200 amino acid residues (Kisseleva *et al.*, 2002). For JAK2, the JH1 domain possesses a critical activation loop that becomes phosphorylated in order to activate the kinase molecule. In 1997, Feng *et al.* demonstrated that phosphorylation of tyrosine residue (Y1007) in the activation loop of JAK2 was essential for JAK2

activation and downstream signaling events using *in vivo* and *in vitro* kinase reactions. The model of JAK activation suggests that in the absence of phosphorylation in the activation loop that substrates (e.g., receptor subunits) and ATP are unable to bind to the JAK molecule, however, after phosphorylation has

occurred on Y1007 a conformational change in the activation loop allows substrates access to specific binding sites in the catalytic groove (Yasukawa, 1999). JH2 is a non-functional catalytic kinase domain consisting of approximately 200 amino acid residues.



**Fig. 1.** Generalized schematic of the JAK-STAT signaling canonical pathway derived from Ingenuity Pathways Analysis (IPA). Shapes denote different cellular molecules: enzymes ( $\diamond$ ), transmembrane receptor ( $\square$ ), kinases ( $\nabla$ ), complex ( $\square$ ), phosphatases ( $\triangle$ ), and other ( $\circ$ ). The JAK-STAT pathway is activated following ligand binding to specific receptors resulting in activation of JAK and STAT molecules. Following translocation of activated STAT dimers to the nucleus, STAT dimers bind to DNA and initiate gene transcription. Arrows correspond to the following relationships: acts on ( $A \rightarrow B$ ), inhibits ( $A \dashv B$ ), leads to ( $A \rightarrow \odot B$ ), translocates to ( $A \rightarrow \triangleright B$ ), and direct interaction ( $A \text{ --- } B$ ).



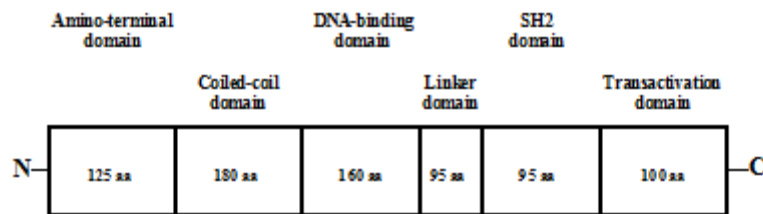
**Fig. 2.** General domain schematic of the Janus Kinase (JAK) protein family. The JAK tyrosine kinase protein family contains four members: JAK1, JAK2, JAK3, and TYK2. Each JAK molecule contains seven distinct regions: JH1-JH7. The JH1 domain is the functional kinase domain that following receptor binding to an appropriate ligand becomes phosphorylated on a specific tyrosine residue (Y1007). The JH2 domain is the pseudo-kinase domain. This domain is believed to play a role in the autoregulatory activities of JAK proteins. The JH6-JH7 domains mediate binding of JAK molecules to cytokine receptor proteins. Adapted from Leonard, 2001.

For JAK2, the JH1 domain possesses a critical activation loop that becomes phosphorylated in order to activate the kinase molecule. In 1997, Feng *et al.* demonstrated that phosphorylation of tyrosine residue (Y1007) in the activation loop of JAK2 was essential for JAK2 activation and downstream signaling events using *in vivo* and *in vitro* kinase reactions. The model of JAK activation suggests that in the absence of phosphorylation in the activation loop that substrates (e.g., receptor subunits) and ATP are unable to bind to the JAK molecule, however, after phosphorylation has occurred on Y1007 a conformational change in the activation loop allows substrates access to specific binding sites in the catalytic groove (Yasukawa, 1999). JH2 is a non-functional catalytic kinase domain consisting of approximately 200 amino acid residues. Although the JH2 domain bears sequence homology to typical tyrosine kinase domains, this domain lacks catalytic activity and therefore is termed the pseudokinase domain. Both the JH1 and JH2 domains are located near the carboxy terminus and comprise the major portion of the JAK molecule (Aringer, 1999; Leonard, 2001; Kisseleva *et al.*, 2002). The JH3-JH5 domains on the JAK molecule are poorly understood and require additional work to elucidate their putative functions. JH6-JH7, amino terminal domains, have been implicated to be important in the association between the JAK molecule and specific cytokine receptors (Kisseleva *et al.*, 2002). Fig. 2 shows a generalized domain schematic of JAK proteins. JAK1<sup>-/-</sup> mice exhibit a lethal phenotype shortly after birth probably resulting from incomplete neuronal development. JAK1<sup>-/-</sup> mice do not respond to cytokines important in neuronal development such as leukemia-inhibitory factor (LIF) and ciliary neurotrophic factor (CNTF). Also, JAK1<sup>-/-</sup> mutant cells do not respond to IL-6, IL-11, IFN- $\gamma$ , IFN- $\alpha$ , IFN- $\beta$ , IL-13, IL-10, IL-2, IL-4, IL-7, IL-9, or IL-15 (Leonard, 2001).

