Corticosteroid inhibits IL-4 signaling through down-regulation of IL-4 receptor and STAT6 activity

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Abstract Corticosteroids are potent anti-inflammatory and immunosuppressive agents which down-regulate cytokine production and action. Yet, contradictory results have been reported for their effects on the interleukin (IL)-4-mediated response. Using type II Fc receptor for IgE/CD23 as a target gene, here we report that corticosteroids at 10^{-4}–10^{-6} M inhibit the IL-4 signaling pathway in human primary immune cells by down-regulation of the IL-4-induced IL-4 receptor expression and STAT6 activation. Although functional antagonism between steroid receptor and STAT6 for their transcriptional activity has been recently described, this is the first report that steroid inhibits the IL-4-induced STAT6 activity at the level of tyrosine phosphorylation and target DNA binding.

Key words: Interleukin-4; STAT6; Corticosteroid; IL-4 receptor; CD23/FcεR II

1. Introduction

Although corticosteroids have been widely used as a potent anti-allergic and anti-inflammatory drug, the effects of steroids on the interleukin (IL)-4-induced allergic response have been variable and often contradictory [1,2]. Specifically, both the positive and the negative regulation of the IL-4-induced response such as IgE production and IL-4 receptor expression, have been reported in different cell systems for varying doses of corticosteroids such as hydrocortisone, methylprednisolone, and dexamethasone [3–5].

Yet, effects of corticosteroids on the PMA- or IL-4-induced CD23/FcεR II (type II Fc receptor for IgE) expression are generally found to be inhibitory in both normal and allergic B cells [6,7]. CD23 serves as an important mediator for allergy and inflammation [8,9]. Two isoforms, CD23a and CD23b, are known in human systems whose expression patterns are distinct. It has been reported that CD23b is a primary response gene induced by IL-4 in human B cells and monocytes with a fast kinetics independent of on-going protein synthesis [10]. Thus, the CD23b gene expression serves as a good model system to study IL-4 signal transduction. Using human immune cells responsive to IL-4 for CD23b induction, we have investigated the inhibition mechanism of steroid on the IL-4-induced signal transduction.

In this report, we demonstrate that corticosteroids at 10^{-4}–10^{-6} M inhibit the IL-4-induced cell surface protein and mRNA expression of CD23 in tonsillar mononuclear cells as well as established human monocytic or B cell lines, and the inhibition was synergized with cotreatment with IFN-γ. Notably, the inhibition was accompanied by the down-regulation of IL-4 receptor expression and by the suppression of STAT6 activity via decreased tyrosine phosphorylation and reduced binding to the target DNA such as the GAS sequence of the CD23b promoter. Together with the recently proposed transcriptional antagonism between glucocorticoid receptor and STAT6 [11], the results of the present study suggest a new mode of steroid action for inhibition of IL-4 signal transduction.

2. Materials and methods

2.1. Cell culture

Human primary immune cells were obtained by isolation from freshly excised tonsils using Ficoll-Hypaque (Sigma, $d = 1.077$) through density gradient centrifugation. Human promonocytic cell line U937 and Burkitt's lymphoma B cell line Ramos were from ATCC. Isolated mononuclear cells (MNCs), U937, or Ramos cells were cultured in complete RPMI media (Gibco, Grand Island, NY, USA) containing 10% FBS at 37°C with 5% CO_2. Cells were treated with IL-4 (R&D; Systems, Minneapolis, MN, USA) with or without methylprednisolone (1-dehydro-6-methylhydrocortisone, Sigma), or IFN-γ (R&D Systems).

2.2. Analysis of surface CD23 and IL-4 receptor by flow cytometry

The surface expression of FcεR II/CD23 on cells was analyzed employing FACS Calibur (Becton Dickinson, Mountain View, CA, USA) using mouse anti-human CD23 mAb-PE (Becton Dickinson) after 24 h culture with IL-4. The expression of IL-4 receptor alpha was analyzed by staining cells with monoclonal anti-IL-4 receptor Ab (M56) and then with goat anti-mouse IgG-FITC (Sigma) as described [12]. The surface protein levels were expressed as the mean fluorescence intensity (MFI). Each experiment was repeated several times and the values represent a mean of two independent determinations.

2.3. Analysis of mRNA levels of CD23 and IL-4 receptor by Northern blot

Total cytoplasmic RNAs were isolated using 4 M guanidinium isothiocyanate and 5 M cesium chloride through ultracentrifugation. RNAs were separated on a 1% agarose gel, transferred to nylon membranes, and hybridized with a [^{32}P]-labeled probe of FcεR II/CD23 or IL-4 receptor cDNA as described [10,12]. Blots were reprobed with the adenosyl phosphoribosyl transferase (APRT) probe as an internal control [13]. A representative blot for each experiment is shown.

