Inhaled Glucocorticoids, Lymphocytes, and Dendritic Cells in Asthma and Obstructive Lung Diseases

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Many of the therapeutic effects of systemic and inhaled corticosteroids can be explained by their ability to modulate immune responses. T lymphocytes in particular have been used to establish some of the key paradigms by which corticosteroids inhibit cell activation and gene expression, and there is now substantial evidence that inhaled corticosteroids potentiate suppress pulmonary immune responses driven by T-helper cells. Inhaled corticosteroids work in part by suppressing T-cell homing to the lung, but they also inhibit T-cell activation within the airways. This article reviews the mechanisms by which inhaled corticosteroids inhibit T-cell homing and activation, including the transcriptional pathways targeted by corticosteroids and the glucocorticoid receptor in T cells. Emerging data point to dendritic cells (DCs) as another cellular target of corticosteroids in the lung. DCs are a key component of the innate immune system, and subtle differences in DC maturation can qualitatively alter T-cell activation and a subsequent immune response. Thus, this article also reviews the mechanisms of DC maturation and DC:T cell cross-talk, including new evidence that corticosteroids might act at this level to inhibit antigen-specific immunity.

Keywords: asthma; chronic obstructive pulmonary disease; dendritic cell maturation; T-cell activation; T-cell homing

Substantial evidence supports the notion that allergic asthma is an immune-mediated disease, driven by T cells directed against aero-allergens and viruses (1). In particular, CD4^+ type 2 T-helper (Th2) cells, which secrete interleukin (IL)-4, IL-5, and IL-13, are thought to contribute to many of the pathophysiologic features of asthma, including airway inflammation, mucus secretion, and airway hyperresponsiveness (2). Much current research is aimed at understanding how Th2 cytokines interact with resident lung cells, including airway epithelium, myofibroblasts, and smooth muscle, to induce the asthmatic phenotype. New research suggests that T cells play a previously underappreciated role in the pathophysiologic of chronic obstructive pulmonary disease (COPD) (3, 4), and at least one study documented increased IL-4 gene expression in the mucus-secreting glands of smokers with bronchitis (5). Thus, knowledge of how corticosteroids affect the regulation of Th2 gene expression should increase our understanding of the efficacy of these agents in asthma and COPD. Because of the expansion of Th2 cells in nonallergic (or “intrinsic”) asthma, possibly reflecting immune activation by unknown allergens, this discussion will also be relevant to the use of ICS in nonallergic subjects with asthma.

The cellular and molecular basis for a Th2-biased immune response involves both genetic factors (e.g., polymorphisms in the Th2 cytokine cluster [6]) and environmental exposures. Because a Th2 bias is characteristic of atopy in general, it seems likely that additional susceptibility genes influence the development of organ-specific atopic diseases, and candidates in this regard are beginning to be identified (e.g., GPRRA in asthma [6]). This review focuses on how T cells and dendritic cells (DCs) interact to generate a pulmonary immune response, with an emphasis on the allergic immune response in asthma. Similarities and differences between asthma and COPD are highlighted.

This article attempts to synthesize studies of human subjects and mouse models into a cohesive picture of how inhaled corticosteroids (ICS) modulate lung immunity. It is not meant to be a comprehensive review of the physiologic and pharmacologic effects that corticosteroids have on T cells and DCs; excellent recent reviews have covered these topics in depth (7, 8).

ICS BLOCK T-CELL HOMING TO THE LUNG

Naive T cells exit the thymus after they have undergone positive selection and have escaped negative selection. Because of their expression of homing receptors, including the peripheral lymph node address, naive T cells recirculate through central immune organs, including lymph nodes and spleen, until they encounter antigen-presenting cells bearing peptide fragments recognized by their surface T-cell receptor (TCR). If the antigen-presenting cell is appropriately activated (see below), then the naive T cell clonally expands, driven in part by autocrine secretion of IL-2. As clonal expansion progresses, many activated T cells undergo activation-induced cell death, a Fas-FasL–mediated process that serves to limit the subsequent immune response. Some T cells escape activation-induced cell death and differentiate into effector (or memory) cells, which are then recruited to peripheral mucosal sites to orchestrate cellular immunity (Figure 1). Some effector cells express tissue-specific homing receptors (e.g., C-TACK in skin-homing T cells), but to date no surface molecule that promotes the homing of T cells to the lung has been identified. A small proportion of activated T cells retain surface chemokine receptors characteristic of naive T cells (e.g., CC chemokine receptor 7 [CCR7]) and continue to recirculate through lymph nodes and other central sites (9) (Figure 1). This so-called effector memory pool probably serves to amplify rapid recall responses. This paradigm of T-cell subset homing has been well worked out in mouse models, and essential features of it appear to translate to humans. Although it has been generally easier to study memory generation in CD8^+ T cells than in CD4^+ cells, the kinetics of memory CD4^+ T-cell generation are beginning to be understood. Interestingly, in a recent paper by Wu and colleagues, the generation of memory CD4^+ Th1 cells was inhibited in cells actively secreting IFN-γ (10). This study shows that active cytokine gene transcription is another level of regulation of memory T-cell generation.

