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Corticosteroids Enhance the Capacity of Macrophages to Induce Th2 Cytokine Synthesis in CD4+ Lymphocytes by Inhibiting IL-12 Production

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We investigated the effects of corticosteroids on IL-12 production by mouse splenic adherent cells and the subsequent capacity of these cells to induce cytokine production by CD4+ T cells. To distinguish the effects of corticosteroids on APCs from those on T cells, only the APCs and not the T cells were exposed to corticosteroids. Treatment of splenic adherent cells with dexamethasone greatly inhibited production of IL-12, a cytokine known to enhance IFN-γ synthesis and decrease IL-4 synthesis by CD4+ T cells. The reduction in IL-12 production by corticosteroid-treated macrophages decreased their ability to induce IFN-γ and increased their ability to induce IL-4 synthesis in Ag-pulsed CD4+ T cells. Spleenic adherent cells from mice treated in vivo with dexamethasone also displayed a reduced capacity to produce IL-12. These results help to resolve previous conflicting observations regarding the effects of corticosteroids on cytokine production by T cells, and indicate that while corticosteroids may directly inhibit Th1 and Th2 cytokine production in T cells, corticosteroids, by reducing IL-12 production in APCs, have the potential to indirectly enhance Th2 cytokine synthesis. Therefore, treatment of diseases such as allergy with chronic corticosteroids may indirectly exacerbate the course of the disease, which is caused primarily by the overproduction of Th2 cytokines in allergen-specific CD4+ T cells. The Journal of Immunology, 1998, 160: 2231–2237.

Corticosteroids are potent immunosuppressive and anti-inflammatory agents and are used therapeutically for a broad spectrum of diseases, including autoimmune and allergic inflammatory diseases and organ transplant rejection. Corticosteroids affect the immune system by modulating cytokine production in lymphocytes and altering the trafficking and function of neutrophils, eosinophils, mast cells, and endothelial cells (1–4). Corticosteroids inhibit the production of most ILs in activated T cells by increasing the production of I-κB, which binds to the transcription factor NF-κB and inhibits its capacity to translocate to the nucleus (5–7). However, the effect of corticosteroids on IL-4 production in lymphocytes is controversial. Some investigators have demonstrated that corticosteroids inhibit IL-4 production in lymphocytes (8), whereas other investigators have demonstrated that corticosteroids enhance IL-4 synthesis in T cells both in vivo and in vitro (9–11). Determination of the precise effect of corticosteroids on IL-4 synthesis is important, since enhancement of IL-4 synthesis by corticosteroids may be clinically undesirable, for example in the setting of allergic disease and asthma, and may reduce enthusiastic use of corticosteroid therapy in asthma, as recommended by the National Institutes of Health (12).

Since many cell types respond to corticosteroids, conflicting results regarding cytokine synthesis in different studies may be due to a neglect in some studies of evaluating the effects of corticosteroids on the APCs used to activate T cells. We therefore wished to distinguish the effects of corticosteroids on the APC used to activate the T cell from direct effects of corticosteroids on the T cell, and performed experiments in which only the APC, and not the T cell, was exposed to corticosteroids. Here we show that corticosteroids affect murine macrophages by inhibiting the production of IL-12, a cytokine that is extremely potent in enhancing IFN-γ and inhibiting IL-4 synthesis in T cells (13, 14). The reduced production of IL-12 by corticosteroid-treated macrophages resulted in a decreased ability to induce IFN-γ and an increased ability to induce IL-4.

These results strongly suggest that corticosteroids have the potential to enhance Th2 cytokine synthesis. Since Th2 cytokines inhibit inflammatory conditions such as diabetes and transplant rejection, such an effect may be beneficial for such inflammatory problems. However, although administration of corticosteroids may benefit acute asthma or allergic disease by directly inhibiting cytokine synthesis in T cells, enhanced production of Th2 cytokines by corticosteroid therapy may indirectly exacerbate allergic disease, which is caused by the overproduction of Th2 cytokines in allergen-specific CD4+ T cells. This deleterious effect would result from a reduction in IL-12 synthesis by corticosteroids, thereby enhancing the production of Th2 cytokines, and limiting the production of Th1 cytokines (which attenuate allergic disease).