JAK2<sup>-/-</sup> mice exhibit an embryonic lethal phenotype probably due to a block in erythropoiesis (Parganas *et al.*, 1998). JAK2<sup>-/-</sup> mutant cells do not respond to stimulatory signals from IL-3, IL-5, IFN- $\gamma$ , or erythropoietin. JAK3<sup>-/-</sup> mice show defects in lymphoid development, B cell maturation, and thymocyte proliferation. JAK3<sup>-/-</sup> cells fail to respond to cytokines that share the common receptor chain,  $\gamma c$ . These cytokines include: IL-2, IL-4, IL-7, IL-9, and IL-15. Recent data regarding TYK2<sup>-/-</sup> mice reveal that loss of TYK2 *in vivo* lead to mice with reduced antiviral activity and a marked decrease in T cell responses. Additionally, TYK2<sup>-/-</sup> cells fail to respond to IL-12 and respond weakly to IFN- $\alpha$ , IFN- $\beta$ , and IL-10. While JAK knockout mice exhibit lethal phenotypes, cells from JAK knockout mice are viable in culture but are unresponsive to particular cytokines (Karaghiosoff *et al.*, 2000).

### Signal transducers and activators of transcription

Signal transducers and activators of transcription (STAT) proteins are a family of latent cytoplasmic transcription factors that act downstream of JAK activation and mediate intracellular signaling from a wide variety of cytokines, growth factors, and hormones. Currently, seven STAT proteins have been discovered in mammals STAT1, STAT2, STAT3, STAT4, STAT5a, STAT5b, and STAT6 (Leonard, 2001). Structurally, all seven STAT proteins share six conserved domains: amino-terminal domain, coiled-coil domain, DNA-binding domain, linker domain, SH2 domain, and the transactivation domain (Horvath, 2000). STAT proteins are variable in length and contain approximately 700-900 amino acid residues (Fig. 3).



**Fig. 3.** General domain schematic of the Signal Transducer and Activator of Transcription (STAT) protein family. The STAT protein family contains seven members: STAT1, STAT2, STAT3, STAT4, STAT5A, STAT5B, and STAT6. STAT molecules share similar structural homology and consist of six domains. The SH2 domain is critical for binding to the phosphorylated tyrosine residues on the cytokine receptor. The transactivation domain contains tyrosine and serine molecules that become phosphorylated following ligand stimulation leading to activation of the cytoplasmic transcription factor. The DNA-binding domain recognizes unique cytokine specific DNA sequences in the nucleus. Adapted from Leonard, 2001.

The transcriptional activator domain (TAD) is located in the carboxy terminus and contains the appropriate tyrosine (Tyr701 - STAT1) or serine (Ser727 - STAT1) residue that undergoes phosphorylation by protein kinases to activate the STAT protein. The SH2 domain (Src homology 2) contains approximately 100 amino acid residues. This domain preferentially binds to phosphorylated tyrosines on proteins. The SH2 domain allows the STAT molecule to function as a docking protein where it binds to the cytoplasmic region of the cytokine receptor at a specific phosphotyrosine-containing residue and activated via JAK-mediated phosphorylation on tyrosine residue Tyr701 (Horvath, 2000). The SH2 domain also mediates dimerization with another activated STAT protein. STATs form homodimers or heterodimers which enter the nucleus and bind DNA at specific sequences and stimulate transcription of ligand specific genes. STAT dimers preferentially bind to gamma interferon activated site (GAS) sequences, promoter element for IFN- $\gamma$  response genes, in the nucleus. These sites are denoted by a consensus sequence, TTNCNNNA. The linker domain is located between the SH2 domain and the DNA-binding domain and may play a role in the regulation of transcription mediated by IFN- $\gamma$  (Horvath, 2000). As the name would imply, the DNA-binding domain is

responsible for nucleotide base recognition on the DNA molecule at specific sequences in the promoter of cytokine related genes. The coiled-coil domain of the STAT molecule is important for binding to transcriptional regulators (e.g., IRF-9) and may be responsible for nuclear export of STAT. The amino-terminal domain plays a role in the binding affinity of STAT homodimers or heterodimers bound to the DNA molecule, nuclear translocation, and binding of transcriptional coactivators such as CBP/p300 (Horvath, 2000).

