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Corticosteroids, IgE, and atopy

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Commentary

Corticosteroids are by far the most effective treatment available for the control of allergic diseases, including asthma, allergic rhinitis, and atopic dermatitis. Their beneficial effects are mainly mediated through multiple anti-inflammatory mechanisms (1). One of the most important actions of corticosteroids in suppressing allergic inflammation is the repression of genes encoding the multiple inflammatory cytokines and chemokines that are important in amplifying and perpetuating allergic inflammation. The molecular mechanisms of suppression of inflammatory genes involve an interaction of glucocorticoid receptors (GRs) activated by corticosteroids interacting with transcription factors that have been activated by inflammatory stimuli. This does not involve binding of GR to DNA recognition sequences, since anti-inflammatory effects of corticosteroids are preserved in mutant forms of GR that do not dimerize and that therefore fail to bind to glucocorticoid-response elements (GREs) in the upstream promoter regions of inflammatory genes (2). Inflammatory stimuli activate transcription factors, such as NF-κB and activator protein-1 (AP-1), that bind to and activate coactivator proteins at the start site of transcription, resulting in acetylation of core histones and increased transcription of inflammatory genes. Corticosteroids suppress the transcription of these inflammatory genes by reversing histone acetylation, in part by recruiting histone deacetylases to the transcription start site, thus repressing inflammatory genes (3). This mechanism accounts for many of the therapeutic effects of corticosteroids in the treatment […]

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Corticosteroids offer by far the most effective treatment available for the control of allergic diseases, including asthma, allergic rhinitis, and atopic dermatitis. Their beneficial effects are mainly mediated by multiple anti-inflammatory mechanisms (1), in particular, the repression of many inflammatory cytokines and chemokines that amplify and perpetuate allergic inflammation. Suppression of inflammatory proteins depends on the interaction of glucocorticoid receptors (GRs), activated by binding to corticosteroids, with various transcription factors that have been activated by inflammatory stimuli. Direct binding of GR to DNA is not required for this response, since mutant forms of GR that do not dimerize — and that therefore fail to bind to glucocorticoid-response elements (GREs) in the promoters of inflammatory genes — nevertheless maintain the ability to mediate the anti-inflammatory effects of corticosteroids (2). Inflammatory stimuli activate transcription factors, such as NF-κB and activator protein-1 (AP-1), which bind to and activate coactivator proteins at the start site of transcription, resulting in acetylation of core histones and increased transcription of inflammatory genes. Corticosteroids suppress the transcription of these inflammatory genes by reversing histone acetylation, in part by recruiting histone deacetylases to the transcription start site, thus repressing inflammatory genes (3). This mechanism accounts for many of the therapeutic effects of corticosteroids in the treatment of allergic diseases.

Paradoxical effects of corticosteroids

Although corticosteroids are highly effective in clinical management of allergic diseases, some of the cellular and molecular effects of these agents are difficult to reconcile with their well established beneficial effects. Th lymphocytes seen in atopic individuals are predominantly of the Th2 subtype, which secretes IL-4 and IL-5, both of which promote allergic responses. Thus, IL-4, together with the related cytokine IL-13, is important for isotype switching of B lymphocytes to secrete IgE, the antibody subtype that underlies atopy. IL-5 is critical for eosinophilic inflammation in allergic disease, as recently demonstrated by the profound fall in circulating eosinophils after anti-IL-5 antibody treatment of atopic asthma patients (4). Corticosteroids inhibit the transcription of IL-4, IL-5, and IL-13, and it is likely that switching off these key cytokines contributes importantly to their efficacy in controlling allergic diseases. Curiously, however, corticosteroids tip the balance towards Th2 cell predominance, perhaps by suppressing IFN-γ, which normally inhibits Th2 differentiation in response to IL-4 (5), or by suppressing IL-12 production and IL-12 receptor function, which promote expression of Th1 cytokines (6, 7).

Corticosteroids might therefore be expected to help polarize the immune response towards the proinflammatory Th2 pattern, were it not for the overriding inhibitory effects of these agents on the secretion of IL-4, -5, and -13. In addition, corticosteroids decrease the survival of T cells and eosinophils by increasing apoptosis, contributing to their suppression of chronic allergic inflammation. Another apparently detrimental effect of corticosteroids involves the IL-4–stimulated production of IgE that is seen in B lymphocytes treated with hydrocortisone (8) and, in vivo, in asthmatic patients after 1 week of treatment with oral prednisolone (9). This observation explains why treatment with corticosteroids, even at high systemic doses, fails to inhibit responsiveness to common allergens in the skin-prick test.

The molecular basis of the paradoxical effects of corticosteroids in atopy is further elucidated by the study of Jabara et al. in this issue of the *JCI* (10).

