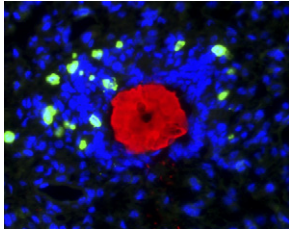


This issue's Immunology Select discusses recent studies on allergic responses in mouse models of human disease as well as how certain drugs, like the glucocorticoid dexamethasone, alleviate the symptoms of allergy.

An Abundant and Unexpected Allergen



Chitin (red) administered to the lungs of mice induces the rapid infiltration of IL-4-expressing cells (green) from blood resulting in the production of a mammalian chitinase capable of digesting chitin. Image courtesy of S. Van Dyken and R. Locksley.

There are many similarities between the immune responses to allergens and to parasitic worms. In their new study, Reese et al. (2007) examined immune responses in the lung tissue of mice infected with the helminth *Nippostrongylus brasiliensis*. This parasitic worm migrates to the lung, where it molts and remodels its stiff pharyngeal feeding tube made of the biopolymer chitin before ascending the trachea and being swallowed, thereby enabling it to access the intestine. In this model of infection, the mammalian proteins acidic chitinase AMCCase and Ym1 and Ym2 (chitinase-like proteins) are produced in response to the transcription factor Stat6. Reese et al. determined that there is Stat6-mediated production of AMCCase and Ym2 in the lungs of mice at 3 days post worm infection. Given that AMCCase is an enzymatically active chitinase, yet mammals lack chitin, the authors next examined whether the immune response could be mediated by the chitin discarded by the molting worms. They administered chitin intranasally to introduce it into the lungs of mice, which resulted in recruitment of eosinophils and basophils within 2 to 3 days. This recruitment was abrogated by pretreatment of the chitin with enzymatically active AMCCase. They next generated mice that overexpressed AMCCase constitutively in the lung. When exposed to chitin, these mice had lowered inflammatory responses. Interestingly, the recruitment of eosinophils and basophils is independent of Stat6 but is dependent

on the eosinophil chemoattractant leukotriene B4 secreted by macrophages. The authors go on to show that a special type of macrophage (an alternatively activated macrophage) appears in the lung tissue upon exposure of mice to chitin. The authors propose a model in which macrophages encountering chitin become alternatively activated and secrete the chemoattractant leukotriene B4 in response to chitin in order to entice eosinophils to enter the tissue. Subsequent production of AMCCase in response to interleukin (IL)-4 and IL-13 produced by inflammatory cells degrades the chitin, thereby attenuating the response. Given the ubiquitous nature of chitin in the environment (it provides structural rigidity to fungi, crustaceans, and insects as well as worms and their eggs) and the incidence of asthma in shellfish workers, chitin may be an important cause of allergy in humans.

T.A. Reese et al. (2007). *Nature* **447**, 92–96. Published online April 22, 2007. 10.1038/nature05746.

The Complex Effects of Osteopontin

Xanthou et al. (2007) examine the role of the cytokine osteopontin (a well-known mediator of the Th1 immune response) in the Th2 immune response induced in a mouse model of allergic airway inflammation. First, they show that during allergic Th2 responses in this model, osteopontin expression is upregulated in the lung. In humans, lung biopsies from asthma patients exhibit increased osteopontin expression in lung tissue. Therefore, the authors next examined the mouse immune response in the absence of osteopontin, which they depleted using a neutralizing antibody to this cytokine. Interestingly, they found that osteopontin has a proinflammatory function at sensitization (first exposure to antigen), whereas it has an anti-inflammatory function during challenge (re-exposure to antigen). During sensitization, blocking osteopontin results in reduced infiltration of leukocytes into the lung, decreased mucus secretion, and reduced levels of interleukins (IL)-4, -13, -10 and the Th2-specific chemokine CCL22 (all indicative of a lessened Th2 response). The authors found that these effects were due to an increased number of plasmacytoid dendritic cells (pDCs), which suppress Th2 responses. During challenge with antigen, however, mice injected with neutralizing antibodies to osteopontin exhibit enhanced Th2 responses, with increased numbers of inflammatory cells and eosinophils in the lung and increased amounts of IL-4, -13, -10, and interferon (IFN)- γ . The enhanced Th2 response was due to the increased recruitment of conventional dendritic cells. Importantly, administering osteopontin intranasally prior to challenge with antigen in the mouse model of allergic airway inflammation resulted in decreased recruitment of immune cells to the lung and abrogation of the inflammatory response.

