The glucocorticoid receptor and STAT6 physically and functionally interact in T-lymphocytes

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Abstract In lymphocytes, glucocorticoids (GC)- and interleukin-4-signaling pathways are known to interact, as evidenced by inhibition of IL-4-mediated proliferation by dexamethasone or suppression of GC-induced apoptosis by IL-4. In this study, we characterized the molecular basis for this reciprocal interference. We report that, in murine CTLL-2 cells, IL-4 inhibits GC-induced MMTV (mouse mammary tumor virus) promoter transactivation, and that GC suppress IL-4-induced transactivation of a STAT6 (signal transducers and activators of transcription 6)-responsive promoter without affecting IL-4-stimulated STAT6 DNA-binding. Moreover, we evidenced a physical association between GC receptor and STAT6, which proved to be functionally relevant, since STAT6 overexpression increased the IL-4 inhibitory effect on GC-induced MMTV transactivation.

Key words: Interleukin-4; Signal transducer and activator of transcription 6; Glucocorticoid receptor

1. Introduction

Interleukin-4 (IL-4) is a critical regulatory cytokine of the immune response. In naive $CD4^+$ T-helper (Th) lymphocytes, IL-4 promotes Th2 cell differentiation, driving allergic and humoral-mediated immunity [1]. The transcriptional response to IL-4 is partly mediated through STAT6 (signal transducers and activators of transcription 6) and mice deficient in STAT6 show impairment of numerous IL-4-mediated functions [2,3]. Glucocorticoids (GC) display profound immunomodulatory properties and are therefore widely used in the therapy of inflammatory and allergic diseases. These molecules exert their biological effects through binding to the GC receptor (GR), which is a ligand-activated transcription factor regulating either positively or negatively the expression of target genes [4]. Apart from the association with GC-responsive elements (GREs) in the promoter regions of these genes, GR can establish protein–protein interactions with other transcription factors such as AP-1 [5–7], NF-κB [8], or members of the STAT family. The latter interactions result in either synergistic enhancement or inhibition of the transcriptional activities of these factors. Indeed, in COS-7 cells stimulated with prolactin, STAT5 synergizes with GC on the β-casein promoter, but antagonizes GC-induced mouse mammary tumor virus (MMTV)-long terminal repeat (LTR) promoter activity [9–12]. In the rat hepatoma cell line H4IIE and in COS-7 cells stimulated with IL-6, STAT3 was shown to synergize with GC on the rat γ-fibrinogen promoter or on the MMTV-LTR promoter [13]. A transcriptional cooperation between STAT1, the GR and the Ets family transcription factor PU.1 was described in monocytes, resulting in the enhancement by the synthetic GC dexamethasone (DEX) of the interferon (IFN) γ-induced expression of FcγRI [14]. Furthermore, GC were recently shown to block IL-12-induced STAT4 phosphorylation without affecting IL-4-induced STAT6 phosphorylation [15]. Taken together, these results show that, despite the high degree of homology existing between the different STAT proteins, their functional interactions with GR do not necessarily display a common mechanism.

DEX was previously shown to block the IL-4-driven proliferation of CTLL-2 cells [16]. In addition, IL-4 specifically inhibits DEX-induced apoptosis in Th2 cells [17]. The aim of this work was to characterize the molecular basis for the functional interaction between IL-4 and the GR transduction pathways. We characterized a transcriptional interference between these two pathways, and could provide evidence for a physical association between the GR and STAT6.

2. Materials and methods

2.1. Chemicals and reagents

Recombinant human IL-2 was a gift from Chiron B.V., Amsterdam, The Netherlands. Recombinant murine IL-4 was a gift of Sterling-Winthrop (Rensealer, USA). DEX was purchased from Sigma (L'Isle D'Abeau, France) and Luciferase Assay System from Promega (Madison, WI, USA).

2.2. Cell culture

The murine IL-2-dependent cytotoxic T-cell line CTLL-2 was cultured in complete medium: RPMI 1640 medium (Gibco) containing 2 mM L-glutamine, 0.1 mg/ml streptomycin, 100 U/ml penicillin (Gibco), 50 μM 2-mercaptoethanol (Sigma), 1% sodium pyruvate (Gibco), 10% fetal calf serum and 1 ng/ml IL-2.