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Abbreviations: IL, interleukin; STAT, signal transducers and activators of transcription; IFN, interferon; FcεR II, type II Fc receptor for IgE; EMSA, electrophoretic mobility shift assay; AP-1, activator protein-1

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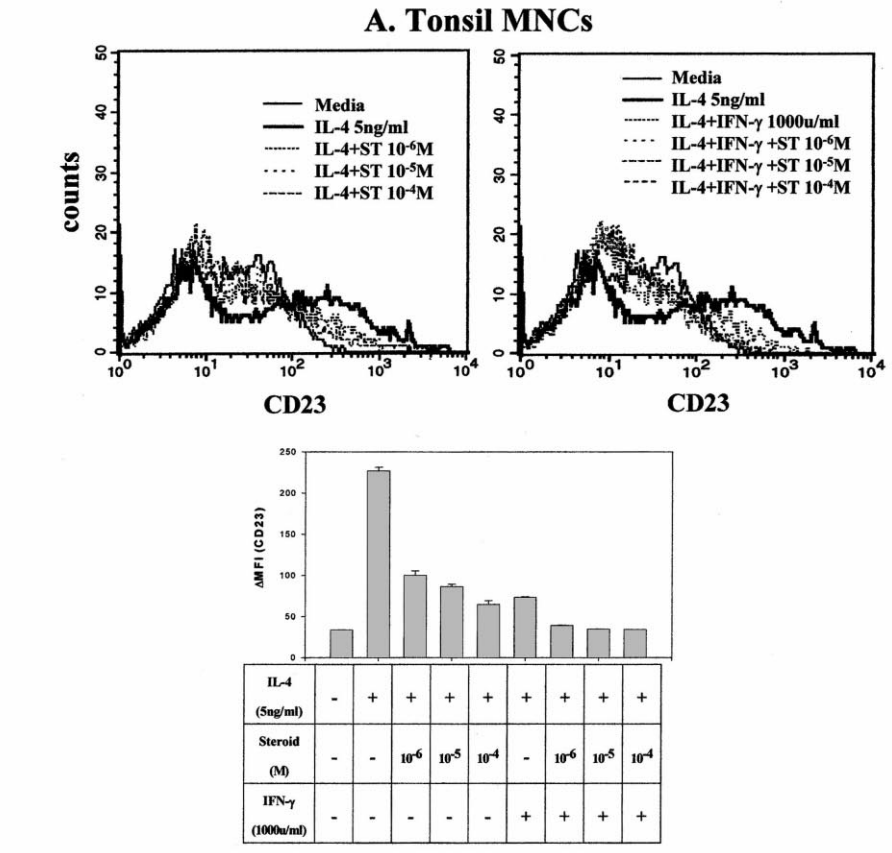
A. Tonsil MNCs
counts
Media
IL-4 5ng/ml
IL-4+ST 10-6M
IL-4+ST 10-5M
IL-4+ST 10-4M
CD23
Media
IL-4 5ng/ml
IL-4+IFN-γ 1000u/ml
IL-4+IFN-γ +ST 10-6M
IL-4+IFN-γ +ST 10-5M
IL-4+IFN-γ +ST 10-4M
CD23
ΔMFI (CD23)
IL-4 (5ng/ml) - + + + + + + + +
Steroid (M) - - 10-6 10-5 10-4 - 10-6 10-5 10-4
IFN-γ (1000u/ml) - - - - - + + + +

