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Transcriptional regulation by STAT6

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Abstract

Signal transducer and activator of transcription (STAT) proteins are critical mediators of cytokine signaling. Among the seven STAT proteins, STAT6 is activated by IL-4 and IL-13 and plays a predominant role in the immune system. However, there is increasing evidence that STAT6 may function in other tissues and organ systems. IL-4, IL-13, and STAT6 promote humoral immunity, clearance of helminthic parasites as well as the pathogenesis of allergic disorders like asthma, food allergies, and atopic dermatitis. In this review, we will describe our current understanding of the biological functions of STAT6 and summarize recent advances in understanding the molecular mechanisms by which STAT6 regulates transcription.

Keywords

Signal transducer and activator of transcription 6; Interleukin-4; Gene expression; Transcription factors; Co-activators

Introduction

STAT6 belongs to the Signal Transducer and Activator of Transcription family of proteins. These proteins transmit signals from a receptor complex to the nucleus and activate gene expression. The seven members of the STAT family are predominantly activated by growth factors and cytokines. STAT6 is principally activated by two cytokines, interleukin-4 and interleukin-13 (IL-4 & IL-13) [1–3]. Once these cytokines bind to their cognate receptors, the associated Janus Kinases (Jak) are activated and phosphorylate conserved tyrosine residues on the receptor. Latent cytoplasmic STAT6 docks onto the phosphorylated receptor via an SH2 domain allowing the Jaks to phosphorylate the conserved tyrosine-641 on STAT6 (Fig. 1). Once phosphorylated, STAT6 forms homodimers and translocates to the nucleus. In the nucleus, STAT6 has the ability to bind directly to DNA via a DNA-binding domain and is able to regulate transcription [4] (Fig. 1). The proximal mechanisms for the activation of STAT6 by IL-4 and IL-13 have been studied extensively, and this has been reviewed in the literature [5–7]. However, the mechanistic basis of STAT6-dependent transcription is still being defined.

The carboxyl-terminal portion of STAT6 is responsible for its transcription activation function [4, 8] (Fig. 1). Two distinct regions within the carboxyl terminus were identified as containing the maximum transactivation potential [9]. Serine 756 within the transactivation domain is phosphorylated upon IL-4 stimulation; however, a functional role for this

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modification has not been determined [10]. This review will summarize the recent advances in understanding the transcriptional regulatory mechanisms initiated by STAT6. We will first review the biological function of STAT6, including a discussion of some of the defined target genes in hematopoietic and non-hematopoietic cells. Next, we will address the molecular mechanism of STAT6 DNA binding and induction of transcription, comment on the other transcription factors STAT6 collaborates with to induce transcription and summarize what is known about the enhanceosome that STAT6 assembles at gene promoters.

STAT6 function in lymphocytes and other cell types

STAT6 is critical for a number of responses in T cells, including the development of T-helper type 2 (Th2) cells and IL-4-stimulated proliferative responses, functions that were demonstrated through the analysis of mice with disrupted *Stat6* alleles [11–13]. The expression of Th2 cytokines including IL-4, IL-5, and IL-13 was diminished in *Stat6*−/− mice [11–13]. STAT6 regulates the expression of Gata3, the master regulator of Th2 differentiation (reviewed in [14]). STAT6 is also required for the development of IL-9-secreting T cells [15–18]. The mechanisms by which STAT6 regulates T-cell proliferation include decreasing the expression of $p27^{Kip1}$, a known cdk inhibitor, which may be at both transcriptional and post-translational levels [19, 20]. In CD8 cells, STAT6 is required for Tc2 differentiation as the production of IL-4 and IL-5 was completely lost with STAT6 deficiency [21]. Taken together, STAT6 is required for IL-4-stimulated T-cell functions.