Materials and Methods

Animals

DBA/2 mice or BALB/c × DBA/2 (CB6F1) mice were obtained from The Jackson Laboratory (Bar Harbor, ME) and were used at 6 to 8 wk of age.

Reagents

9-Fluoro-16-methyl-prednisolone (dexamethasone, or DXM)3 was purchased from Sigma Chemical Company (St. Louis, MO).

3 Abbreviations used in this paper: DXM, dexamethasone; KLH, keyhole limpet hemocyanin; Sp/AC, splenic adherent cells; HKL, heat killed Listeria monocytogenes; cDMEM, complete DMEM.
Steroids inhibit IL-12 production by splenic adherent cells

Culture medium
Cells were cultured in DMEM (HyClone Laboratories, Logan, UT) supplemented as described previously (15) and containing 10% FCS (HyClone Laboratories, Logan, UT) cDMEM.

Immunizations
To generate primed CD4⁺ T cells, mice were primed with 150 μg of keyhole limpet hemocyanin (KLH, Calbiochem, San Diego, CA) in CFA in the footpads 9 days before use.

Monoclonal Abs
Monoclonal anti-Ly 2.1 (HB129), anti-I-A⁺ (MK66), anti-CD24 (TIB183), and anti-I-E⁺ (14.4.4s) Ab-secreting hybridomas were obtained from ATCC (American Type Culture Collection, Rockville, MD) and purified from ascites fluid by ammonium sulfate precipitation. Anti-IL-12 p40 mAbs C17.8 and C15.6 (provided by Dr. Giorgio Trinchieri, Wistar Institute of Anatomy and Biology, Philadelphia, PA), monoclonal anti-IFN-γ Abs R4–6A2 (ATCC) and XMG1.2 (obtained from Dr. Tim Mosmann, University of Manitoba, Edmonton, Canada), monoclonal anti-IL-10 Abs JES-2A5 and SXC.1 (Dr. M. Howard, DNAX Research Institute, Palo Alto, CA), and monoclonal anti-IL-4 Abs BVD4–1D11 and BVD6–24G2 (Dr. M. Howard, DNAX) were purified from ascites fluid by ammonium sulfate precipitation followed by DEAE-Sephadex chromatography (Sigma).

Lymphokines
Recombinant murine IL-12 was generously provided by Dr. Stanley Wolf (Genetics Institute, Cambridge, MA). Recombinant murine IL-4 was a generous gift of Dr. M. Howard (DNAX). Recombinant murine IFN-γ was provided by Dr. M. Palladino, Genentech (San Francisco, CA).

Preparation of splenic adherent cells (SpAC)
Splenic cells were cultured at 10⁶/ml in cDMEM medium in tissue culture dishes (Falcon 3003; Becton Dickinson, Mountain View, CA) for 2 h at 37°C. The nonadherent cells were removed by washing with warm cDMEM until visual inspection revealed a lack of lymphocytes (>93% of the cell population). The adherent cells were removed from plates by incubating for 15 min with ice-cold PBS and rinsing repeatedly.

Stimulation of SpAC with heat-killed Listeria monocytogenes (HKL) or LPS
The isolated SpAC population was stimulated in the presence or absence of DXM at 10⁻⁴, 10⁻³, 10⁻², and 10⁻¹ M at 1 x 10⁸ per well in 96-well culture plates with either 0.5 μg/ml of LPS or with HKL at 2 x 10⁶ bacteria per well, prepared as previously described (16). Supernatants were collected after 18 h and analyzed for IL-12 content. In some experiments, the SpAC were incubated overnight in media in the presence or absence of DXM, then washed with warm cDMEM three times to remove DXM before addition of HKL, LPS, or CD4⁺ T cells. Supernatants were collected after 18 h and assayed for cytokine content by ELISA.

Purification of CD4⁺ T cells
Draining axillary, popliteal, and inguinal lymph nodes were removed from mice 9 days after priming with KLH in CFA in the footpads. Lymphocytes were depleted of B cells by adherence to goat anti-mouse Ig-coated dishes for 1 h at 4°C. Nonadherent cells were depleted of CD8⁺ T cells, residual B cells, and other accessory cells by treating the cells with a mixture of anti-CD8, anti-class II, anti-CD24 Abs on ice for 10 min, followed by addition of baby rabbit C’ (Pel Freeze, Rogers, AR) and incubation at 37°C for 45 min.