Studies in which STAT genes have been mutated or targeted have provided essential details into the precise functions of these transcription factors. STAT1 knockout mice fail to respond to type I or type II interferons confirming that STAT1 proteins play a significant role in interferon mediated biological responses. STAT2 knockout mice also failed to produce a biological response to type I interferons (Leonard, 2001). The STAT3 knockout mouse exhibits an embryonic lethal phenotype and fails to respond to IL-6 and IL-10 signaling. STAT4 knockout mice fail to respond to IL-12 mediated signaling. STAT5a and STAT5b knockout mice fail to respond to growth hormone and prolactin stimulation respectively, while STAT6 knockout mice are defective in IL-4 and IL-13 signaling. STAT6  $-/-$  mice demonstrate a decrease in

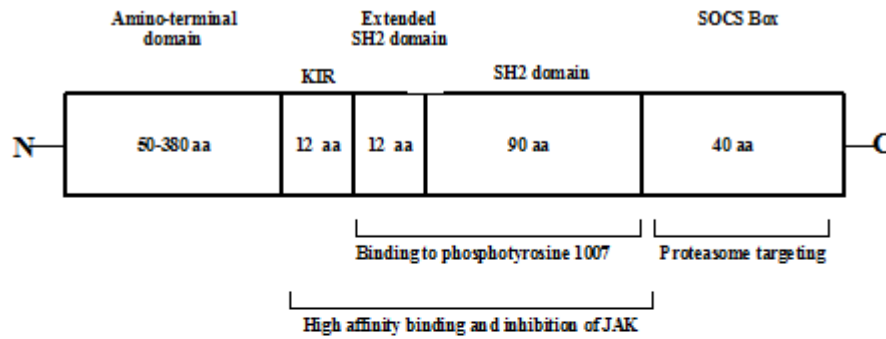
their ability to form T<sub>H</sub>2 (T helper 2) T-cell populations and a reduction in B-cell proliferation (Leonard, 2001).

### **Negative regulation of the JAK-STAT pathway and SOCS proteins**

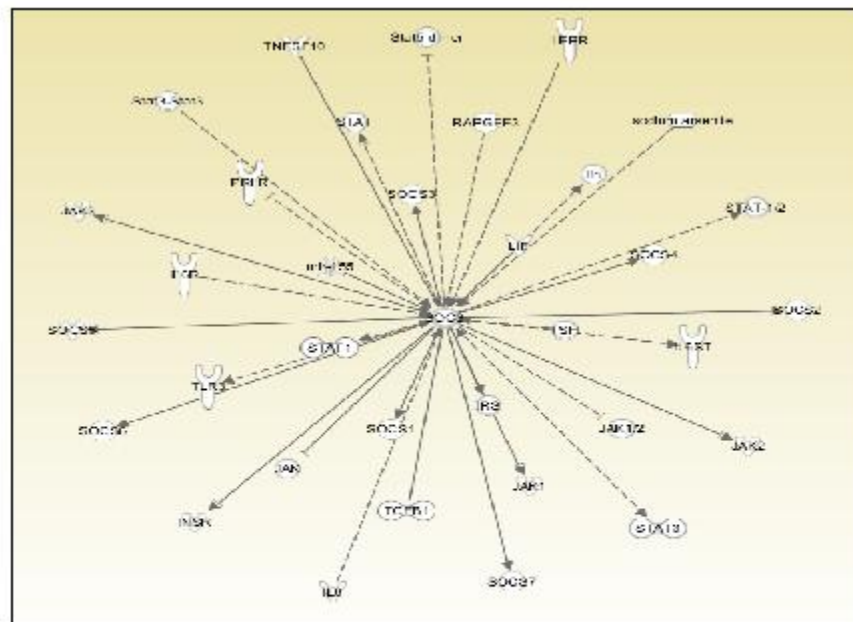
The activity of JAK tyrosine kinases, and consequently signaling via the JAK-STAT pathway, is negatively controlled by members of the suppressors of cytokine signaling family (SOCS). Currently, there are eight identified members of the inducible SOCS family, SOCS1 to SOCS7 and CIS (Alexander, 2002). SOCS1, SOCS3, and CIS have been extensively studied while data regarding the other SOCS proteins is relatively scarce. SOCS proteins inhibit the JAK-STAT pathway by blocking activation of JAK molecules by directly binding to JAK molecules or molecules of the cytokine receptor complex. SOCS1 contains approximately 200 amino acids and has a predicted molecular weight of 24 kDa. A unique feature of SOCS proteins is that they can only bind to phosphotyrosine residues. Of the eight identified members of the SOCS protein family relatively little is known about SOCS4-SOCS7, therefore the current review will primarily focus on SOCS1 and SOCS3, the most studied SOCS proteins. Several SOCS proteins (e.g., SOCS1) inhibit cytokine activity by binding to the activated receptor and competing with STAT for binding sites to the activated cytokine receptor. By blocking STAT docking sites, activation of STAT molecules are inhibited and the resulting cytokine-mediated signal is terminated. SOCS proteins contain three important structural domains (Fig. 4). The SOCS family of regulatory proteins contain a 12-amino acid region called the kinase inhibitory region (KIR) which is located near the amino-terminal domain, a centrally located SH2 domain that acts in part with KIR, and a SOCS box located near the carboxy-terminal region and thought to play a role in targeting proteins bound to SOCS proteins for proteasomal degradation (Alexander, 2002; Fujimoto and Naka, 2003). An additional 12-amino acid region located downstream of the SH2 domain (extended SH2 domain) is also critical for