Several studies have documented increased numbers of activated CD4^+ T cells in the lungs of subjects with asthma. It is generally assumed that these cells represent antigen-specific memory cells, although this is technically difficult to confirm with certainty (11). Recent studies in mouse models suggest that ongoing T-cell recruitment is much more important than expansion of resident lymphocytes in explaining effector cell
Immune responses can be divided into central and peripheral components. The central component involves interactions in lymph nodes (LNs) between dendritic cells (DCs) and T lymphocytes. T-cell subsets have different homing properties based on their expression of chemokine receptors. Naive and central memory T cells (TCM) express CC chemokine receptor 7 (CCR7) and migrate to lymph nodes in response to EBI-1 ligand chemokine (ELC) and secondary lymphoid-tissue chemokine (SLC). Activated effector memory T cells (TEM) express different chemokine receptors; an example is that some Th2 effector cells express CCR4. These cells are recruited by the chemokines MDC and TARC, which are expressed by structural lung cells and inhibited by corticosteroids. Dendritic cell precursors also migrate to the lung and lymph nodes. After exposure to inflammatory signals, immature DCs (iDC) take up antigen, differentiate into mature DCs (mDC), and migrate to regional LN. The ability of ICS to inhibit cell recruitment to the lung is indicated. ICS also block expression of cytokines, including the Th2 cytokines IL-4 and IL-13, in resident lung T cells. HEV indicates high endothelial venule.

Accumulation in the lung and other nonlymphoid organs (12, 13). For example, in a model of allergic sensitization and challenge, Harris and coworkers recently showed that activated T cells migrate from the regional lymph nodes to the lung and airway, where they secrete IL-4 but are unable to further divide (12). In this regard, the ability of topical corticosteroids to inhibit T cell recruitment likely helps explain their efficacy in inflammatory diseases such as asthma. Several clinical trials have documented the ability of inhaled or intranasal corticosteroids to diminish T cell numbers in the airway (14–16). Although this could be due in part to apoptosis of resident T cells, it should be noted that corticosteroids antagonize TCR-driven apoptosis (7), and T cells from individuals with asthma may be resistant to Fas-induced apoptosis (17). Corticosteroids can also block ongoing T cell recruitment by potently suppressing the production of T cell-attracting chemokines by epithelial cells and other structural lung cell types (see the article by Schleimer in this issue, p. 222). Particularly important for an airway Th2 response is the recently described ability of corticosteroids to block epithelial production of two Th2-attracting chemokines, thymus- and activation-regulated chemokine (TARC or CCL17) and macrophage-derived chemokine (MDC or CCL22) (19–20) (Figure 1). The ligand for IL-4 gene expression is controlled at the level of transcription by factors that bind to a proximal promoter region (indicated in blue) and other regulatory elements not indicated. Nuclear factor of activated T cells (NFAT) comprises a family of calcium-sensitive factors that bind multiple purine-rich regions termed the P elements. A single-nucleotide polymorphism (SNP) that creates an NFAT site and is associated with asthma severity is indicated. NFAT proteins are dephosphorylated by the phosphatase calcineurin (CN), which is blocked by the immunophilin drugs cyclosporin A (CsA) and FK-506. Corticosteroids antagonize NFAT-driven transcription of the IL-4 promoter, which may involve protein-protein interactions between the GR and NFATc. In the interest of clarity, not all possible factors that can bind the promoter are indicated. PKC indicates protein kinase C; AP-1, activator protein-1.
TARC and MDC is CC chemokine receptor 4 (CCR4), which is preferentially expressed on some Th2 cells (Figure 1).

