
Review article

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Understanding the pathogenesis of allergic asthma using mouse models

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Objective: This paper reviews the current views of the pathogenesis of airway eosinophilic inflammation and airway hyperresponsiveness (AHR) in allergic asthma based on mouse models of the disease. The reader will also encounter new treatment strategies that have arisen as this knowledge is applied in practice.

Data sources: MEDLINE searches were conducted with key words *asthma*, *mouse model*, and *murine*. Additional articles were identified from references in articles and book chapters.

Study selection: Original research papers and review articles from peer-reviewed journals were chosen.

Results: Although the mouse model does not replicate human asthma exactly, the lessons learned about the pathogenesis of allergic airway inflammation and AHR are generally applicable in humans. Type 2 T helper lymphocytes (Th2) orchestrate the inflammation and are crucial for the development of AHR. Cells and molecules involved in T cell activation (dendritic cells, T cell receptor, major histocompatibility complex molecule, and costimulatory molecules) are also vital. Besides these, no other cell or molecule could be shown to be indispensable for the establishment of the model under all experimental conditions. There are at least three pathways that lead to AHR. One is dependent on immunoglobulin E and mast cells, one on eosinophils and interleukin-5 (IL-5), and one on IL-13. Eosinophils are probably the most important effector cells of AHR. Radical methods to treat asthma have been tested in the animal model, including modifying the polarity of lymphocyte response and antagonizing IL-5.

Conclusions: AHR, the hallmark of asthma, is attributable to airway inflammation ultimately mediated by helper T cells via three pathways, at least. The mouse model is also a valuable testing ground for new therapies of asthma.

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INTRODUCTION

An influential review published a decade ago identified the T cell as a major pathogenic factor of asthma.¹ The experimental support of this eventually came from the mouse model of asthma, which has subsequently proven to be invaluable

in the elucidation of other pathogenic mechanisms as well.²

Certain properties of the mouse model make it ideal for the study of the immunology and pathophysiology of asthma (Table 1). We shall discuss how this model is established and what its shortcomings are. Then we shall review the pathogenic mechanisms that have been investigated with this model and the resultant new drugs and treatment strategies.

Although this model does not replicate human disease perfectly, much of what is known about the immunobiol-

ogy of allergic pulmonary inflammation and airway hyperresponsiveness (AHR) is applicable in humans.³ We have summarized the current knowledge as a basis for understanding subsequent reports of experiments based on this model. The interested reader may also refer to other reviews.^{3–7}

DISCUSSION

Characteristics of the Mouse Model of Asthma

The model was designed to exhibit the two cardinal features of asthma, bronchial eosinophilic inflammation and AHR. To produce the model, the test animal is injected with the antigen parenterally to induce systemic sensitization, then the same antigen is administered through the airways to focus the inflammatory process in the bronchi and lungs.

Four hours after airway challenge, the eosinophil count rises in the bone marrow, peaking in 4 to 8 hours. The cells then migrate to the lungs, leaving a low eosinophil number in the marrow for the next 3 to 14 days. Eosinophilic infiltration of the lung tissue begins in 8 hours and peaks in 48 hours.⁸ These eosinophils appear in the bronchoalveolar lavage (BAL) in 24 hours and reach maximum numbers in 2 to 3 days.⁹ These cells have a predilection for the peribronchial and perivascular regions and are not scattered in the lung parenchyma. The number of neutrophils rises markedly in the BAL 8 to 24 hours after an airway allergen challenge, but the role of this leukocyte in the production of AHR is unclear.⁸

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Table 1. Advantages of the Model of Asthma

Proximity to human disease (including production of specific IgE antibody, the mast cell, T-lymphocytic and eosinophilic tissue infiltrate, Th2 cytokine pattern, and airway hyperresponsiveness to nonspecific bronchoconstrictor)
Ability to study the histopathology of any murine tissue, particularly the bronchoalveolar lavage (BAL), airways, lungs, regional lymph nodes, marrow, serum and blood cells
Ability to study the physiology of murine airway
Availability of antibodies and reagents specific to the mouse
Availability of genetically altered mice (both transgenic and gene knock-out)
Ability to evaluate potential therapeutic agents of asthma

Lung inflammation disappears fully in 6 weeks.⁹

After a single allergen challenge, the AHR is increased after 24 hours and returns to normal beyond 48 hours.⁸ However, when the airway challenge is administered on 3 successive days, the early-phase AHR begins in 5 minutes, reaches its zenith in 15 minutes, and normalizes in 60 minutes, whereas the late phase develops after 3.5 hours, maximizes in 6 hours, and returns to baseline by 8.5 hours.¹⁰