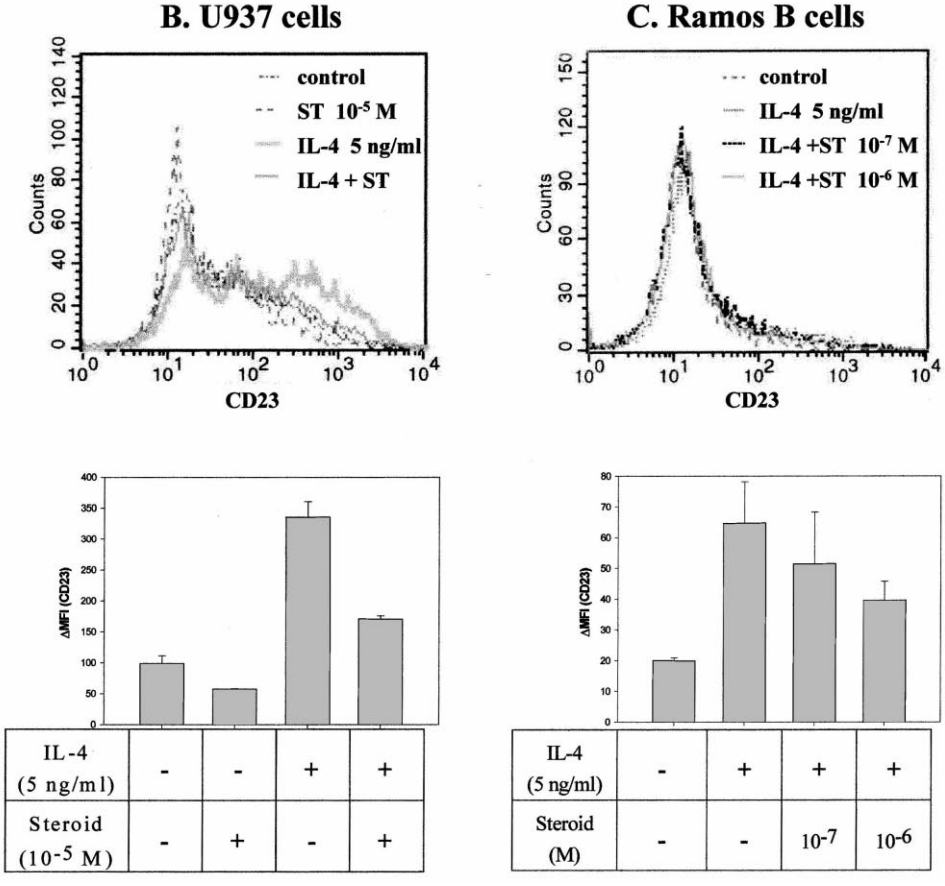
B. U937 cells
Counts
control
ST 10-5 M
IL-4 5 ng/ml
IL-4 + ST
CD23
ΔMFI (CD23)
IL-4 (5 ng/ml) - - + +
Steroid (10-5 M) - + - +
C. Ramos B cells
Counts
control
IL-4 5 ng/ml
IL-4 +ST 10-7 M
IL-4 +ST 10-6 M
CD23
ΔMFI (CD23)
IL-4 (5 ng/ml) - + + +
Steroid (M) - - 10-7 10-6

Fig. 1. Inhibition of the IL-4-induced surface FcεR II/CD23 expression by steroid (ST) in various human immune cells. Tonsil MNCs (A), U937 cells (B), and Ramos cells (C) were seeded in 24-well plates (2×10^5 cells/well), and treated with IL-4 (5 ng/ml), methylprednisolone (10^{-4}–10^{-6} M), or IFN-γ (1000 U/ml) as indicated. After 24 h culture, FACScan analysis of surface CD23 was performed using monoclonal anti-CD23-PE as in Section 2. ΔMFI was calculated as MFI of anti-CD23-PE-stained sample − MFI of unstained control.
←

2.4. Electrophoretic mobility shift assay (EMSA)

Preparation of nuclear extracts for EMSA was done after stimulation of cells with IL-4 as described [14]. IL-4RE GAS oligomer, CD23b GAS1 containing the STAT6 binding site of human CD23b, was labeled with [^{32}P]dCTP (3 000 Ci/mmol, NEN) by Klenow [15]. In addition CD23b GAS2 probe (5′-GGTGAATTTCTAAGAAAGGGACTGGTGTGAGTAAGGAG-3′) representing a longer native sequence of human CD23b promoter (−234 to −199) containing both the STAT6 binding site and the activator protein-1 (AP-1) binding site was also used. The extracts (5–10 μg) were incubated with the labeled oligomer in the binding buffer for 20 min at room temperature. Mobility shift of the oligomer was then analyzed by 5% PAGE in 0.5× TBE buffer.

2.5. Immunoprecipitation and immunoblotting

Cells were pretreated with corticosteroid for various durations and stimulated with IL-4, after which total cell extracts were prepared using a lysis buffer containing 1% NP40 as described [16]. The extracts were immunoprecipitated with mouse monoclonal anti-phosphotyrosine (4G10) or rabbit polyclonal anti-STAT6 Abs (UBI, Lake Placid, NY, USA), and then with respective secondary antibody conjugated with agarose. After fractionation on a 10% denaturing SDS–PAGE and transfer to PVDF membranes, immunoblotting was performed using anti-STAT6, anti-IL-4 receptor (R&D Systems), anti-Jak1 (UBI), or anti-phosphotyrosine antibodies as indicated. After stripping, the blot was reprobed with anti-STAT6 Ab. All blots were developed using an ECL detection kit (Amersham).