G. Xanthou et al. (2007). *Nat. Med.* **13**, 570–578. Published online April 15, 2007. 10.1038/nm1580.

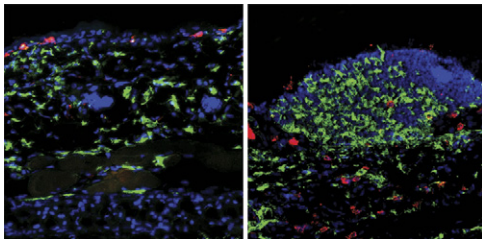
The Ins and Outs of Mast Cells

The sphingolipid, sphingosine-1-phosphate (S1P), induces a Th2 immune response and causes an increase in circulating IgE molecules resulting in enhanced release of histamines and other inflammatory molecules from

mast cells. S1P is generated in many immune cell types, including mast cells by phosphorylation of sphingosine by the sphingosine kinases, SphK1 or SphK2. Olivera et al. (2007) created mice lacking SphK1 and/or SphK2 to evaluate how these kinases contribute to mast cell function. They found that SphK2 mediates mast cell responses by regulating S1P production, mediating calcium ion influx, activating NF- κ B, producing cytokines, and inducing degranulation of mast cells. Loss of SphK2 reduced mast cell degranulation by 60%, and calcium ion signaling in SphK2-deficient mast cells was impaired. Meanwhile, increased intracellular calcium ion levels rescued the degranulation defect. Absence of SphK2 prevented translocation of protein kinase C to the cell membrane and NF- κ B activation. In contrast, mice lacking SphK1 had reduced amounts of circulating S1P and a defect in the anaphylaxis response. These anaphylaxis-resistant SphK1-deficient mice had low concentrations of circulating S1P, but mast cell degranulation was normal indicating that their mast cells are functional. Thus, it appears that although both kinases regulate allergic responses, SphK1 is unexpectedly an extrinsic regulator important for anaphylaxis and controlling levels of circulating S1P, whereas SphK2 is an intrinsic regulator of mast cells.

A. Olivera et al. (2007). *Immunity* **26**, 287–297. Published online March 8, 2007. 10.1016/j.immuni.2007.02.008.

In the Fight against Allergies, Steroids Reign Supreme



Dexamethasone treatment during the challenge phase of contact hypersensitivity reduces the infiltration of CD68-positive macrophages (green) in wild-type skin (left) but not in skin expressing a glucocorticoid receptor that cannot bind to DNA (right). Image courtesy of J. Tuckermann and G. Schütz.

Regulatory T cells (Tregs) suppress immune responses including allergic responses mediated by Th2 cells. Signaling through the glucocorticoid-induced tumor necrosis factor receptor related protein (GITR), which is expressed by Tregs, alleviates Treg-mediated suppression of the immune system. The ligand of this receptor, GITRL, is present on dendritic cells including plasmacytoid dendritic cells (pDCs), a specialized population of dendritic cells that produce large amounts of type I interferon. Grohmann et al. (2007) reveal that reverse signaling via GITRL counteracts signaling via membrane-bound GITR in mice. They find that pDCs express GITRL, which—upon stimulation with GITR—activates indoleamine 2, 3-dioxygenase (IDO). This enzyme catabolizes tryptophan, an essential amino acid, thereby suppressing growth. They also show that activation of IDO depends on the noncanonical NF- κ B pathway. When administered to mice, the glucocorticoid dexamethasone induced the expression of GITR by CD4⁺ T cells and GITRL by pDCs. In an experimental mouse model of allergic

bronchopulmonary aspergillosis (a Th2-mediated allergic response), treatment of mice with dexamethasone reduces the symptoms in an IDO-dependent manner. Thus, the GITRL-dependent modulation of tryptophan catabolism could be one way in which glucocorticoids alleviate symptoms of allergy.

Although topical application of glucocorticoids are known to alleviate symptoms of contact allergies, such as those generated upon contact with poison ivy, it is not clear which cells they target and how they mediate their effects. Glucocorticoids suppress many kinds of genes encoding inflammatory molecules including cytokines and chemokines. Their effects are mediated through the glucocorticoid receptor (GR), a nuclear hormone receptor. Tuckermann et al. (2007) induced contact hypersensitivity in a mouse model of human contact allergy and found that dexamethasone treatment did not affect the allergic response during the first exposure to the allergen (the sensitization phase). However, treatment with dexamethasone 1 hr before reapplication of the contact allergen, i.e., during the challenge phase, prevented the inflammatory response. Which cell types are sensitive to glucocorticoid action? Using GR mutant mice, the authors found that dexamethasone did not suppress the immune response when contact hypersensitivity was induced in the absence of GR in myeloid cells (macrophages and neutrophils). The authors go on to show that dimerization of GR and the ability of the dimer to bind to DNA and presumably activate transcription are required for dexamethasone to suppress the immune response. The authors show that dexamethasone treatment prevents production of several cytokines and chemokines by macrophages and neutrophils that normally induce leukocytes to migrate the site of contact. This study indicates how dexamethasone helps to suppress inflammation in response to contact allergens.

U. Grohmann et al. (2007). *Nat. Med.* **13**, 579–586. Published online April 8, 2007. 10.1038/nm1563.

J.P. Tuckermann et al. (2007). *J. Clin. Invest.* **117**, 1381–1390. Published online April 19, 2007. 10.1172/JCI28034.

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