Human and Mouse Asthma

A major difference between mouse and human asthma is that airway inflammation persists longer in the latter.^{10,11} Even when the mice were given an intraperitoneal injection of *Schistosoma mansoni* eggs and challenged with egg antigen, the inflammation only lasted 2 weeks.¹² Repeatedly exposing mice to aerosolized allergen may produce chronic airway inflammation,¹³ but it can also lead to immune tolerance.¹⁴ Kanehiro et al¹⁵ have rechallenged previously sensitized and challenged animals on day 72, but the relation of this particular model to human asthma is not defined. Thus, there is still no satisfactory murine model of chronic airway inflammation.

As discussed, the perivascular and peribronchial distribution of eosino-

phils is similar in mice and human.¹¹ Recent studies suggest that eosinophilic degranulation is absent in the lungs of asthmatic mice,^{16,17} contrary to previous reports.^{18,19} Both intact and degranulated eosinophils are found in humans and their proportion bears no relation to asthma severity.¹¹

Limitations of Different Experimental Protocols

Different laboratories perform murine experiments differently. When comparing reports, we have to ensure that the outcomes are truly attributable to the study variable and not to confounding differences in mouse strain or experimental protocol.

Dose of Allergen

In BALB/c mice, maximal AHR is achieved by administering intraperitoneal antigen on days 1 and 14, intranasal antigen on day 14, and intranasal challenge each on days 25 to 28.²⁰ Different investigators use variations of this protocol.

The dose of ovalbumin (OVA) for systemic sensitization varies from 1 μg ²¹ to 8,000 μg ,²² but researchers tend to select one in the 10- to 50- μg range. In a dose-comparison study, 10 μg of OVA successfully established the asthma model, whereas 1,000 μg paradoxically did not.²³

The concentration of specific IgE in mice that are sensitized and challenged is higher than in those that are sensitized but not challenged.²⁴ Intensifying the airway challenge produces greater AHR and eosinophilic inflammation.^{24,25}

Route of Administration

When the antigen is administered only through the respiratory route, mice develop AHR without histologic airway inflammation.^{18,26} This mucosal induction route is effective in certain strains only, namely, BALB/c, AKR, FVB, and SWR.^{18,20,24,26}

Type of Allergen

The chosen allergen affects the quality of IgE and cytokine production also. BALB/c mice produce a stronger IgE response to OVA than to Der p 1.³

When administered alone, glutathione S-transferase of *S.mansoni* invokes a neutral T cell response, but when it is coadministered with *Dermatophagoides pteronyssinus* (Der p 1), a Th2 response develops instead.²⁷ In addition, Der p 1 is such a potent allergen that only 1 μg is sufficient to generate the asthma model.²⁸

Method of Measuring AHR

The technology to study the airway physiology of the mouse was adapted from that developed for larger rodents.²⁹⁻³¹ Airway responsiveness in the intact animal depends on tracheal smooth airway contractility, chest wall compliance, bronchiolar mucus plugging, airway fibrosis, and other factors.³² AHR is a function of both airway hyperactivity (an increased response to a given dose of bronchoconstrictor) and airway hypersensitivity (the ability to respond to a smaller dose of bronchoconstrictor).⁶

There are three ways to measure AHR.³³ The ex vivo technique examines the contractility of dissected tracheal smooth muscle stimulated by electricity or methacholine. The first in vivo method measures the airway pressure (or insufflation overflow pressure)³⁴ of an anesthetized animal with a transtracheal cannula and body plethysmography.³⁰ The second in vivo method uses unanesthetized and unrestrained animals in a plethysmography box to produce a mathematically derived parameter called the enhanced pause (P_{enh}) that reflects airway obstruction.³³

The ex vivo method differs from in vivo measurements because it neglects the effects of edema, mucus, or chest wall recoil on airway narrowing. The first in vivo method is destructive and requires the difficult techniques of subclavian, or tail vein, and trachea cannulations. Further, antigen challenge can not be administered during airway pressure determination. The second in vivo method is nondestructive, and uninterrupted measurements can be made, enabling the evaluation of early- and late-phase bronchial responses and the discernment of airway hyperactiv-

ity and airway hypersensitivity.³⁵ Fortunately, the nasopharynx does not contribute significantly to the total airway resistance with this method.⁸

Problems with Inbred Mouse Strains

Different strains of inbred mice produce different experimental outcomes even if all other conditions are kept constant.