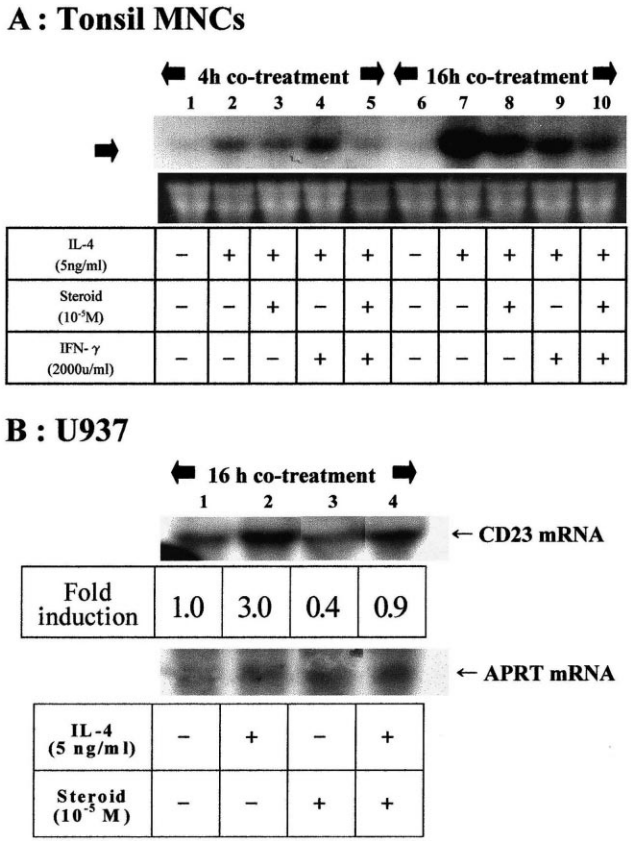

Fig. 2. Inhibition of the IL-4-induced CD23 mRNA expression by steroid. A: Inhibition kinetics and the effect of IFN-γ cotreatment in tonsillar mononuclear cells. Mononuclear cells (1×10^8) were treated with IL-4 (5 ng/ml), methylprednisolone (10^{-5} M), and IFN-γ (2000 U/ml) for the indicated time periods. Cells were harvested for RNA isolation and the subsequent Northern analysis using the full-length cDNA probe of CD23 as described. Top: Northern autoradiogram. Bottom: EtBr-stained RNA gel. B: Inhibitory effect of steroid on the IL-4-induced CD23 mRNA expression in U937 cells. U937 cells (1×10^7) were treated with IL-4 (5 ng/ml) and methylprednisolone (10^{-5} M). The total RNAs were isolated and subjected to Northern analysis (top). The membrane was stripped and reprobed with an APRT probe as described (bottom).

3. Results and discussion

3.1. Corticosteroid inhibits the IL-4-induced CD23 surface expression: synergistic action with IFN-γ

The up-regulation of CD23 expression is one of the major phenotypical changes induced by IL-4 in B cells and monocytes [17]. In fact, CD23 is regarded as a differentiation antigen important for IgE production by B cells, for allergen uptake and presentation by antigen presenting cells, and for inflammation by accessory cells including basophils and eosinophils [8,9,18,19]. Using tonsillar mononuclear cells, we have observed that a corticosteroid, methylprednisolone, effectively suppresses the IL-4-induced CD23 up-regulation in a dose-dependent manner (60–85% inhibition at 10^{-4}–10^{-6}M). IFN-γ, a known antagonist of the IL-4-induced CD23 expression, acted synergistically with the steroid, and resulted in a nearly complete suppression (90–95%) upon cotreatment (Fig. 1A). Such inhibitory effects of the corticosteroid were also observed with U937 and Ramos, established monocytic and B cell lines, respectively, which were both responsive to IL-4 for the induction of CD23 expression (Fig. 1B,C). A similar inhibitory effect was obtained with other corticosteroids, hydrocortisone or dexamethasone at 10^{-4}–10^{-7}M (data not shown).