In B cells, STAT6 promotes immunoglobulin class switching to IgE and IgG1 and the expression of some of the cell surface molecules responsible for antigen presentation by B cells. The levels of IgE are dramatically reduced in STAT6-deficient mice when the mice are either sensitized with antigen or infected with *N. brasiliensis* [11–13]. No differences were observed in immunoglobulin class switching to IgG1 when *Stat6*−/− and control mice were immunized with IgD [11, 12], but in an infection model with *N. brasiliensis* or *S. mansoni*, the levels of IgG1 were reduced in STAT6-deficient mice [13, 22]. The expression of several cell surface molecules responsible for antigen presentation by B cells is induced by IL-4; these include MHC II, CD80, and CD86. Experiments with *Stat6*−/− B cells and mice expressing a constitutive form of STAT6 have demonstrated that the IL-4-mediated induction of these molecules is dependent on STAT6 [11–13, 23]. The expression of other cell surface molecules like CD23 and IL-4R-alpha is also induced by STAT6 [11–13, 23] (Fig. 2). CD23 is the low-affinity Fc receptor for IgE and also is a B-cell differentiation marker. The induction of IL-4R-alpha by STAT6 indicates that STAT6 promotes an autocrine-positive feedback loop for IL-4-dependent signaling. STAT6 is required for IL-4-stimulated proliferation in B cells, similar to the role in T cells described above [12, 13]. Moreover, IL-4 prevents apoptosis in B cells in a STAT6-dependent manner [24].

In addition to a requirement in T and B cells, STAT6 also functions in macrophages and dendritic cells. In macrophages, STAT6 promotes IL-4-induced differentiation of alternatively activated macrophages (AAM) and mediates IL-13-induced expression of genes such as MHC class II [25, 26]. STAT6 activity in AAMs is associated with the suppression of T-cell proliferation [27]. Recently, STAT6 was shown to facilitate the transcription mediated by PPAR-gamma receptor in macrophages and dendritic cells [28]. In dendritic cells, STAT6 is capable of down-regulating the production of IL-10 and promoting the production of IL-12 to promote a Th1 response [29]. Thus, STAT6 is a critical molecule in regulating the balance of inflammatory and allergic immune responses.

STAT6 also functions in other tissue, including mammary gland, lung, and skin. In mammary glands, the IL-4/IL-13/STAT6 axis promotes luminal mammary epithelial

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development reviewed in [30]. Delayed lobuloalveolar development was observed in STAT6-deficient animals and lactogenic hormones induced the mammary epithelial cells to produce IL-4, IL-5, and IL-13 [31]. In lung epithelium, STAT6 mediates the effect of IL-13 to induce airway hyperreactivity and mucus production [32], reviewed in [33, 34]. The expression and activation of STAT6 have been observed in primary human bronchial epithelium indicating that STAT6 contributes to the function in these cells [35] (Fig. 2). The genes of the epidermal differentiation complex in keratinocytes including loricrin and lnvolucrin are regulated by STAT6 [36, 37] (Fig. 2). This implicates STAT6 in the progression of atopic dermatitis (AD). Mice expressing constitutively active STAT6 develop a disease mimicking AD [37, 38]. These studies demonstrate that STAT6 also plays a critical role in non-immune cells, indicating a requirement for STAT6 in multiple cell types during the development of immunity and disease.

STAT6 in disease states

STAT6 is clearly required for the development of allergic inflammation. Mice lacking STAT6 expression have greatly attenuated pulmonary inflammation in various models of allergic airway disease, food allergy, eosinophilic esophagitis, and atopic dermatitis [33, 37–43]. Moreover, mice expressing a constitutively active STAT6 are predisposed toward allergic disease [37, 38]. Importantly, the requirement for STAT6 is not solely in T cells. Studies using adoptive transfer of wild-type T cells into *Stat6*−/− mice demonstrated a requirement for STAT6 in resident cells as well [44]. In support of this, mice that only have STAT6 expression in airway epithelial cells, in the presence of an IL-13-expressing transgene, develop many features of allergic airway inflammation [32]. The requirement for STAT6 in additional cells in the immune system continues to be investigated [45].