2.3. Plasmids

pLTR-Luc plasmid contains the entire MMTV-LTR coupled to the luciferase reporter gene [18]. p200-Luc plasmid displays a 5′-end dele-

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Abbreviations: IL, interleukin; DEX, dexamethasone; GC, glucocorticoids; GR, glucocorticoid receptor; STAT, signal transducers and activators of transcription; MMTV, mouse mammary tumor virus

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tion up to the −200 position relative to the transcriptional initiation site (+1). p2GRE104-Luc plasmid was constructed by inserting two synthetic consensus GREs immediately upstream of the proximal region of the promoter (−104/+1). The GRE_5-EBV-TATA-CAT plasmid was a kind gift of S. Mader [19]. The STAT6-Luc and $pcDNA_{3.1}$-myc-STAT6 plasmids were a kind gift of A. Duschl (University of Würzburg, Germany).

2.4. Transfections

CTLL-2 cells (10^7) were electroporated using a Bio-Rad gene pulser (Ivry-Sur-Seine, France) set at 250 V and 960 μF. Selection of stably transfected clones (CTLL-2 pLTR, CTLL-2 p200 or CTLL-2 p2GRE104) was performed using 800 μg/ml G418 (Gibco) and limiting dilution. Several clones were tested to assess the variability due to the site of integration in the cellular genome and experiments were performed with representative clones of CTLL-2 pLTR, CTLL-2 p200 and CTLL-2 p2GRE104 cells.

2.5. Reporter gene assays

2.5.1. Luciferase assay. Luciferase levels were measured according to the manufacturer's protocol (Promega). Protein extracts in equivalent protein concentration samples were mixed with 100 μl of Luciferase Assay Reagent. Luciferase activity was determined at 25°C after 1 min with a luminometer (LKB Wallac, Turku, Finland). CAT (chloramphenicol acetyl transferase) assay: CAT assay was performed as previously described [20] and conversion of chloramphenicol was quantified using a Storm 840 Phosphorimager and the Imagequant software (molecular Dynamics, Sunnyvale, USA).

2.6. DNA affinity precipitation of STAT proteins

DNA affinity precipitation method was performed as previously described [21] using a 5′-biotinylated double-stranded GAS (IFNγ-activated sequence) linked to streptavidin-agarose beads (Sigma). Western blot analysis was subsequently performed with a specific anti-STAT6 antibody (M200, Santa Cruz Biotechnology, USA), or with an anti-STAT5 rabbit polyclonal antiserum raised in the laboratory.

2.7. Co-immunoprecipitation assays

CTLL-2 cells were deprived of IL-2 for 12 h, and then stimulated for 1 h with IL-4 (5 ng/ml) and/or DEX (100 nM), or left untreated. Nuclear or cytoplasmic extracts were first incubated for 30 min at 4°C with Protein A Sepharose beads (Sigma) and pre-immune serum. The pre-cleared lysate was then incubated overnight at 4°C with either an anti-GR antibody (M20, Santa Cruz) or an anti-STAT6 antibody (M200, Santa Cruz) pre-coupled to Protein A Sepharose beads. Immune complexes were washed three times with lysis buffer, and analyzed by SDS–PAGE using anti-STAT6 or anti-GR antibodies, respectively.

3. Results and discussion

3.1. Effect of IL-4 on DEX-induced GR transcriptional activity

CTLL-2 is a murine IL-2-dependent T-lymphocyte cell line that also responds to IL-4. Indeed, IL-4 promotes survival and proliferation of these cells in absence of IL-2 and protects them from DEX-induced apoptosis (data not shown). The effect of IL-4 on GR transcriptional activity was evaluated in CTLL-2 cells stably transfected with the pLTR-Luc plasmid containing the MMTV promoter coupled to the luciferase reporter gene (CTLL-2 pLTR cells). A 12 h treatment of CTLL-2 pLTR cells with 100 nM DEX results in a 10-fold induction of luciferase activity (Fig. 1A). IL-4 alone does not affect the promoter activity (data not shown). Concomitant addition of increasing amounts of IL-4 (1, 5 or 10 ng/ml) with DEX produces a concentration-dependent inhibition of GR transcriptional activity (0, 51 and 67% inhibition, respectively). In its proximal region, upstream of the TATA box, the MMTV promoter is composed of a cluster of four GREs, as well as of binding sites for ubiquitous transcription factors