3.2. Inhibition of the IL-4-induced CD23 mRNA by corticosteroid

To investigate the mechanism of CD23 inhibition by steroid, we have examined the regulatory effect of steroid on CD23 mRNA level and the kinetics of inhibition. As shown in Fig. 2, the steroid suppressed the IL-4-induced CD23 mRNA levels in a time-dependent manner. Contrary to IFN-γ whose inhibitory effect was not observed during the early time of IFN-γ treatment ([20], Fig. 2A, lanes 2 vs. 4), the suppressive effect of corticosteroid appeared by 4 h and became significant by 16 h (Fig. 2A, lanes 2 vs. 3 and 7 vs. 8). The synergistic inhibition was noted upon cotreatment of cells with steroid and IFN-γ (lanes 7 to 10). A similar result was obtained with U937 cells for the suppressive effect of steroid on CD23 mRNA (Fig. 2B). These results indicate that steroid inhibition of the IL-4-induced CD23 protein expression observed in Fig. 1 proceeds via down-regulation of CD23 mRNA in these immune cells.

3.3. Down-regulation of IL-4 receptor expression by corticosteroid

As one of the mechanisms of the steroid-mediated inhibi-

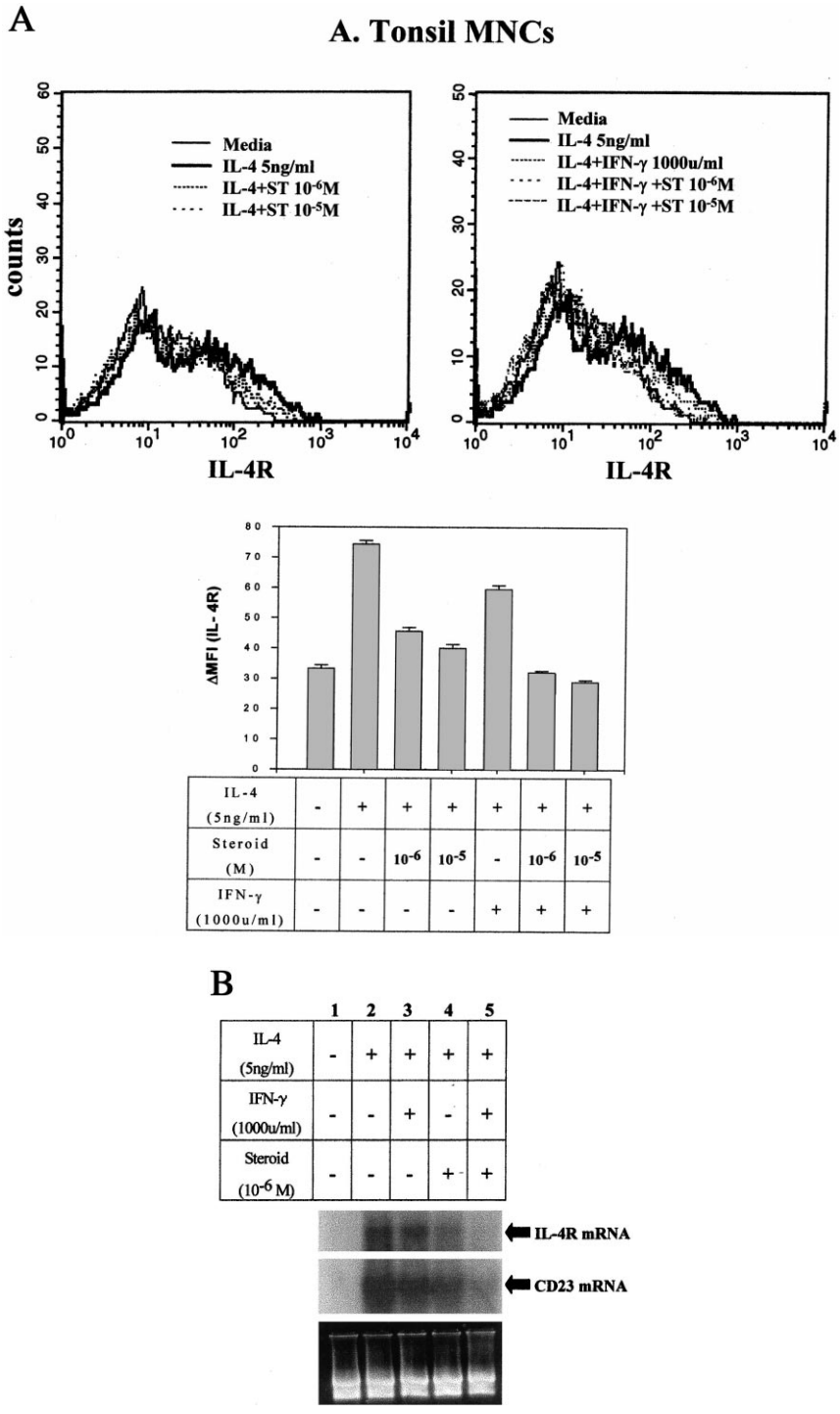

Fig. 3. Down-regulation of the IL-4-induced IL-4 receptor by steroid. A: Inhibitory effect of steroid on the surface IL-4 receptor expression. Tonsillar mononuclear cells (1×10^6) were treated with IL-4 (5 ng/ml), methylprednisolone (10^{-5} M), and IFN-γ (1000 U/ml) for 24 h. Cells were harvested and stained with mouse monoclonal anti-human IL-4Rα Ab (M56) and then with anti-mouse-IgG-FITC as described. ΔMFI was calculated as MFI of anti-IL-4R Ab and anti-mouse IgG-FITC – MFI of cells stained with anti-mouse IgG-FITC alone. B: Inhibitory effect of steroid on the IL-4 receptor mRNA expression – coordinated regulation with CD23 mRNA. Mononuclear cells (1×10^8) were treated with IL-4 (5 ng/ml), IFN-γ (1000 U/ml) or steroid (10^{-6} M) and cultured for 16 h. Total RNAs were isolated and processed for Northern analysis. The blot was probed with an IL-4R cDNA probe (top) and then with a CD23 cDNA probe after stripping (middle). The EtBr-stained RNA gel is also shown (bottom).