STAT6 is also required for efficient immunity to helminthic parasites including *Nippostrongylus brasiliensis*, *Heligmosomoides polygyrus*, *Trichinella spiralis*, *Schistosoma mansoni* [13, 22, 46–49]. In these infections, STAT6 functions in B cells to produce IgE, T cells to generate Th2 cells, in mast cells, and in tissue-resident cells to produce chemokines for inflammation and mucus for clearing of infection.

As a result of the lack of Th2 immunity, *Stat6*−/− mice have increased inflammatory immunity. The increase of inflammatory Th1 and Th17 cells leads to increased autoimmune inflammation in various models including EAE and diabetes [50, 51]. However, the increased inflammatory responses also confer protective immunity to mice infected with *Trypanosoma cruzi* and Ectromelia [52, 53].

A few reports described results where STAT6 was not required for Th2 development in vivo or where allergic inflammation could develop in *Stat6*−/− mice [54, 55]. There are several explanations for these discrepancies, which may include background of the mice as well as compensatory pathways, such as activation of STAT5, which also contributes to allergic inflammation [56, 57]. However, a major confounding factor may be the origin of the mice. While mice developed in Boston and Osaka have consistently displayed the phenotypes described above, a recent report compared mice derived in Boston and Memphis in parallel EAE experiments and demonstrated differing phenotypes [58]. *Stat6*−/− mice from Memphis had less inflammatory disease and did not display a complete loss of Th2 generation. This correlated with the production of a mutant STAT6 protein in mice from Memphis and no detectable protein in mice from Boston. Thus, as with any gene disruption model, caution must be used in drawing conclusions using mice that carry hypomorphic alleles versus mice that lack production of any gene product.

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STAT6 and DNA binding

All of the STAT proteins bind a palindromic consensus sequence TTC(N)$_{2-4}$GAA. STAT6 binds an element consisting of either 3 or 4 nucleotides between the dyad half-sites [59, 60]. Recently, the genome-wide analysis of STAT6-regulated genes by high-throughput ChIP-seq analysis has revealed the exact nature of sites to which STAT6 binds in T cells [61, 62]. In the study, using human T cells, 79% of the sites that bound STAT6 contained STAT consensus elements. Among these, 58% were sequences with a 4-nucleotide spacer between the palindrome and 26% contained 3 nucleotides [61]. Genome-wide analysis of STAT6-bound genes in mouse T cells showed 30% of genes contained the N4 site [62]. These data indicate that binding specificity of STAT6 may be subtly different in humans and mouse. The human study also analyzed the location of the STAT6 site within the gene loci and showed that 66% of the STAT6 sites were present in intragenic regions, mainly within the first two introns, with the rest were present either upstream of the transcription start site or downstream of the transcription end site [61]. The ChIP-seq genome-wide approach and the development of algorithms to analyze isolated sequences have provided the ability to closely analyze the nature of sites to which transcription factors bind and hence understand better the mechanisms used by these factors to regulate transcription.

STAT6 targets

Two approaches have been used to identify target genes that are regulated by STAT6 on a genomic scale. Initially, studies were done using microarrays using the gene expression Affymetrix platform. In a study performed in B cells comparing the gene expression profiles of IL-4-stimulated B cells from wild-type and *Stat6*−/− mice, 70 known genes were differentially expressed between the two genotypes: 31 genes were expressed at higher levels in STAT6 competent mice and the expression of 39 genes were lower as compared to *Stat6* −/− B cells. These data indicated that STAT6 is both a negative and positive regulator of transcription [63]. This study identified transcription factors, various kinases, kinase inhibitors, other enzymes, cytokines, cell surface receptors, immunoglobulins, and other genes under the regulatory control of STAT6 [63] (Fig. 2). There have been numerous studies that have determined on a genomic level the identity of genes controlled by STAT6 in T cells. The first of these studies was a microarray analysis done using mouse T cells isolated from STAT6-competent and STAT6-deficient mice differentiated toward a Th2 phenotype [64]. This study identified both STAT6-dependent and STAT6-independent genes under the control of IL-4. Another study done by the same group used an alternate approach by using metabolic labeling of proteins and 2-D electrophoresis and identified at the protein level the differential expression in wild type vs *Stat6* −/− cells [65]. Some of the genes identified by this approach were unique and were not part of the list generated by the microarray analysis. These included CBFb2 and CNBP [64, 65].