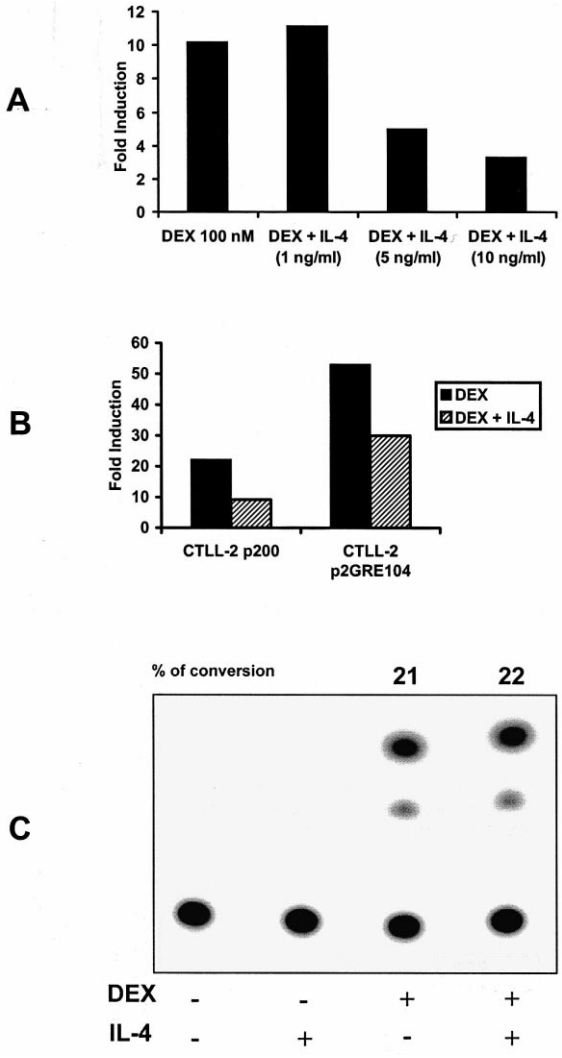

Fig. 1. Effect of IL-4 on DEX-induced GR transcriptional activity in CTLL-2 cells. A: IL-4 inhibits DEX-induced MMTV-LTR activity in stably transfected CTLL-2 pLTR cells. CTLL-2 pLTR cells were treated for 12 h with DEX (100 nM) and/or IL-4 (1, 5 or 10 ng/ml), or left untreated. Fold induction was calculated as the ratio of arbitrary luciferase units in cells treated with DEX compared to untreated cells, or in cells treated with DEX and IL-4 compared to cells treated with IL-4 alone. The value 1 was consequently affected to the basal level measured in non-treated cells. A representative experiment out of four is shown here. B: The most proximal region of the MMTV-LTR promoter (−104/+1) is necessary and sufficient to mediate the inhibitory effect of IL-4. CTLL-2 p200 and CTLL-2 p2GRE104 cells were treated for 12 h with DEX (100 nM) and/or IL-4 (5 ng/ml), or left untreated. Results of a representative experiment out of three. C: IL-4 does not inhibit DEX-induced GRE_5-EBV-TATA-CAT activity in CTLL-2 cells. CTLL-2 cells were transiently transfected with the GRE_5-EBV-TATA-CAT plasmid, and treated for 12 h with DEX (100 nM) and/or IL-4 (5 ng/ml), or left untreated. Percentage of chloramphenicol conversion represents the ratio between acetylated chloramphenicol and total chloramphenicol (acetylated and non-acetylated). A representative experiment out of two is shown here.

such as NF-1 and Oct-1. The 5′-end of the promoter was described to contain numerous cell type-specific positive or negative regulatory regions. Given the composite nature of this promoter, we explored, by the mean of 5′-end deletions of the promoter, the existence of one (or more) regulatory element(s) responsible for the inhibitory effect of IL-4. The