ICS BLOCK TH2 CYTOKINE GENE EXPRESSION

In addition to their effects on cell recruitment, ICS block the expression of effector cytokines in airway T cells, in particular the Th2 cytokines IL-4, IL-5, and IL-13 (14–16, 18), in keeping with prior studies of systemic corticosteroids. The inhibitory effects of ICS on lymphocyte Th2 cytokine gene expression extend outside of the airway to circulating T cells (19). In several studies, topical corticosteroids inhibited Th2 cytokine gene expression more than IFN-γ expression (16, 18, 19). This is in keeping with the finding of Umland and associates that topical corticosteroids are more efficacious at inhibiting the Th2 cytokines IL-4 and IL-5 than the Th1 cytokine IFN-γ in T cells activated in vitro (20). The molecular mechanisms by which corticosteroids inhibit Th2 gene expression are beginning to be understood. The following sections focus on the regulation of IL-4 gene expression because this is arguably the best understood of the Th2 genes. In effector T cells, IL-4 gene expression is controlled largely at the level of gene transcription by the coordinated action of many transcription factors that bind to a proximal promoter as well as to distal enhancers (21). Nuclear factor of activated T cells (NFAT) comprises a family of calcium-sensitive transcription factors that is particularly important for IL-4 gene expression (22). NFAT proteins are constitutively cytoplasmic but rapidly translocate to the nucleus after dephosphorylation by the phosphatase calcineurin. The IL-4 promoter contains at least six purine-rich NFAT sites (termed the P elements P0 to P5), and current thinking is that these sites interact with other regulatory elements and transcription factors to maximally enhance the rate of IL-4 transcription in effector Th2 cells (21) (Figure 2). A single-nucleotide polymorphism is located upstream of the IL-4 promoter, and interestingly it creates an NFAT site that correlates with asthma severity (23). Experiments using gene-targeted and chimeric mice uncovered a particularly important role for NFATc (also called NFAT2) in IL-4 gene regulation (24). We demonstrated in T-cell lines that corticosteroids interfere with NFATc-driven IL-4 promoter activity, and we observed a novel protein–protein interaction between the GR and NFATc (25). Therefore, NFATc represents a likely molecular target of ICS in airway Th2 cells (Figure 2). Glucocorticoids also block other signal transduction and transcription factor pathways in T cells, including activator protein-1 and nuclear factor-κB (NF-κB) activation (26, 27). In this regard it is noteworthy that NF-κB is not essential for IL-4 transcriptional regulation (28), although less is known about how NF-κB regulates IL-5 and IL-13 gene expression. The roles of newer cytokines in the pathogenesis of asthma and COPD, including IL-18 (29) and the Th2-inducing cytokine IL-25 (30), are under active investigation. Whether these represent potential targets of ICS remains to be determined.

CORTICOSTEROIDS AND TH2 DIFFERENTIATION

In addition to the “acute” transcriptional events outlined above, which occur after TCR- and co-stimulatory molecule–dependent activation of NFAT and other factors, the transition of a naïve Th cell into a Th2 effector is also regulated at the level of chromatin remodeling. According to this model, chromatin structure at the Th2 cluster in resting naïve T cells and Th1 cells is generally permissive for transcription because of tight interactions between histone (and other) proteins and the DNA template. After T cell activation, chromatin is remodeled into a more permissive form that allows easier access of NFAT and other transcription factors required for IL-4 gene expression. Under Th2-biasing conditions (e.g., strong IL-4 receptor plus weak TCR signals), remodeled states of chromatin are passed on to daughter cells after mitosis and represent an “epigenetic” trait (31). The precise biochemical basis of chromatin remodeling at the Th2 cluster is still under investigation, but it is known that it can involve post-translational modification of histones (e.g., acetylation) as well as demethylation of DNA (32, 33). Although heritable chromatin remodeling clearly occurs at the Th2 cluster under highly polarizing conditions in vitro, it is uncertain whether this is a feature of airway Th2 cells in asthma. Furthermore, it is unknown whether chromatin remodeling per se is inhibited by corticosteroids in Th cells, whereas it has been established that acute transcription of Th2 cytokines is targeted by corticosteroids and the GR. It should be noted that at least in the case of IL-4, some of the transcription factors that are required for initially opening chromatin structure (e.g., signal transduction-activated transcription factor-6 [STAT-6] and GATA-3) are probably dispensable for subsequent transcriptional activation (34, 35). To date, there is little evidence that corticosteroids target the STAT-6 pathway in T cells; whether corticosteroids affect GATA-3 activation is an important unanswered question.