More recently, high-throughput sequencing of chromatin immunoprecipitated DNA has identified genes bound by STAT6. One study compared genes bound by STAT6 in wild-type and *Stat6* −/− Th2 cells, and these data were compared to epigenetic modifications across the genome [62]. In this study, 60% of the binding sites for STAT6 co-localized with H3K4me3. Some of the STAT6-bound regions coincided with various permissive epigenetic marks, and the corresponding genes include *Il4*, *Gata3*, *Il24*, *Plcd1,* and *Hipk2* [62] (Fig. 2). Another study used human Th2 cells and compared the STAT6 binding to genes between cells where the expression of STAT6 was knocked down by RNAi and cells with normal STAT6 expression [61]. This study performed a kinetic analysis and determined the identity of STAT6-dependent genes during the Th2 polarization process and found that the 80% of IL-4 regulated genes were dependent on STAT6 at the 48-h time point. *GATA3*, *CRTH2*, *IL24*, *LTB*, *SOCS1* were some of the genes regulated by STAT6. High-throughput screening

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for STAT6-regulated genes provides a resource which can be used for further research to define further roles of STAT6 in T and B cells. As there is emerging evidence that STAT6 can function in other immune cells, as well as other non-immune cells, it will be important to determine the nature of genes that are regulated by STAT6 in these tissues.

STAT6 and other transcription factors

Efficient induction of gene expression requires the action of multiple enhancer binding proteins, some activated by distinct signaling pathways. Integration of individual stimuli within the cell results in coordinated regulation of gene expression. This paradigm is also true for STAT6-dependent transcription (Fig. 3). The most distinct example of this is regulation of IgE class switching in B cells. This process requires the coordinated signals of IL-4 and CD40 ligation that respectively activate STAT6 and NF-κB. Germline transcription of IgE is dependent on a single STAT6-binding site and two NF-κB-binding sites in the Iε promoter [66, 67]. One of the NF-κB sites on the promoter binds the classical p50/p65 heterodimers and the other binds p50/relB [67]. A synergism between these two transcription factor complexes relies on direct association of STAT6 with NF-κB and cooperative binding to their respective promoter elements [68]. Other immunoglobulin genes are similarly regulated including the germline promoter elements associated with the gamma4 and the gamma3 immunoglobulin isotypes [69, 70]. The gamma4 promoter is synergistically activated by c-Rel and STAT6 [69] and the gamma4 element cooperatively bound p50/p65/c-Rel and STAT6 [70]. The low-affinity IgE receptor Fcer2a is also regulated by STAT6 and p50/p65 subunits of NF-κB [71, 72]. The activation-induced cytidine deaminase (AID), which is required for immunoglobulin class switching, is also regulated by CD40 and IL-4, and this is dependent upon NF-κB and STAT6 [73]. As mentioned in a previous section, STAT6 plays an important role in the recruitment of eosinophils, where it induces the expression of the chemoattractant eotaxin or CCL11. Eotaxin is induced by NF-κB, which is activated by TNF-alpha, and IL-4 activated STAT6 in an airway epithelial cell line [74]. In addition to the involvement of the classical NF-κB signaling pathway with STAT6, IL-4-induced expression of MHCII and CD86 in splenic B cells is dependent on STAT6 and the non-canonical NF-κB pathway involving the processing of p100 to p52 [75]. Processing relied upon IL-4-dependent activation of PI-3-kinase, and the inhibition of this signaling pathway resulted in a loss of IL-4-dependent activation of the MHCII and CD86 genes [75]. Thus, STAT6 and members of the NF-κB family of proteins act in conjunction with each other to regulate transcription of multiple IL-4-induced genes.