p200-Luc construct, which displays the proximal part of the promoter (including the four GREs), was stably transfected in CTLL-2 cells (CTLL-2 p200 cells). IL-4, at 5 ng/ml, reduced by 60% the DEX-induced transactivation of the promoter (Fig. 1B), indicating that sequences located upstream of the −200 position can be deleted without impairing the IL-4 inhibitory effect. To further investigate the role played by elements located in the region spanning from −200 to −104, we constructed the p2GRE104-Luc plasmid and stably transfected this plasmid in CTLL-2 cells. Again, IL-4 displayed an inhibitory effect on DEX-induced luciferase activity (Fig. 1B), suggesting that the IL-4 inhibitory effect on GC-induced MMTV transactivation requires the most proximal part of the promoter to occur. A possible explanation could be that IL-4 might prevent binding of GR to GREs. However, the inhibitory effect of IL-4 on GR transcriptional activity was not found with a simple synthetic promoter, composed of five palindromic GREs adjacent to a minimal TATA box (GRE_5-EBV-TATA-CAT) (Fig. 1C). These results suggest that the inhibitory effect of IL-4 on GC-stimulated MMTV promoter activity is dependent on the promoter context, and does not rely on an IL-4-driven impairment of GR–DNA or ligand-binding activity.

3.2. *Effect of STAT6 on GC-induced MMTV-luc transactivation*

We then attempted to identify the IL-4 signal transduction pathway responsible for the inhibition of GC-induced MMTV transactivation. Several STAT family transcription factors were previously described as modulators of the GR transcriptional activity, particularly STAT5 [9–12]. We first verified that, in CTLL-2 cells, IL-4 induces STAT6 but not STAT5, since in the murine pro-B-cell line Ba/F3 and in pre-activated human T-cells, IL-4 was shown to activate the STAT5 transcription factor in addition to STAT6 [22]. We then used a 5′-biotinylated GAS oligonucleotide linked to streptavidin-agarose beads to measure IL-4-stimulated DNA-binding activity of STAT5 and STAT6 in CTLL-2 cells. GAS-bound proteins were probed with both anti-STAT5 and anti-STAT6 antibodies. After 1 h of IL-4 treatment (Fig. 2), a strong activation of STAT6–, but not of STAT5–DNA-binding is measured, ruling out any participation of STAT5 in the inhibitory effect of IL-4 on GR transcriptional activity. Furthermore, IL-2 stimulates STAT5 DNA-binding activity, but the combination of the two cytokines does not affect the levels of STAT5 or STAT6 activation (Fig. 2).

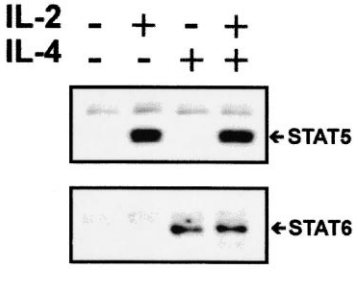

Fig. 2. Induction by IL-4 of STAT6– but not STAT5–DNA-binding activity. CTLL-2 cells were deprived of IL-2 for 3 h, and then treated for 1 h with IL-2 (1 ng/ml), IL-4 (5 ng/ml), IL-2 and IL-4, or left untreated. DNA-binding of STAT5 and STAT6 was then measured by the DNA affinity precipitation method and bound proteins were probed with either an anti-STAT5 or an anti-STAT6 antibody.

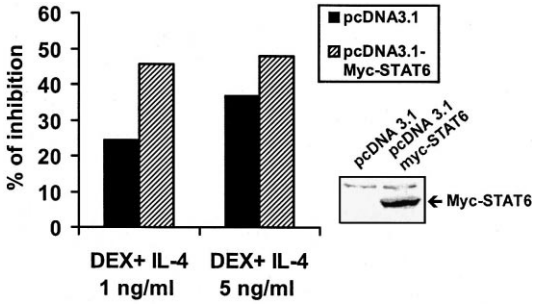

Fig. 3. Effect of STAT6 overexpression on MMTV-luc transactivation. CTLL-2 p2GRE104-Luc cells (clone 19) were transiently transfected with $pcDNA_{3.1}$-myc-STAT6 or with a control vector ($pcDNA_{3.1}$). Cells were treated for 12 h with DEX (100 nM) and/or IL-4 (1 or 5 ng/ml), or left untreated. Fold induction was calculated as the ratio of arbitrary luciferase units in cells treated with DEX compared to untreated cells, or in cells treated with DEX and IL-4 compared to cells treated with IL-4 alone. Results are expressed in percentage of inhibition. Representative results out of two experiments.