DC AND THE INNATE IMMUNE RESPONSE

Dendritic cells are the most potent antigen-presenting cells, and it is becoming clear that they play an essential instructive role during both Th cell differentiation and effector T cell activation (36). In peripheral tissues, immature DCs efficiently capture antigens. Upon exposure to “danger” signals (e.g., bacterial products or lipopolysaccharide), they undergo a maturation process characterized by increased expression of MHC–peptide complexes, higher expression of co-stimulatory molecules, altered expression of chemokine receptors that facilitate movement into regional lymph nodes, and synthesis of chemokines and cytokines that influence T cell differentiation (notably IL-12 and IL-10) (37). Many of these danger signals are transduced in DCs by Toll-like receptors (or TLRs). TLRs are highly conserved pattern recognition receptors that recognize a variety of microbial breakdown products including peptidoglycan and lipopeptides (TLR2), double-stranded RNA (TLR3), lipopolysaccharide (TLR4), flagellin (TLR5), and CpG DNA (TLR9) (see Reference 38, and review by Schleimer in this issue). Strong signaling by TLRs is known to result in the differentiation of highly activated DCs, which secrete large amounts IL-12, thus biasing naïve T cells toward the Th1 phenotype. However, the notion that plasticity of DC maturation can fine-tune immune responses is gaining wide acceptance (39), and there are probably multiple DC phenotypes that can influence Th differentiation in distinct manners (Figure 3). The intimate contact between T cells and DCs involves multiple adhesion receptor pairs as well as soluble signals and has been referred to as the “immunological synapse” (40). The outcome of interactions between T cells and DCs determines whether tolerance or immune activation will occur (41). This model of T cell instruction by activated DCs provides a cellular and molecular framework in which to reframe the hygiene hypothesis of asthma. One simple possibility is that exposure to allergen in the presence of strong TLR signaling (analogous to “poor hygiene”) will result in the differentiation of allergen-specific Th1 clones which are poor inducers of airway inflammation. However, the absence of TLR-signaling (i.e., "good hygiene") does not automatically result in the maturation of a pro-Th2 DC phenotype, and much current research is aimed at dissecting the requirements for and strength of TLR signaling in allergen-dependent activation of DCs.

In the context of a pulmonary immune response, studies in
Dendritic cells can mature into different phenotypes with distinct abilities to activate naive precursor T cells (Thp). DCs that secrete high levels of IL-12 (DC-Th1) will favor differentiation of Th1 cells. DCs that actively promote transcription of IL-4 in naive T cells (DC-Th2) should favor Th2 differentiation. Some DCs may secrete IL-10 (DC-Tr1) and promote the differentiation of IL-10–producing Tr1 cells. Corticosteroids block the differentiation of DC-Th1 and DC-Th2, and they inhibit DC maturation in general. The distinction between an immature DC and a DC-Tr1 is not entirely clear.

Mouse models show that after airway DCs take up inhaled allergen, they migrate to regional intrathoracic lymph nodes, where they can present processed peptides to T cells (42) (Figure 1). Airway DCs appear to preferentially induce a Th2 immune response, although the precise basis for this phenomenon is unclear (43). Circulating DC precursors are also recruited to the airways after allergen challenge (44, 45), and at least in the upper airway this recruitment can be blocked by topical corticosteroids (46). Thus, as in the case of T cells, ICS can blunt a pulmonary immune response by inhibiting ongoing DC recruitment (Figure 1). It seems likely that corticosteroids block the expression of DC-recruiting chemokines, but this awaits formal demonstration. Large doses of corticosteroids can induce apoptosis of airway DCs in the rat lung (47), but it is unknown whether ICS have similar effects in humans. The precise identity of the circulating DC precursor that is recruited to the lung is under study, and it is probably of myeloid lineage (48).

In addition to inhibiting DC recruitment to the lung, corticosteroids can affect other aspects of DC function that are potentially of relevance to how ICS work in asthma. For example, corticosteroids inhibit the differentiation of immature DCs from myeloid precursors, and they block terminal maturation in response to microbial products and other signals (8). In general, corticosteroids appear to arrest DCs in an immature state characterized by retained endocytic activity and reduced expression of MHC II, costimulatory receptors, and T cell–activating cytokines such as IL-12 (49, 50) (Figure 3). Corticosteroid-treated DCs were hindered in their ability to stimulate T cells in some studies (50), but not others (49, 51). The ability of corticosteroids to block DC IL-12 production helps explain the apparent paradox that while corticosteroids inhibit IL-4 gene expression in T cells, they can also enhance Th2 differentiation in some experimental systems (52) (Figure 4).