Classes of transcription factors that are constitutively expressed can also participate with the STAT6 signaling pathway (Fig. 3). An example of this is observed for the germline promoter for IgE. Two independent groups have shown that in addition to NF-κB, the monocyte-specific transcription factor PU.1 synergizes with STAT6 to regulate the Iε promoter [76, 77]. Binding sites for both PU.1 and STAT6 were found within the promoter region of this gene [77], and it was demonstrated that both the DNA-binding domain and the transactivation domain of PU.1 are required for the synergism observed between STAT6 and PU.1 [76]. C/EBP-beta but not C/EBP-alpha or C/EBP-gamma also cooperate with STAT6 for induction of the human Iε promoter [78, 79]. C/EBP-beta was shown to stabilize the binding of STAT6 to its promoter element [79]. However, at the mouse Iε gene, C/EBP-beta inhibits transcription, and AP-1 transcription factors (Fos and Jun) cooperate with STAT6 [80]. STAT6 and C/EBP regulate other genes such as FIZZ1 and arginase 1 [81–83] (Fig. 2). FIZZ1 participates in allergic inflammation and is regulated by IL-4 from a promoter-containing functional STAT6 and C/EBP-binding sites [83]. The macrophage-specific arginase 1 that modulates NO in asthma and bacterial and worm infections is also regulated by both STAT6 and C/EBP-beta [81, 82].

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Most recently, our group has demonstrated that STAT3 cooperates with STAT6 to promote Th2 differentiation [84]. The expression of the Th2-specific transcription factors such as *Gata3*, *Maf*, *Batf,* and *Irf4* that are regulated by STAT6 was reduced in the absence of STAT3. This impacted the production of the Th2 cytokines including IL-4, IL-5, and IL-13. Mechanistically, it was determined that STAT3 defined the binding pattern of STAT6 on the *Gata3*, *Maf*, *Batf,* and *Irf4* promoters [84].

In addition to cooperating with other enhancer-binding factors, STAT6 facilitates the transcription mediated by peroxisome proliferator-activated receptor *γ* (PPAR*γ*) that is active in macrophages and dendritic cells (DCs) [28]. STAT6 was shown to be required for most of the PPAR*γ* target genes that are augmented by IL-4. STAT6 aided the binding of PPAR*γ* to its response element and associated with PPAR*γ* itself [28]. Taken together, it has been extensively demonstrated that STAT6 does not regulate gene expression in isolation, and IL-4 and STAT6 need the cooperation of other transcription factors to induce gene expression efficiently. It has been suggested that the array of transcription factors assembled at promoters forms a platform with their transactivation domains to recruit additional coactivators into a complex termed an enhanceosome that is required for transcription to proceed.