To investigate the involvement of STAT6 in the inhibitory effect of IL-4 on GR transcriptional activity, we transiently transfected CTLL-2 p2GRE104-Luc cells with an expression vector for the wild type form of STAT6 fused to a myc tag ($pcDNA_{3.1}$-myc-STAT6) or with a control vector ($pcDNA_{3.1}$). Expression of the Myc-STAT6 protein was obtained after transfection by a 24 h culture in presence of 500 pg/ml IL-2 (see Fig. 3, right insert). At the concentration of 1 ng/ml, IL-4 inhibition of GC-induced p2GRE104-Luc transactivation is enhanced by a 2-fold factor in cells overexpressing STAT6 (46% inhibition) compared to cells transfected with the control vector (25% inhibition) (Fig. 3). The difference is less marked at 5 ng/ml IL-4 (48 versus 37%), suggesting that the maximum achievable inhibition was reached in STAT6 overexpressing cells. These results strongly support the hypothesis that STAT6 is an important modulator of GR-mediated MMTV transactivation.

3.3. *Effect of GC on IL-4-induced STAT6 transcriptional activity*

To further document the functional interaction between GR and STAT6, we transfected CTLL-2 cells with a STAT6-Luc reporter construct, containing five STAT6-responsive elements from the human IgE class switching promoter coupled to a minimal TATA box. Compared to cells treated with IL-4 alone, incubation of the cells with a saturating dose of DEX (100 nM) and 0.1 or 0.2 ng/ml IL-4 results in 44 and 46% inhibition of the transcriptional activation of the promoter, respectively (Fig. 4A). But increasing the concentration of IL-4 (1 and 5 ng/ml) causes a fall in the percentage of inhibition (30 and 7%, respectively). These results suggest a mechanism of inhibition where DEX-activated GR might be a rate limiting component compared to IL-4-stimulated STAT6. In COS-7 cells transiently transfected with STAT6 and GR, Moriggl and collaborators measured an enhancement by DEX of IL-4-induced activation of β-casein gene transcription [23]. The effect of GC on STAT6 transcriptional activity may thus depend on the promoter context, and also probably on the cell type.

We then assessed if DEX treatment could impair IL-4-stimulated DNA-binding activity of STAT6. Results presented in Fig. 4B show that STAT6 DNA-binding activity is not modified when cells are concomitantly incubated with DEX and IL-4 for 15 or 30 min. Recently, it was reported that a 6 or 18 h pretreatment of T-lymphocytes with DEX does not alter the IL-4-induced STAT6 phosphorylation [15]. Despite the different experimental procedure, these latter results are in accordance with our findings. We can thus rule out the inhibition of STAT6 DNA-binding activity as a mechanism of inhibition of STAT6 transcriptional activity by GC.

3.4. Physical interaction between STAT6 and the GR

We postulated that STAT6 might physically interact with the GR, explaining the transcriptional interference existing between the two factors. Co-immunoprecipitation experiments were performed with an anti-GR antibody using cytoplasmic and nuclear extracts from CTLL-2 cells deprived of IL-2 for 12 h and treated for 1 h with DEX (100 nM) or DEX and IL-4 (5 ng/ml). Blotting of the GR immuno-complex with an anti-STAT6 antibody allowed us to detect co-precipitated STAT6 (Fig. 5A). Indeed, an association between GR and STAT6 was evidenced, in the cytoplasmic as well as in the nuclear compartment. Apparently, the GR–STAT6 complex is more abundant in the cytoplasmic compartment. Moreover, the interaction is weak in DEX-treated cells, but is strongly enhanced by a concomitant treatment with IL-4. The physical interaction between GR and STAT6 was confirmed by immunoprecipitation experiments on cytoplasmic extracts with an anti-STAT6 antibody, and subsequent immunoblotting with an anti-GR antibody (Fig. 5B). Our results suggest that the anti-STAT6 antibody we are using more efficiently recognizes the activated form of the protein. Consequently, only a qualitative interpretation of these results can be made, concluding in a physical association of GR and STAT6 in the presence of DEX or DEX and IL-4. It remains to be clarified whether GR–STAT6 interaction is direct or not, and which role is played by the IL-4 activation of STAT6 in this interaction. It is interesting to note that this physical interaction does not impede the DNA-binding activity of STAT6 (see Fig. 3B). A physical association between the GR and STAT5 [9], or STAT3 [13], but not STAT1 [14], was previously described. We report here for the first time that GR and STAT6 physically interact with each other in T-lymphocytes.