SOCS function in cells. Mutations in isoleucine (I) at position 68 and leucine (L) at position 75 abrogated or reduced the binding between SOCS and JAK proteins suggesting that these two amino acid residues in the extended SH2 domain are responsible for binding affinity between the SOCS and JAK molecules. Moreover, mutations of amino acid residues at positions 56(F), 59(F), 64(D), or 65(Y) abolish inhibitory functions and reduce binding suggesting that amino acids located in the KIR domain are essential for the suppressor actions of SOCS proteins.

It has been suggested that the KIR region structurally mimics the activation loop of the JH1 region of JAK and thereby inhibit JAK function by serving as a nonfunctional analogous substrate (Larsen and Röpke, 2002). The amino-terminal region contains a variable length domain, which shows very little sequence homology to other SOCS proteins. It was shown by analysis of amino acid sequences that SOCS1 and SOCS3 are more closely related to each other than other SOCS proteins. As stated previously, much less information is known about SOCS4-7, compared to SOCS1 and SOCS3. Protein sequence data however, demonstrates that SOCS4 and SOCS5 share a higher sequence similarity and that SOCS6 and SOCS7 share amino acid sequence similarity when compared to other members of the SOCS proteins (Hilton *et al.*, 1998). Additionally, the N-terminal regions of SOCS4-SOCS7 are extended compared to SOCS1 and SOCS3. The extended N-terminal regions may assist in providing supplementary levels of negative regulation not observed in other SOCS proteins. Homology of primary amino acid sequences may account for overlapping biological properties (Hilton *et al.*, 1998). Specifically, both SOCS1 and SOCS3 bind to JAK tyrosine kinases as determined using immunoprecipitation studies following cytokine stimulation of various cell lines. In addition, human SOCS proteins share high amino acid sequence similarity with both mice and rats suggesting a conserved function in other mammalian species (Larsen and Röpke, 2002).



**Fig. 4.** General domain schematic of the Suppressor of Cytokine Signaling (SOCS) protein family. SOCS proteins contain four distinct regions: amino-terminal domain, SH2 domain, extended SH2 domain, and the SOCS box. The central SH2 domain binds to a phosphorylated tyrosine residue on Janus kinase (JAK) or receptor proteins. The 12-amino acid region, extended SH2 domain, which extends from the SH2 domain contains essential residues for SOCS binding. An additional 12-amino acid region called the kinase inhibitory region (KIR) is located in the amino-terminal region and is critical for kinase inhibition. The 40-amino acid residue SOCS box is thought to mediate proteasomal degradation of the SOCS molecule and its associated JAK kinase binding partner. Adapted Larsen and Röpke, 2002.



**Fig.-5.** Gene network for SOCS generated using Ingenuity Pathway Analysis (IPA). Shapes denote different cellular molecules: cytokines/growth factor (Y), complex (O), transcription regulator (M), chemical (C), microRNA (Q), transmembrane receptor (V), and other (O). Arrows correspond to the following relationships: acts on (A)→(B), inhibits (A)→(B), acts on and inhibits (A)→(B), direct interaction (A)---(B), and indirect interaction (A)---(B).