tion of the IL-4-induced CD23 expression, we have next examined effects of steroid on the modulation of IL-4 receptor expression. Although IL-4 receptor has been shown to be subject to regulation by cytokines and steroid, contradictory results have been obtained depending on the cell types and dose of steroid [5,12]. Using human tonsillar mononuclear cells, we have observed that 10^{-5}–10^{-6}M methylprednisolone effectively down-regulates the IL-4-induced IL-4 receptor ex-

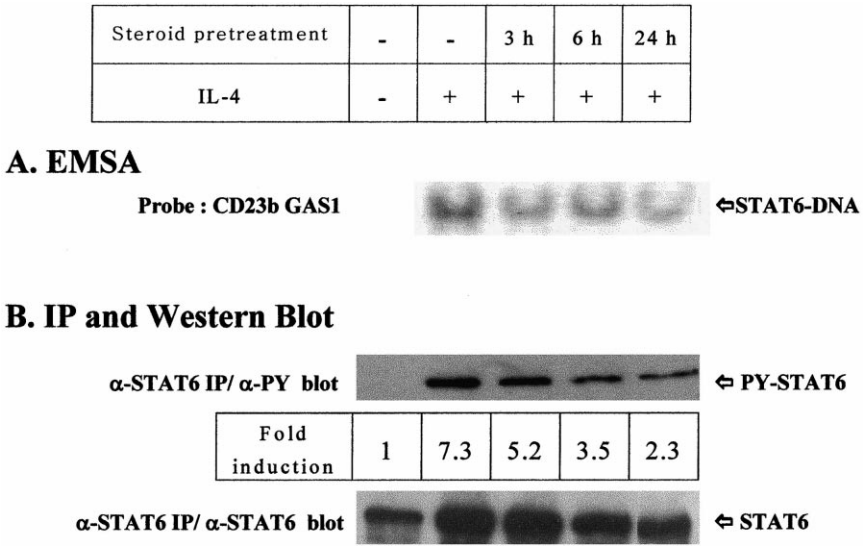

Fig. 4. Suppression of the IL-4-induced STAT6 activation by steroid: reduced DNA binding and tyrosine phosphorylation of STAT6 by steroid. A: Tonsillar mononuclear cells (1×10^8) were treated with steroid (10^{-5} M) for various durations prior to the stimulation with IL-4 (5 ng/ml) for 30 min. Cells were harvested and nuclear extracts were prepared to perform EMSA using the CD23b GAS1 probe as described in the text. B: The total cell lysates were prepared from the same cultures as in A. The lysates (1 mg) were subjected to immunoprecipitation with anti-STAT6 Ab followed by immunoblotting with anti-phosphotyrosine Ab and then with anti-STAT6 Ab as described.

pression (Fig. 3A). Such inhibitory effect was also manifested at the IL-4 receptor mRNA level (Fig. 3B). While IFN-γ (1000 U/ml) induced a modest inhibition of the IL-4-induced IL-4 receptor levels, steroid at 10^{-5}–10^{-6} M caused a more potent inhibition. Upon cotreatment, IFN-γ and steroid acted in a synergistic manner to further reduce the IL-4 receptor level. It should be noted that the modulation of IL-4 receptor mRNA coordinately occurred with that of CD23 mRNA as indicated in earlier studies [21]. This suggests that the suppressive effect of corticosteroid and/or IFN-γ on CD23 expression is partly mediated via inhibition of IL-4 receptor gene expression by these agents.