STAT6 and the enhanceosome

One of the main functions of transcription factors is to recruit other coactivators to specific regions of a gene, which in turn modify nucleosomes and chromatin locally to activate transcription [85]. These coactivators are also thought to bridge the enhancer to the basal transcriptional machinery in an enhanceosome complex [85, 86]. Several studies indicate that STAT6 assembles an enhanceosome at target gene promoters (Fig. 3). CBP/p300 is recruited by STAT6, and this association results in increased STAT6-dependent transcription [87, 88] (Fig. 3). The carboxyl-terminal domain of STAT6 mediates this association with the region corresponding to 1850–2176 of CBP [87] (Fig. 1). The adenoviral protein E1A that is known to associate with CBP/p300 was shown to inhibit the function of STAT6 suggesting that it competes with STAT6 for CBP/p300 [87, 88]. In addition to CBP/p300, other coactivators belonging to the p160 steroid receptor nuclear coactivators (NcoAs) play an important role in STAT6-dependent transcription [89–91]. NCoA-1 is directly recruited by STAT6 via its carboxyl-terminal domain, and this association is dependent on the LXXLL motif found in the TAD of STAT6 [90, 92, 93] (Figs. 1, 3). Further, the PAS-B domain of NCoA-1 is the contact point for binding STAT6 [93]. This interaction is specific because NCoA-2 and NCoA-3, two other members of the nuclear coactivators family, are unable to interact with STAT6 or provide coactivation for transcription [91, 93]. However, NCoA-3 might play an indirect role in coactivating STAT6-dependent transcription through its interaction with p300 [89] (Fig. 3). Data with chimeric STAT6 molecules suggested that specific sets of coactivators are recruited by STAT6 to provide specificity for promoter activation [90, 94]. As discussed earlier, there is overlap in the consensus DNA-binding sequences among the different STAT factors, although there is remarkable specificity for the genes that each STAT factor regulates. Therefore, the recruitment of specific sets of coactivators by individual STAT proteins suggests another paradigm by which each STAT molecule mediates promoter specificity.

Part of the mechanism through which coactivators such as CBP/p300 and NCoAs activate gene expression is by providing histone acetyltransferase (HAT) activity. HAT activity acetylates histones locally, making the chromatin accessible for the binding of transcription factors and the basal transcription machinery. An example for the requirement of acetylation for STAT6-mediated transcriptional activation is the 15-lipoxygenase-1 gene (*ALOX15*) [95]. At this locus, STAT6 and histones are acetylated by CBP/p300, and this activity is

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required for the efficient transcriptional activation of the *ALOX15* gene by IL-4 [95]. More recently, our group has performed a kinetic study where we have demonstrated that after the binding of STAT6 to the *Fcer2a* and Iε gene promoters, CBP, NCoA-1, and NCoA-3 are inducibly associated with these promoters prior to histone acetylation [96] (Fig. 3). STAT6 has been implicated in the maintenance of long-term acetylation for the IL-4 promoter and enhancer in differentiating Th2 cells, and in the absence of STAT6, the acetylation of histones is markedly reduced in Th2 cells [97, 98]. STAT6 is thought to indirectly regulate the accessibility of Th2 cytokine loci via Gata3 and other Th2-specific transcription factors. Although there is little direct evidence for this, it is possible that CBP/p300 and the NCoA factors are recruited by STAT6 to these regions of the IL-4 promoter. These factors then acetylate the histones to make this region transcriptionally accessible in Th2 cells. Other factors like the polycomb (PcG) and trithorax (TrxG) complex regulate transcription accessibility by regulating methylation of histones. The polycomb complex is associated with the repressive mark of H3-K27Me3, and the trithorax complex is associated with the permissive mark, H3-K4Me3. Recently, it has been demonstrated that STAT6 plays a role in displacing the PcG with TrxG for the long-term maintenance of GATA3 expression [99]. STAT6 is also involved in the recruitment of BRG1, a subunit of the SWI/SNF nucleosome remodeling complex [100, 101]. BRG1 is recruited to the Th2 cytokine locus control region with the aid of STAT6 [101], and STAT6 is also required for the association of BRG1 to the distal regulatory sites in the *Gata3* gene [100].

Another role for the components of the enhanceosome is to bridge the enhancer to the basal transcriptional machinery. In the STAT6-dependent enhancer complex, it has been shown that p100 (staphylococcal nuclease and tudor domain containing 1 (SND1)) functions as a bridging factor between STAT6 and the basal transcription complex [102]. SND1/p100 was shown to interact with the STAT6 TAD via its SN-like domain and to also associate with the large subunit of RNA polymerase II, thus providing the bridging function between STAT6 and the polymerase complex [102] (Fig. 3). SND1 recruits another factor to the STAT6 transcriptosome, RNA helicase A (RHA). RHA and SND1 enhance the association of STAT6 to target gene promoters [103] (Fig. 3).