Induction of cytokine synthesis in CD4⁺ T cells
Purified CD4⁺ T cells were incubated in 96-well plates at 4 x 10⁵/well with SpAC and KLH (10 μg/ml) in 0.15 ml of cDMEM in quadruplicate. Culture supernatants were harvested on day 2 or 4 as indicated and assayed for levels of IL-4, IL-10, IL-12, and IFN-γ by ELISA. In some experiments, T cells were recovered after 4 days of culture and stimulated at 4 x 10⁵/well with fresh normal SpAC (10⁵/well) and Ag (KLH, 10 μg/ml). Supernatants were harvested at 24 h after restimulation.

Cytokine ELISA
Cytokine content in supernatants was determined by ELISA. In brief, 96-well plates were coated overnight with primary anti-cytokine capture Ab, Plates were washed, blocked, and dilutions of supernatants or standards were added. Dilutions of culture supernatant were incubated overnight at 4°C, and after washing, the wells were incubated with biotin-conjugated anti-cytokine-detecting mAb. After a 2-h incubation, the plates were washed and a horseradish peroxidase-streptavidin conjugate (Southern Biotechnology Associates, Inc., Birmingham, AL) was added. The plates were incubated for an additional hour, and after washing, O-phenylenediamine (OPD) substrate was added. After developing, the OD was determined at 492 nm. The amount of cytokine in each supernatant was extrapolated from the standard curve. The Ab pairs used were as follows, listed by capture/ biotinylated detection: IL-4, BVD4–1D11/BVD6–24G2; IFN-γ, R4–6A2/XMG1.2; IL-12, C17.8/C15.6. The standards were cytokine curves generated in 24 h dilutions from 500 to 39 pg/ml for IL-4, 20 to 0.156 ng/ml for IFN-γ, and 4000 to 30 pg/ml for IL-12. Standards for IL-4, IL-10, and IFN-γ are culture supernatants of Th2 or Th1 clones generated in our lab, which were calibrated against recombinant cytokines. The IL-12 standard used was a culture supernatant of SpAC stimulated with HKL, which was calibrated against rIL-12.

Lymphokine assays
IL-2 was assayed by using the T cell growth factor-dependent line HT2 (generously provided by Dr. Sam Strober, Stanford University, Palo Alto, CA). HT2 cells (5 x 10⁶/well) were added to dilutions of test samples in 96-well plates. Differential blocking of IL-4 or IL-2 was achieved by adding the anti-IL-4 mAb 11B11, or the anti-IL-2 mAb S4B6, or both. Test samples were diluted such that the mAbs were present in excess, as demonstrated by complete inhibition of HT2 proliferation in the presence of both mAbs. After 18 h, cells were pulsed with 1 μCi of [³H]thymidine in 4 h. Cultures were harvested with a PHD harvester (Cambridge Technology, Cambridge, MA) and [³H]thymidine was measured using standard liquid scintillation counting techniques. Units of IL-2 present in culture supernatants were calculated using recombinant murine IL-2 as a standard.

Results
Treatment of adherent cells with DXM inhibits IL-12 production
Previous studies demonstrated that DXM acts directly on T cells to inhibit cytokine production. We wished to determine whether DXM could also influence T cell cytokine synthesis indirectly via an effect on IL-12 production by APCs. SpAC were isolated from naive DBA/2 mice and incubated with HKL or LPS for 24 or 48 h in the presence or absence of DXM. Figure 1 shows that SpAC produced large quantities of IL-12 when cultured with HKL or LPS, and that such IL-12 production was greatly inhibited by the presence of DXM. The inhibition of IL-12 synthesis was dose dependent over a wide range of DXM concentrations, and occurred when the adherent cells were stimulated with either HKL or LPS. Furthermore, the reduction in IL-12 synthesis occurred both in cultures in which DXM remained and in those in which DXM was washed out after 6 to 8 h of pretreatment of monocytes with DXM before stimulation with Listeria (Fig. 2).