More interesting results were obtained when corticosteroids were applied to DC:T cell co-cultures. Matsue and colleagues nicely demonstrated the inhibitory effects that corticosteroids have on the bidirectional signals that occur during DC:T cell cross-talk, which included reduced IL-4 generation in T cells (53). Several groups made the additional observation that exposure to corticosteroids during DC:T cell co-culture resulted in the differentiation of T cells secreting high levels of the immunoregulatory cytokine IL-10 (49, 54). In one study, these T cells...
were able to suppress antigen-specific immune responses consistent with their having a role as regulatory (or Tr1) cells (54). Studies using mouse models suggest that allergic lung inflammation reflects a failure of Tr1-dependent tolerance, which may be due in part to reduced DC IL-10 production (55). It is interesting to speculate that ICS might work on DCs to promote the differentiation of IL-10–producing Tr1 cells capable of downregulating antigen-driven reactions in the lung. Although clinical evidence supporting this notion is currently lacking, one recent study showed that an 8-week course of inhaled triamcinolone increased serum IL-10 levels in asthmatic children (56). The potential for Tr1 cells (or suppressor CD4+ CD25+ T cells) to dampen inflammation in asthma and COPD will require further study.

After allergen inhalation, the relative importance of DC:T cell interactions in the airway versus regional lymph nodes is unknown. Based on different homing properties of naive versus memory T cells, lymph nodes may be the major site of interaction between DC and naive lymphocytes, whereas the airway is probably the site of effector Th-cell activation by DC (and other cells). If so, then one might predict that ICS would inhibit effector T cell activation more than naive T cell differentiation. However, ICS could affect DC maturation that begins or occurs in the airway, and DCs could retain this phenotype after they migrate to regional lymph nodes. Of note, there is precedence for the idea that DCs can act as a reservoir of drugs (8), suggesting that ICS may have long-lasting effects in lung DCs even outside of the airway. It will be interesting to determine whether and how ICS modulate DC phenotype in vivo and to what extent this explains their efficacy in asthma and COPD.

COPD

In contrast to our knowledge of the allergic asthmatic response, our understanding of the immunopathology of COPD is rudimentary. Studies during the past several years documented the presence of lung inflammation both in subjects with stable COPD as well as during disease exacerbations. There are several characteristics of lung inflammation in COPD that are different from that in asthma (reviewed in Reference 57). For example, in smokers with COPD the numbers of CD8+ lymphocytes tends to be higher than CD4+ cells both in the large and small airways, resulting in a lower CD4:CD8 ratio (58, 59). This contrasts with the characteristically higher CD4:CD8 ratio observed in airways of subjects with asthma. Similar findings were observed in the regional lymph nodes of smokers with COPD, arguing that the CD8+–preponderance extends outside the airway (60). The reasons for the apparent expansion of CD8+ T cells within the lungs of smoking subjects with COPD are not known. One possibility is that this reflects antigen-driven expansion of specific T cell clones, possibly in response to recurrent or latent airway viral infections. Alternatively, recurrent smoke inhalation might lead to polyclonal T cell activation through nonspecific mechanisms. It should be noted that not all studies show a CD8+-predominance, particularly in severe COPD. For example, Turato et al. found that both CD4+ and CD8+ cell numbers were increased in surgical biopsy specimens from subjects with severe airflow limitation (3), whereas Di Stefano and colleagues found that the numbers of CD8+ lymphocytes were lower in airway biopsies of subjects with severe COPD compared with control subjects (61). The reasons for these apparent differences in immunopathology between severe and mild COPD remain to be determined.

Little is known about the role of activated lymphocytes in COPD pathophysiology. CD8+ cells can secrete cytokines capable of directly leading to lung damage (e.g., TNF-α), and can also kill virally infected cells. Like CD4+ cells, CD8+ lymphocytes can also secrete cytokines including IL-4, -5, and -13, which as discussed above can lead to mucus hypersecretion and airway eosinophilia. Interestingly, exacerbations of COPD are characterized by the influx of eosinophils (and neutrophils) into the lung, but the role of T cell–derived cytokines in this process has not been determined (62, 63). In a recent study, Zhu and coworkers found that IL-4 and IL-5 gene expression were increased in the submucosal glands of smokers with COPD, which was not co-localized to CD8+ cells (5). Future studies better characterizing the role of immune activation and cytokine production in COPD should prove worthwhile.