SOCS1 and SOCS3 are found in a wide variety of mammalian tissues such as the spleen, lungs, and liver and are relatively undetected in cells unstimulated by cytokines. However, following stimulation from a diverse array of cytokines, SOCS mRNA expression is readily detectable following analysis of gene expression (Sakamoto *et al.*, 1998; Fujimoto and Naka, 2003). Expression of SOCS1 and SOCS3 is usually rapid (30 min) and typically persists for several hours ( $\leq 8$  hours). Emanuelli *et al.* (2000) showed that SOCS genes contain STAT-binding regions using electrophoretic mobility shift assays (EMSA) providing compelling evidence that SOCS proteins are primarily induced by STAT molecules via interaction with specific SOCS genes. SOCS proteins regulate biological activity of cytokine signal transduction in negative feedback loops by inhibiting or attenuating activation of JAK or STAT molecules, reducing STAT translocation to the nucleus, reducing STAT homo- or heterodimerization, and reducing transcription of cytokine specific response genes (Larsen and Röpke, 2002). In addition, despite their name SOCS proteins have also been shown to be induced by hormones such as insulin. Previous work has demonstrated that insulin stimulation of murine adipocytes is capable of increasing SOCS3 mRNA expression (Emanuelli *et al.* 2000). Fig. 5 shows predicted and known SOCS molecular associations based on bioinformatics analysis.

Employing transfection studies using truncated SOCS1 deletion mutants, it was shown that SOCS1 specifically binds to the phosphorylated tyrosine residue 1007 in the activation loop of the cytoplasmic kinase protein.

Specifically, it was shown for SOCS1 and SOCS3 that the SH2 domain, an extended SH2 domain, and the kinase inhibitory region are necessary for the inhibition of JAK-mediated signal transduction (Larsen and Röpke, 2002). These studies demonstrated that the SH2 domain is necessary for binding but alone does not contribute to the kinase inhibitory properties of the molecule. It is now known that while SOCS1 interacts directly with JAK proteins,

SOCS3 must first bind to the activated receptor subunits to mediate its suppressive effects on JAK molecules.

Interestingly, SOCS induction is not specific to the JAK-STAT pathway. Ohya (1997) demonstrated the induction and association of SOCS1 with a novel nonreceptor tyrosine kinase molecule known as Tec. Tec is believed to play a primary role in T cell function and development (Lucas *et al.*, 2003). Since SOCS proteins negatively regulate signal transduction pathways associated with hematopoietic cell development, differentiation, and proliferation it is not surprising that defective SOCS proteins may play a role in a variety of diseases associated with uncontrolled cytokine signaling (Alexander, 2002). It was shown by Alexander and others (1999) that mice lacking a functional SOCS1 gene (SOCS1  $-/-$ ) die within a month of birth with a clinical condition characterized by lymphopenia, T cell activation, and liver necrosis. Conversely, SOCS3 knockout mice die during embryogenesis due to defects in placental development (Roberts *et al.*, 2001). Additionally, based on the biological role of SOCS proteins it is conceivable that SOCS1 and other SOCS proteins may play key therapeutic roles in many human abnormalities (Kubo *et al.*, 2003). An example of the use of SOCS1 as a potential therapeutic was demonstrated in the TEL-JAK2 model system (Peeters *et al.*, 1997; Monni *et al.*, 2001; Frantsve *et al.*, 2001; Ho *et al.*, 2002). TEL-JAK2 an oncogene, associated with human leukemia, arises from a chromosomal translocation leading to the fusion of the carboxyl-terminal segment of the JAK2 gene and the amino-terminal segment of the TEL gene. The resulting fusion product known as the TEL-JAK2 fusion protein contains the necessary domain required for JAK2 autophosphorylation (JH1) and thereby renders JAK2 constitutively active in cells leading to malignant cell proliferation. In the hematopoietic cell line Ba/F3, SOCS1 was shown to act as a potent tumor suppressor and shown to effectively inhibit the kinase activity of the TEL-JAK2 fusion protein *in vitro*



(Lacronique *et al.*, 1997). Recently, exploration into the efficacy of modulating SOCS proteins for therapeutic benefit has been the topic of several research studies. Zhang and others (2012) investigated the potential of using SOCS1 as a molecular marker and chemotherapeutic target in cancer identification and cancer therapy. Other researchers have studied the utilization of SOCS1 to treat autoimmune diseases such as multiple sclerosis primarily by inhibiting Th17-cell differentiation and related disease-promoting cytokines (Ramgolam and Markovic-Plese, 2011). Moreover, it was recently determined that viruses induce SOCS protein expression to block antiviral signal transduction pathways and thereby facilitate virus survival in the host cell (Akhtar and Benveniste, 2011). It is clear that targeting specific signal transduction mechanisms using SOCS proteins as a therapeutic approach represents an exciting field of research with numerous potential benefits.

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