3.4. Suppression of STAT6 activity by corticosteroid

The IL-4 signal transduction leading to CD23 gene expression is thought to proceed via STAT6-dependent pathways [22,23]. STAT6 acts as a signal transducer immediately downstream of IL-4 receptor activation via tyrosine phosphorylation by Jak-1 and Jak-3, IL-4 receptor-associated tyrosine kinases [24]. In fact, role of STAT6 in the IL-4-induced gene expression has been well established during recent years.

Thus, we have examined whether STAT6 is a target of steroid action to suppress CD23 gene activation. Steroid when cotreated to cells with IL-4 for 10–30 min did not exert any inhibitory effects on the IL-4-induced STAT6 binding to

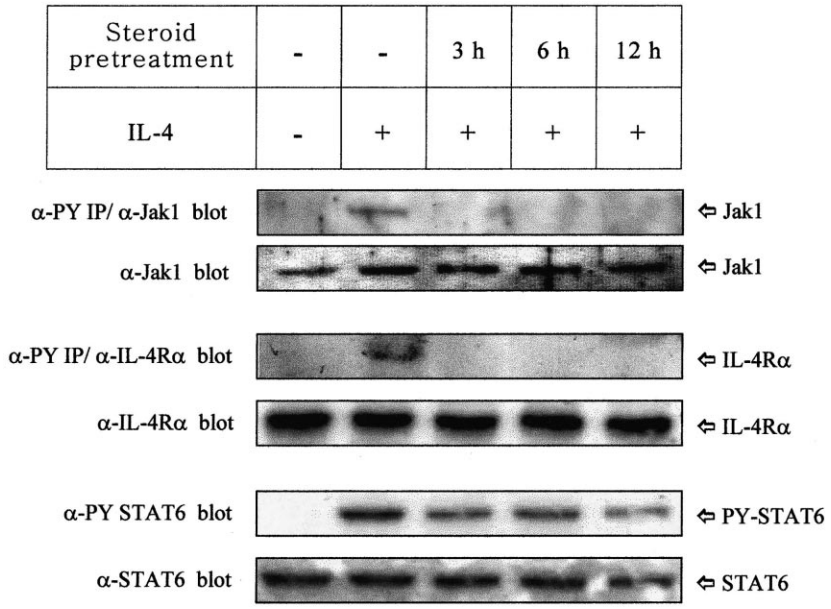

Fig. 5. Suppressive effects of steroid on the IL-4-induced tyrosine phosphorylation of Jak1 and IL-4 receptor. Tonsillar mononuclear cells (1×10^8) were treated with steroid (10^{-5}M) for various durations. Cells were then stimulated with IL-4 for 10 min, after which cell extracts were prepared for the analysis of tyrosine phosphorylation and protein level of Jak1, IL-4 receptor, and STAT6 by immunoprecipitation and Western blot.

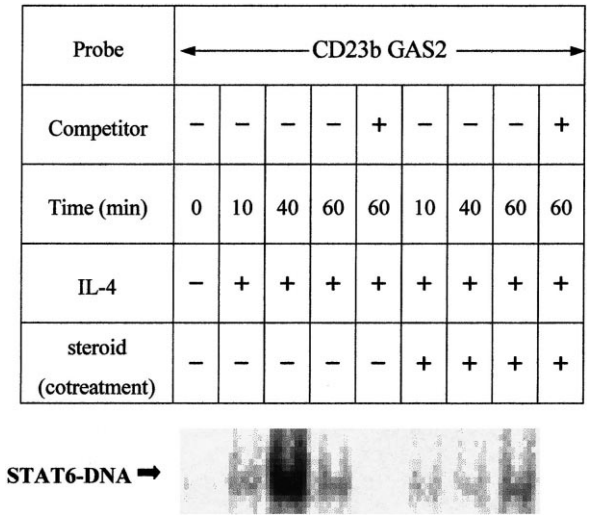

Fig. 6. Inhibitory effect of steroid cotreatment on the IL-4-induced STAT6 binding to the CD23b promoter. Mononuclear cells (1×10^8) were cotreated with IL-4 (5 ng/ml) and methylprednisolone (10^{-5} M) for indicated durations, after which nuclear extracts were prepared to perform EMSA using the native CD23b promoter sequence (CD23b GAS2) as described in the text. Where indicated, 100-fold molar excess of cold oligomers was added to the reaction as competitor prior to the addition of labelled oligomers. The formation of a single complex was noted with IL-4-treated extracts, and the identity of the complex as STAT6-DNA was confirmed by supershift assay using anti-STAT6 Ab.