More recently, PARP-14 was identified as a factor that associates with STAT6 but not STAT1 and provides transcriptional enhancement to IL-4-dependent, but not IFN-gamma-dependent, gene activation [104]. PARP-14 belongs to the poly-ADP ribose polymerase (PARP) family of proteins and is catalytically activity. This enzymatic activity was determined to be essential for the transcriptional enhancement function of PARP-14 [105] and played a role in the binding efficiency of STAT6 to its target promoters [96]. PARP-14 was shown to regulate STAT6-dependent transcription by functioning as a transcriptional switch from a transcriptionally repressed to an active state. PARP-14 recruited HDAC 2 and 3 in the absence of cytokine stimuli to repress transcription, and upon IL-4 stimulation, the PARP activity of PARP-14 modified itself and the HDACs to relieve the repression [96]. These data indicate that STAT6-dependent transcription is regulated not only by HATs but also by an additional level of regulation and is dependent on a unique PARP enzyme (Fig. 3).

Conclusions

STAT6 has diverse biological functions within the immune system where it was first identified and more recently in non-immune tissue as well. STAT6 contributes to the normal functioning of the immune system, although altered STAT6 activation may also be involved in the pathogenesis of several diseases. Due to its role in progression of allergic responses, lymphomas and leukemias, targeting the function of STAT6 has become an attractive possible therapy for these diseases. To achieve this goal, it will be important to understand

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the molecular mechanisms by which STAT6 functions and imperative to identify all the genes that are regulated by STAT6 in immune and non-immune cells. As future work identifies how STAT6 activates genes, and the critical genes that are activated during specific immune responses, we will be better able to define how STAT6 contributes to human disease.

Acknowledgments

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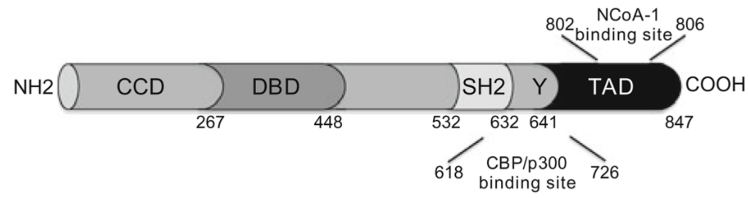

Fig. 1.

Schematic of STAT6. The STAT6 molecule contains a N-terminal coiled coil domain (*CCD*), a DNA-binding domain (*DBD*), a SH2 domain, a conserved tyrosine, and the C-terminal transactivation domain (*TAD*). The TAD has specific regions that associate with transcriptional coactivators CBP/p300 and NCoA-1

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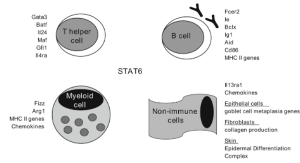

Fig. 2.
Target genes of STAT6 in various cell types

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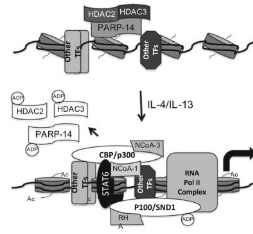

Fig. 3.

Model for STAT6-regulated transcription. Under non-stimulating conditions, PARP-14 is bound to STAT6-responsive promoters and recruits HDAC 2 and 3 and keeps the gene silent. Upon IL-4 stimulation, STAT6 is activated and binds to its promoter element and induces the PARP-14 enzymatic activity that modifies itself, p100, HDAC 2 and 3 in the complex. This results in the dissociation of PARP-14 and the HDACs from the promoter and allows for p300/CBP, NCoA-,1 and NCoA-3 to be recruited to the promoter for histone acetylation. The p100 complex with RNA helicase A forms a bridge between STAT6 and the RNA polymerase II complex. STAT6 collaborates with several other transcription factors to activate transcription