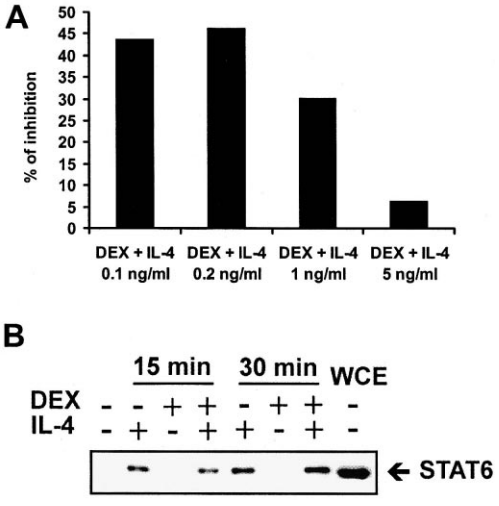

Fig. 4. Effect of GC on IL-4-induced STAT6 transcriptional activity and DNA-binding. A: CTLL-2 cells were transiently transfected with the STAT6-Luc plasmid and treated for 12 h with DEX (100 nM) and/or IL-4 (0.1, 0.2, 1 or 5 ng/ml), or left untreated. Fold induction was calculated as the ratio of arbitrary luciferase units in cells treated with IL-4 compared to untreated cells, or in cells treated with IL-4 and DEX compared to cells treated with DEX alone. Results are expressed in percentage of inhibition. B: CTLL-2 cells were deprived of IL-2 for 3 h, and then treated for 15 and 30 min with IL-4 (5 ng/ml), in the presence or in the absence of DEX (100 nM), or left untreated. DNA-binding of STAT6 was then measured by the DNA affinity precipitation method. Bound proteins were probed with an anti-STAT6 antibody. WCE: whole cell extract. Representative results out of three experiments.

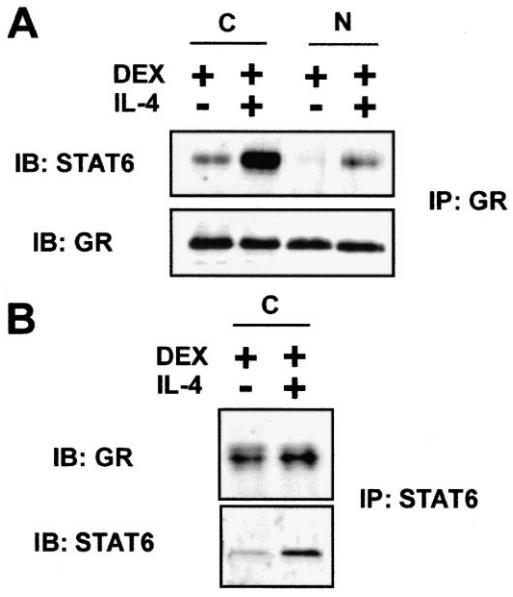

Fig. 5. Physical interaction between STAT6 and the GR. CTLL-2 cells deprived of IL-2 for 12 h and treated for 1 h with DEX (100 nM) and IL-4 (5 ng/ml). Nuclear or cytoplasmic lysates were immunoprecipitated with an anti-GR (A) or an anti-STAT6 (B) antibody. Immuno-complexes were separated by SDS–PAGE, transferred to PVDF membrane, and detected with an anti-STAT6 antibody (A). N: nucleus, C: cytoplasm, IP: immunoprecipitation, IB: immunoblot. Representative experiment out of two.

3.5. Concluding remarks

In this work, we provide evidence for a functional and physical interaction between GR and STAT6. Further studies are needed to elucidate the mechanism of GR and STAT6 mutual transcriptional repressive activities. A protein–protein interaction could cause sterical hindrance and prevent GR and STAT6 to establish appropriate contacts with the basal transcriptional machinery as recently suggested for NF-κB [24]. GR and STAT6, which have both been described to interact with the coactivator CBP (CREB-binding protein)/p300 [25,26], could compete for limiting amounts of CBP within the cell, as previously described for the AP-1 inhibition by nuclear receptors [26]. GR and STAT6 could also form a ternary complex with CBP, as recently described for the mutual antagonism between GR and NF-κB [27]. We are currently investigating these hypotheses.

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