the CD23b GAS1 sequence (data not shown). While the IL-4-induced STAT6 activation occurs generally within a few minutes, reaches to maximum during 20–40 min, and then significantly declines after 2 h [25], the inhibitory effect of steroid on the IL-4-induced CD23 gene expression is prominent after 4 h (Fig. 2). In order to assess the effect of steroid on the IL-4-induced STAT6 activity, we have thus pretreated cells with steroid for 3–24 h and then stimulated with IL-4 for 30 min. Under these conditions, a significant inhibition of the IL-4-induced STAT6 activity was observed for target DNA binding (Fig. 4A). This appears due to the reduced tyrosine phosphorylation of STAT6 (Fig. 4B). In order to further delineate the molecular mechanism of steroid action for STAT6 inhibition, we have analyzed the effect of steroid on the activation status of Jak1 and IL-4 receptor, upstream components of STAT6 in IL-4 signaling. As shown in Fig. 5, steroid effectively suppressed the IL-4-induced tyrosine phosphorylation of STAT6 with concomitant inhibition of Jak-1 and IL-4 receptor activation as shown by specific abrogation of tyrosine phosphorylation of these molecules. The results indicate that the corticosteroid-induced inhibition of IL-4 signaling occurs via the suppression of STAT6 activation by blocking tyrosine phosphorylation of Jak1 and IL-4 receptor, which would inhibit docking of STAT6 to the receptor and the subsequent phosphorylation of STAT6, nuclear translocation, and the target DNA binding. A steroid-inducible STAT, such as Jak-binding protein/suppressor of cytokine signaling/STAT-induced STAT inhibitor may be involved in this process [26–28]. In addition, a more direct role of steroid on STAT6 suppression during IL-4-induced CD23 gene expression is suggested by data in Fig. 6. That is, when an extended native promoter sequence of CD23b (−234 to −199) which contains the STAT6 site and the adjacent AP-1 site was used, the inhibition of STAT6 binding was clearly observed even when cells were simultaneously treated with IL-4 and steroid for 10–40 min. While the mechanism of the observed inhibition is not clear at present, a possible role of AP-1 sequence in mediating steroid action via interaction with steroid receptor is to be examined.

Taken together, these results suggest that a direct inhibition of corticosteroid on the STAT6 binding to CD23b promoter as well as an indirect action through the induction of a STAT inhibitor are both responsible for the inhibitory action of steroid on the IL-4-induced CD23 gene activation. As much as the role of STAT6 has been implicated in the induction of IL-4 receptor gene expression [29], it is possible that down-modulation of IL-4 receptor by steroid observed upon prolonged treatment with IL-4 in Fig. 3 occurs via inhibition of the IL-4-induced STAT6 activity. Unlike murine systems, however, a definitive role of STAT6 in regulating human IL-4 receptor gene expression has not been demonstrated, partly due to the unavailability of the exact promoter structure of the human IL-4 receptor. Still, the observed down-regulation of IL-4 receptor by steroid would in part account for the suppressive action of corticosteroid on the IL-4-mediated CD23 induction and other cellular responses occurring in later phase of IL-4 action.

Modulation of STAT activity by steroids has been suggested for functional cooperation as well as antagonism between STATs and steroid receptors through reciprocal regulation of their transcriptional activities as observed with STAT1, STAT3, STAT5, and STAT6 [11,30–33]. In particular, Biola et al. [11] have recently reported that the transcriptional antagonism between the glucocorticoid receptor and STAT6 involves physical interaction of the two molecules without change in DNA binding of STAT6. The present report is the first to demonstrate that corticosteroid targets STAT6 at the level of tyrosine phosphorylation and DNA binding, which suggests a novel mode of steroid action regulating IL-4 signal transduction. Identification of steroid-induced STAT inhibitors blocking tyrosine phosphorylation of STAT6 as well as the elucidation of inhibition mechanism of steroid action to directly suppress the STAT6 binding to the CD23b promoter warrant further investigation.

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