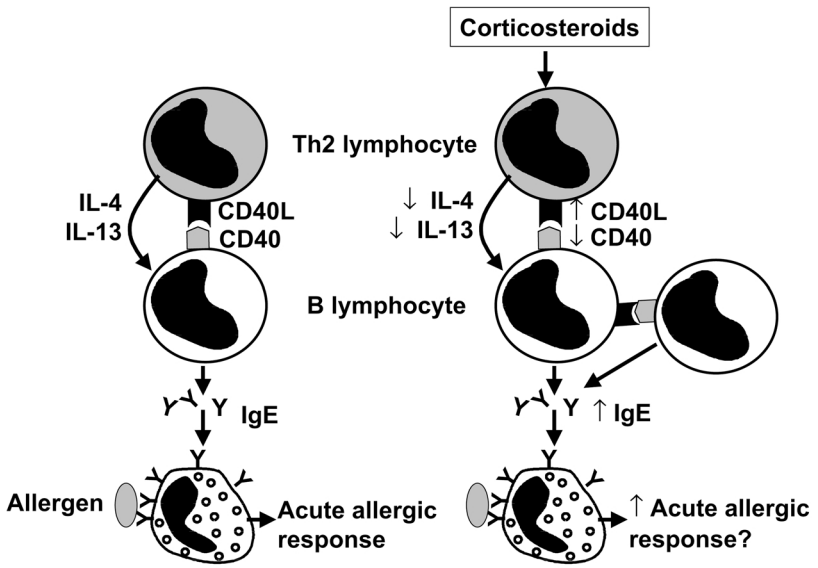

Figure 1

Interaction of T and B lymphocytes. The left panel shows interaction of a $CD4^+$ Th2 cell with a B lymphocyte. The release of cytokines IL-4 and IL-13 and interaction of CD40L and CD40 result in IgE synthesis and the sensitization of mast cells, which can then be triggered by allergen to activate an acute allergic response. The right panel shows the complex effects of corticosteroids, which increase the expression of CD40L in T and B cells, thereby increasing IgE formation and potentially acute allergic responses. On the other hand, corticosteroids also decrease expression of CD40L and the synthesis of IL-4 and IL-5, thus counteracting these effects.

These authors demonstrated that corticosteroid-induced IgE synthesis, in the presence of IL-4, depends on increased expression of the costimulatory molecule CD40 ligand (CD40L), a transmembrane glycoprotein belonging to the TNF superfamily. CD40L is normally expressed on activated T lymphocytes, where it interacts with CD40, a surface glycoprotein related to TNF receptors that is expressed on all B lymphocytes (Figure 1). The interaction between CD40L and CD40 is critical to the induction of IgE synthesis by IL-4 and IL-13 (11). Interestingly, the gene for CD40L, which maps to the X chromosome, is mutated in patients with X-linked hyper-IgM syndrome (12). Such individuals have low levels of secreted immunoglobulins, and they fail to induce IgE synthesis in response to corticosteroids. Similarly, as Jabara et al. report, a blocking CD40-Ig fusion protein inhibits the effects of hydrocortisone on IgE synthesis in normal B cells (10). The effect of corticosteroids on CD40L is mediated by GR, as it is blocked by the GR antagonist mifepristone (RU486). The molecular mechanism for increasing transcription involves interaction of GR with coactivators and subsequent acetylation of core histones, leading to increased gene transcription (3).

Unlike the anti-inflammatory effects described above, which involve repression of inflammatory genes (1), the induction of IgEs by corticosteroids may require direct DNA binding by GR, since the promoter region of *CD40L* has several potential GREs. This pathway leads to increased transcription and surface expression of CD40L not only on T lymphocytes, but also on B lymphocytes, cells that do not normally express this protein. $CD40L^+$ B cells may then interact with other B cells that express CD40. Interestingly, a previous study showed that corticosteroids can inhibit CD40L expression in human peripheral blood $CD4^+$ lymphocytes (13), suggesting that the response to steroids differs between cell types or in the absence or presence of IL-4. Although corticosteroids increase CD40L in B lymphocytes, other studies show that in the same cells they suppress the expression of CD40, which acts as a receptor for CD40L, thus potentially diminishing any functional effect of corticosteroids on IgE production (14). Furthermore, as noted above, corticosteroids suppress the synthesis of IL-4 and IL-13, which are necessary for IgE production. The suppressive effects of corticosteroids on inflammatory genes, such as IL-4 and CD40, are seen at lower concentrations than the effects that involve increased transcription, such as the increase in CD40L.