Pretreatment of adherent cells with DXM inhibits their capacity to induce IFN-γ and enhances their capacity to induce IL-4 production by T cells
Since IL-12 has been shown to have potent effects on cytokine production by CD4⁺ T cells, we asked if the cytokine profiles of CD4⁺ T cells responding to Ag presented by DXM-pretreated APC would be altered. Direct effects of DXM on T cells were eliminated by pretreatment of SpAC from naive DBA/2 in vitro with DXM for 18 h and washing them to remove DXM, before culture with synergistic CD4⁺ T cells purified from lymph nodes of KLH-primed mice and the Ag KLH. Figure 3A shows that IL-12 production in cultures of DXM-pretreated SpAC was significantly decreased in comparison with untreated SpAC. In the absence of DXM treatment, stimulation with KLH resulted in the development of T cells producing high levels of IFN-γ. However, pretreatment of SpAC with DXM for 18 h greatly inhibited their capacity to induce the development of IFN-γ production by T cells (Fig. 3B) and significantly increased production of IL-4 (Fig. 3C).
DXM-pretreated APC induced robust amounts of IL-4 and IL-5 in purified T cells, indicating that these cells are viable. No cytokine production by T cells was detected in the absence of APC, demonstrating that the DXM-treated APC are inducing the cytokine production. Thus, pretreatment of monocytes with DXM enhances their capacity to preferentially induce Th2 and inhibit Th1 cytokine synthesis.

Pretreatment of adherent cells with DXM enhances their capacity to induce IL-5 and reduces their capacity to induce IFN-γ production by T cells

SpACs pretreated with DXM developed an increased capacity to induce another Th2 cytokine, IL-5 (Fig. 4A), and a reduced capacity to induce IL-2 (Fig. 4B). In these experiments, CD4⁺ T cells were purified from lymph nodes of KLH-primed mice and cultured with DXM-pretreated SpAC or control SpAC in the presence of the Ag KLH. T cells stimulated with control APC produced very low levels of IL-5 in the initial culture, while T cells stimulated with DXM-pretreated SpAC produced much greater quantities of IL-5. Moreover, the change in cytokine profile induced by DXM-pretreated SpAC was made more pronounced when the T cells in the initial culture were restimulated after 4 days with normal APC and KLH (Fig. 4). These results indicate that T
cells stimulated with DXM-treated SpAC and Ag become committed to a Th2 pattern of cytokine synthesis.

**Addition of IL-12 to cultures of DXM-pretreated SPAC restores the induction of IFN-γ and inhibits induction of IL-4 synthesis by T cells**

To determine whether the diminished capacity of DXM-pretreated SpAC to induce IFN-γ synthesis in T cells was a result of their diminished production of IL-12, we reconstituted cultures of DXM-pretreated monocytes and T cells with rIL-12. In cultures of primed T cells and untreated SpAC, IFN-γ production is stimulated by endogenous production of IL-12 since addition of anti-IL-12 Ab blocks production of IL-12 (Ref. 17, and data not shown). Figure 5 shows that addition of 5 or 1 pg/ml of IL-12 to cultures of DXM-pretreated SpAC and T cells greatly reduced IL-4 production and enhanced IFN-γ production in these cultures to levels seen in control cultures. These results suggest that reduction of IL-12 synthesis by DXM-treated monocytes was a major effect that determined the capacity of monocytes to regulate cytokine synthesis in T cells.

**APCs from mice treated in vivo with DXM**

To demonstrate that DXM had a consequential effect on APCs in an in vivo setting, mice were injected with a therapeutic dose of DXM (100 μg i.p.). After 24 h, SpAC were purified from the DXM-pretreated mice, or from control injected mice. Figure 6 shows that SpAC from DXM-pretreated mice produced much lower amounts of IL-12 in response to either HKL or LPS than SpAC from control mice. To determine whether proliferation or cytokine production by Ag-primed T cells would differ in the presence of Ag presented by SpAC from mice treated in vivo with DXM, SpAC were purified from DBA/2 mice 24 h following i.p. injection of DXM (100 μg), and cultured with CD4+ T cells from KLH-primed mice, and KLH. Figure 7 demonstrates that proliferation of KLH-primed T cells was greatly reduced when stimulated with Ag and SpAC from DXM-treated animals compared with SpAC from control mice. Production of IL-12 in cultures containing T cells and SpAC from DXM-treated mice was also reduced. Moreover, SpAC from animals injected with DXM induced significantly lower amounts of IFN-γ and greater amounts of IL-4 than SpAC from control mice. These results show that in vivo treatment with DXM alters the capacity of APC to induce IFN-γ and IL-4.