Relatively little is known about whether corticosteroids inhibit CD8+–dependent immunity, and at least two studies suggest that CD8+ T cells are relatively corticosteroid-resistant. For example, Syed and associates found that mitogen-driven CD4+ T cell proliferation was potently suppressed by fluticasone propionate ex vivo, whereas CD8+ T cell proliferation was only partially suppressed (64). Furthermore, in a 1-week clinical trial of prednisolone in patients with asthma, surface markers of cell activation were found to be inhibited in CD4+, but not CD8+, T cells by Corrigan and colleagues (65). These studies raise the possibility that expansion of CD8+ T cells may help explain the relatively corticosteroid insensitivity in COPD. In support of this notion, Hattotuwa and coworkers recently reported the results of a 3-month placebo-controlled trial of fluticasone propionate in 31 smokers with COPD. Interestingly, there were no differences in CD8+ cell numbers in airway biopsies from subjects receiving ICS versus placebo, whereas mast cell numbers decreased significantly (66). Future studies specifically investigating T cell subsets and corticosteroid responsiveness in COPD should prove worthwhile in this regard. Potentially relevant to the immunology of COPD is the recently observed ability of corticosteroids to induce IL-10 production in CD8+ cells (67). In this study, Richards and coworkers found that when incubated with antigen-presenting cells and corticosteroids, CD8+ cells differentiated into a phenotype of high IL-10 production and low IL-4 production (67). This is directly analogous with the effects of corticosteroids on IL-10–producing CD4+ Tr1 cells described previously, but whether IL-10–producing CD8+ cells have a similar immunoregulatory phenotype in COPD remains to be determined.

CORTICOSTEROIDS AND OTHER LYMPHOCYTES

This article has focused primarily on how corticosteroids affect T cell function, either directly or by indirect effects on DC. Corticosteroids can also affect other lymphocytes, including B cells, natural killer (NK) cells, and NK T (NKT) cells. Corticosteroids synergize with other signals to enhance isotype switching and IgE synthesis in B lymphocytes (68), but the clinical relevance of this finding is unclear. Because ICS actually decrease germline IgE transcription in vivo, the inhibitory effects of ICS on B cell–stimulating cytokines (e.g., IL-4) probably outweigh their direct effects on B cells themselves (69). NK cells play a key role in the immune surveillance against viral infections and tumors, and NK activity appears to be reduced in at least some subjects with COPD (70). Whether ICS might affect NK cell function has not been well studied.

NKT cells are an interesting subset of T lymphocytes that typically circulate in low numbers. Unlike canonical T cells, which express a diverse repertoire of rearranged TCRs, NKT cells express a limited set of TCRs (including invariant Vα24 in humans and Vα14 in mice) and recognize antigens presented by the MHC I–like CD1 family of molecules (71). The observation that NKT cells recognize synthetic glycolipids (e.g., α-galactosyl ceramide [64]) challenged the traditional notion that T cells respond only to peptide antigens. The endogenous lipids that
control the activation of CD1-restricted NKT cells in vivo are unknown. NKT cells can secrete large amounts of both IL-4 and IFN-γ, and their ability to promote Th polarization is controversial. Early studies suggested that these cells might represent the primordial source of IL-4 driving Th2 differentiation, but this was not substantiated in mice bearing a targeted deletion of the CD1 gene (72). It now appears that the duration of NKT activation is a critical factor affecting their T-cell differentiating ability, with repeated glycolipid stimulation favoring Th2 differentiation (71). Intriguingly, in a mouse model of asthma, Akbari and associates recently reported that NKT cells (producing both IL-4 and IL-13) played an essential role in airway hyperreactivity following allergen sensitization and challenge (73). The potential role of NKT cells in airway inflammation in asthma and COPD in humans is unknown, and their responsiveness to corticosteroids has not been systematically investigated. In one study, IL-4–secreting NK1.1+ T cells were resistant to corticosteroid–induced apoptosis (74), but how this relates to the efficacy of these agents in vivo remains to be determined.

CONCLUSIONS
Our understanding of the cellular and molecular regulation of immune responses has increased at a dramatic pace. New cell types and candidate molecules have been identified that both amplify and dampen antigen-driven pulmonary immunity. Given their widespread impact in inflammatory diseases, including asthma, it is perhaps not surprising that corticosteroids act at many levels to exert their therapeutic effects. Future challenges will be to translate the wealth of knowledge gained from in vitro and animal experiments into a better understanding of the mechanisms of action of corticosteroids in vivo.

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