Clinical outlook

The clinical implications of these findings are not yet clear. Corticosteroids may induce CD40L in T lymphocytes, which may also activate other CD40-expressing inflammatory cells, such as macrophages and eosinophils. The effect of this induction would again be a paradoxical increase in inflammation in the short-term (although if corticosteroids also suppress CD40 expression in these cells, such a proinflammatory effect may be minor). Indeed, corticosteroids, while very effective at suppressing chronic allergic inflammation, are less effective against acute allergic events that are mediated by interaction of allergen with IgE bound to mast cells. However, there is no clinical evidence that IgE-mediated responses are worsened by corticosteroid treatment. In part, this may be because of counteracting beneficial effects of corticosteroids on these acute responses, as treatment with topical steroids reduces the number of mast cells in the mucosa, so that allergen is less able to activate these cells (15). Nevertheless, this apparent adverse effect of corticosteroids on the acute allergic response suggests that therapies that block the increased IgE levels could be useful adjuncts to corticosteroid therapy.

A humanized monoclonal antibody to IgE, which profoundly reduces circulating IgE concentrations (16), has recently been found to provide surprising benefit in patients with severe steroid-dependent asthma, reducing the requirement for oral corticosteroids and allowing some patient to discontinue oral steroids completely (17). This can now be understood, as the high doses of systemic corticosteroid therapy may maintain high IgE levels by the mechanisms described by Jabara and colleagues (10). This effect can be overcome by anti-IgE therapy, which appears to be of greater benefit in patients with more severe disease who are steroid dependent.

1. Barnes, P.J. 1998. Anti-inflammatory actions of glucocorticoids: molecular mechanisms. *Clin. Sci.* **94**:557–572.
2. Reichardt, H.M., et al. 1998. DNA binding of the glucocorticoid receptor is not essential for survival. *Cell.* **93**:531–541.
3. Ito, K., Barnes, P.J., and Adcock, I.M. 2000. Glucocorticoid receptor recruitment of histone deacetylase 2 inhibits IL-1β-induced histone H4 acetylation on lysines 8 and 12. *Mol. Cell. Biol.* **20**:6891–6903.
4. Leckie, M.J., et al. 2000. Effects of an interleukin-5 blocking monoclonal antibody on eosinophils, airway hyperresponsiveness and the late asthmatic response. *Lancet.* **356**:2144–2148.
5. Ramirez, F. 1998. Glucocorticoids induce a Th2 response *in vitro*. *Dev. Immunol.* **6**:233–243.
6. Wu, C.Y., Wang, K., McDyer, J.F., and Seder, R.A. 1998. Prostaglandin E_2 and dexamethasone inhibit IL-12 receptor expression and IL-12 responsiveness. *J. Immunol.* **161**:2723–2730.
7. Visser, J., et al. 1998. Differential regulation of interleukin-10 (IL-10) and IL-12 by glucocorticoids *in vitro*. *Blood.* **91**:4255–4264.
8. Jabara, H.H., Ahern, D.J., Vercelli, D., and Geha, R.S. 1991. Hydrocortisone and IL-4 induce IgE isotype switching in human B cells. *J. Immunol.* **147**:1557–1560.
9. Zieg, G., Lack, G., Harbeck, R.J., Gelfand, E.W., and Leung, D.Y. 1994. *In vivo* effects of glucocorticoids on IgE production. *J. Allergy Clin. Immunol.* **94**:222–230.
10. Jabara, H.H., Brodeur, S.R., and Geha, R.S. 2001. Glucocorticoids upregulate CD40 ligand expression and induce CD40L-dependent immunoglobulin isotype switching. *J. Clin. Invest.* **107**:371–378.
11. Spriggs, M.K., et al. 1992. Recombinant human CD40 ligand stimulates B cell proliferation and immunoglobulin E secretion. *J. Exp. Med.* **176**:1543–1550.
12. Aruffo, A., et al. 1993. The CD40 ligand, gp39, is defective in activated T cells from patients with X-linked hyper-IgM syndrome. *Cell.* **72**:291–300.
13. Bischof, F., and Melms, A. 1998. Glucocorticoids inhibit CD40 ligand expression of peripheral $CD4^+$ lymphocytes. *Cell. Immunol.* **187**:38–44.
14. Jirapongsananuruk, O., and Leung, D.Y. 1999. The modulation of B7.2 and B7.1 on B cells by immunosuppressive agents. *Clin. Exp. Immunol.* **118**:1–8.
15. Laitinen, L.A., Laitinen, A., and Haahtela, T. 1992. A comparative study of the effects of an inhaled corticosteroid, budesonide, and of a β_2-agonist, terbutaline, on airway inflammation in newly diagnosed asthma. *J. Allergy Clin. Immunol.* **90**:32–42.
16. Barnes, P.J. 2000. Anti-IgE therapy in asthma: rationale and therapeutic potential. *Int. Arch. Allergy Immunol.* **123**:196–204.
17. Milgrom, H., et al. 1999. Treatment of allergic asthma with monoclonal anti-IgE antibody. *N. Engl. J. Med.* **341**:1966–1973.