We next examined the duration of the effect of DXM on the SpAC. (CByD2)F1 mice were injected with DXM 1 to 7 days before sacrifice. SpAC were purified from the DXM-treated mice...
and stimulated with LPS or HKL. Figure 8A shows that IL-12 production by SpAC was still significantly reduced from that of control 3 days after injection. However, by 7 days after injection of DXM, IL-12 production by SpAC returned to levels comparable to that seen in untreated mice (Fig. 8B).

**Discussion**

We demonstrated that DXM treatment of SpACs inhibits their subsequent capacity to produce IL-12. The in vitro pretreatment of SpAC with DXM resulted in an increased capacity of the SpAC to induce IL-4 and IL-5 and a reduced capacity to induce IFN-\(\gamma\) and IL-2 in CD4\(^+\) T cells. Moreover, SpAC pretreated in vivo with DXM, by i.p. injection of mice with DXM, were similar to in vitro DXM-pretreated SpAC in producing significantly reduced levels of IL-12. These results demonstrate that corticosteroids can enhance the production of IL-4 in T cells indirectly via effects on APC, and help to resolve conflicting data generated in different laboratories regarding the effects of corticosteroids on cytokine production, particularly of IL-4 in CD4\(^+\) T cells.

Previous studies have shown that corticosteroids could either inhibit or enhance IL-4 synthesis in T cells. Corticosteroids inhibited the transcription of multiple cytokines, including IL-4 and IFN-\(\gamma\) (18, 19), as well as TNF-\(\alpha\), granulocyte macrophage-CSF, IL-3, and IL-5 (2, 20, 21). The inhibition of transcription and synthesis of IL-4, IL-5, and IFN-\(\gamma\) by corticosteroids was demonstrated in both in vivo and in vitro studies, using both resting T cells as well as effector T cell clones (18, 19). On the other hand, several studies showed that corticosteroids enhance IL-4 synthesis (9, 10) and may enhance IFN-\(\gamma\) synthesis in vivo (22). That corticosteroids have the capacity to enhance IL-4 synthesis in T cells is consistent with the observation that administration of corticosteroids in vivo increases IgE synthesis (11).

The contrasting past results regarding the effects of glucocorticoids on cytokine synthesis in different systems may be due to the fact that glucocorticoids have a wide range of effects on intracellular biochemistry in a variety of different cell types, including T cells and APC. Glucocorticoids affect cytokine synthesis in T cells by binding to and activating cytoplasmic glucocorticoid receptors. The receptor-corticosteroid complex then translocates to the nucleus, where it regulates the transcription of target genes through several mechanisms (23). First, the activated receptor complex inhibits transcription of cytokine genes by binding to the transcription factor AP-1 (composed of c-Fos and c-Jun), and preventing AP-1 from binding to the promoter regions of cytokines (24–26). In addition, the activated glucocorticoid receptor complex functions as a positive transcription factor that increases transcription of the I-\(\kappa B\alpha\), a protein that blocks the translocation into the nucleus of NF-\(\kappa B\), another potent positive regulator of many cytokine and cell adhesion genes (5, 6). Inhibition of transcription of cytokine genes by corticosteroids occurs in both resting and in activated effector T cells, and therefore corticosteroids are important in inhibiting acute disease in which cytokine production is ongoing, as well as in functioning to prevent the actual development of allergy-inducing effector cells.

In our cultures, DXM decreased the production of IL-12 by SpAC, and altered their subsequent capacity to induce IL-4 and IFN-\(\gamma\) production in T cells. The effect of corticosteroids on cytokine production in T cells was indirect, since the T cells in these cultures were never directly exposed to the corticosteroids. It is very unlikely that even small amounts of contaminating DXM were present when the T cells were added, since the pretreated adherent cells were washed extensively, and since contaminating DXM would directly affect the T cells by inhibiting rather than enhancing IL-4 synthesis. These results indicate that a short incubation of SpAC with DXM can have persistent effects on the ability of SpAC to regulate cytokine synthesis in T cells. Since we and
others have shown that the cytokine profiles of activated effector T cells are difficult to modify (14, 27, 28), we believe that corticosteroid-pretreated SpAC altered the cytokine profiles of uncommitted but memory CD4+ T cells, rather than differentially expanding a subset of T cells already committed toward the Th2 profile (29).

Although corticosteroids may affect cytokine production in T cells in several ways, we believe that inhibition of IL-12 production in SpAC is a major mechanism by which corticosteroids affect cytokine synthesis (and enhance IL-4 synthesis) in T cells, particularly since IL-12 is extremely potent in inhibiting IL-4 and enhancing IFN-γ synthesis in both unprimed as well as resting memory T cells (13, 14, 28). Although the IL-12 determinations performed in our experiments utilized an IL-12 p40 ELISA, which does not measure the presence of the IL-12 p35 chain, in studies in which both IL-12 p40 and IL-12 p70 were measured, IL-12 p40 levels correlated directly with those of IL-12 p70, though levels of IL-12 p70 were lower (17). The levels of IL-12 p40 correlated directly with that of IFN-γ, consistent with the idea that the major biologic effects of IL-12 are to enhance Th1 cytokine synthesis (30).

Corticosteroids might also enhance IL-4 production in T cells by increasing the production of IL-10 in SpAC. We have recently observed that corticosteroids enhance IL-10 production (but decrease IL-12 production) in human peripheral blood mononocytes (31), but corticosteroid treatment did not affect IL-10 production in the murine APC that we tested. Since reconstitution of our DXM-pretreated cultures with rIL-12 reversed the effects of corticosteroids on IL-4 and IFN-γ synthesis, we believe that reduction of IL-12 production in SpAC by corticosteroids was the major immunoregulatory mechanism that occurred in our system. IL-12 has been reported to increase IL-10 production by T cells in systems using established T cell lines rather than resting T cells (32), or in systems using IL-12 in the presence of anti-IL-4 mAb (33), but these effects appear to occur mainly when very high concentrations of IL-12 (10 ng/ml, or 1000 times what was placed in our cultures) are used.

Our observations demonstrating that pretreatment of APC with corticosteroids inhibit IL-12 production and enhance their capacity to induce IL-4 but not IFN-γ have significant clinical implications. For example, current therapy for asthma focuses on early intervention with inhaled corticosteroids, which eliminate pulmonary eosinophilia and reduce Th2 cytokine synthesis by activated T cells in the lung. During subsequent immune responses, circulating T cells that become activated against Ag presented by resident APC that produce reduced quantities of IL-12. Activation of such T cells in the absence of IL-12 would drive the production of Th2 cytokines in these newly arriving T cells, but limit synthesis of IFN-γ. Similar situations could arise with systemic corticosteroid therapy, in particular because of the very short half-life of most synthetic corticosteroids. Since we demonstrated that in vivo exposure (as well as in vitro exposure) to corticosteroids clearly results in a reduction of IL-12 production (Fig. 5), which persists for at least several days, a short burst of systemic corticosteroid therapy is likely to reduce the capacity of APC to produce IL-12 (and greatly reduce cytokine synthesis in activated but not resting T cells). If, however, resting (cytokine-uncommitted) T cells are subsequently activated by APC preexposed to corticosteroids, enhanced IL-4 production but limited IFN-γ synthesis would be induced. Although therapy for autoimmune inflammatory disease or solid organ transplant rejection may benefit by such enhanced IL-4 production in CD4+ T cells, the long-term course of allergic diseases may be negatively affected by intermittent or chronic inhaled corticosteroid therapy that enhances Th2 cytokine synthesis. In the allergic patient with chronic disease, the effect would be insidious and difficult to detect, since T cells in allergic individuals are already predisposed toward the production of Th2 cytokines, and since the immediate inhibitory effects of corticosteroids on eosinophilic inflammation are so dramatic.

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