Differences in airway responsiveness. Sensitized BALB/c mice have greater AHR than sensitized C57BL/6 ones.^{24,36} Even isolated tracheal smooth muscle segments from BALB/c mice are more contractile than those from C57BL/6 ones.¹⁸ The relative AHR of twelve strains of OVA-sensitized mice has been ranked in this increasing order: A/J, 129/Sv, CBA, C3H/He, C57BL/6, C57BL/10, BALB/c, DBA/1, DBA/2, AKR, FVB, and SWR.²⁴

Early work suggested that murine AHR is inherited recessively,³⁷ but it is now known that it is multigenetic.^{38,39} This genetic difference resides in the T cells because the AHR of C57BL/6 mice doubles when they receive a marrow transplant from C57BL/6XA animals, but not when the donor marrow is first T cell-depleted.⁴⁰

C57BL/6 mice have a point mutation for the mast cell protease 7 gene.⁴¹ Because mast cell tryptase partly mediates AHR, this may explain why C57BL/6 mice are more resistant to bronchoconstrictors.⁴² C57BL/6 mice also translate interleukin (IL)-9 defectively. As IL-9 affects mast cell development and immunoglobulin (Ig)E release from B cells, it is reasoned that this cytokine may mediate bronchial response in mice.⁴³ Despite these technical problems, C57BL/6 mice are often used in asthma model experiments because genetically engineered animals are often of this strain.⁴⁴ Changing the genetic background of these knock-out animals with back-cross mating is not a complete answer, as unexpected results have occurred.⁴⁵

Different IgE production in inbred mouse strains. The propensity to generate IgE is not uniform in every mouse strain. BALB/c and A/J mice produce OVA-specific IgE on primary

immunization, C57BL/6, C3H, CBA, and DBA/1 mice on secondary challenge, and NZB and SJL mice not at all.⁴⁶ BALB/c mice generate four to five times as much total IgE and specific IgE as C57BL/6 mice.³⁶

The relationship between IgE response and the AHR is not straightforward. SJL mice show greater AHR than AZL mice, although they have lower IgE concentrations.⁴⁷ Also, BALB/c mice with less total and specific IgE exhibit greater AHR than B6D2F1 mice.²¹

Different cellular and cytokine responses. Some^{21,36} but not all researchers²⁰ found that BAL from sensitized BALB/c mice contains more cells than that from C57BL/6 ones. Cytokine levels in the BAL³⁶ and bronchial lymph nodes¹⁸ are also significantly higher in sensitized BALB/c than C57BL/6 mice.

Sensitized BALB/c mice produce more total IgE, specific IgE, proinflammatory cytokines, and inflammatory cells and have more reactive airways than C57BL/6 mice. As these are the two commonest strains used in asthma studies, we must be careful not to extrapolate findings between the two strains.

Dissecting the Pathogenic Mechanisms

The murine asthma model has helped us understand many of the biologic pathways leading from the histopathology of asthma to the pathophysiology of asthma.

Immune system, antigen, antigen-presenting cells, and T-lymphocytes. To establish the model, the same antigen must be used both in sensitization and airway challenge. Asthma does not develop with 1) sham sensitization followed by sham challenge; 2) sham sensitization followed by antigen challenge; 3) antigen sensitization followed by sham airway challenge; or 4) antigen sensitization followed by an irrelevant allergen challenge.

An intact immune system is crucial for mouse asthma as severe combined immunodeficiency disease and recombination activating group-1-deficient mice simply cannot develop the condi-

tion.^{48,49} The innate immune system modulates the asthmatic response, too.^{50,51}

T-lymphocytes orchestrate the adaptive immune system yet they do not interact directly with antigen. Professional antigen-presenting cells (APC), such as the dendritic cells, macrophages, and B cells, process and present the antigen for T cell recognition in the context of the major histocompatibility complex class II (MHC class II) molecule, together with costimulatory molecule CD80 (also known as B7-1) or CD86 (B7-2). The critical importance of the MHC class II molecule in murine asthma has been proven.⁵²

Dendritic cells are located along the basement membrane of the airway epithelium and are well placed to capture inhaled allergens. They are the most important APCs in the development of allergic asthma.⁵³

Helper T-lymphocytes can be classified as type 1 (Th1) and type 2 T-helper (Th2) cells based on the cytokines they produce.⁵⁴ Interferon- γ (IFN- γ), tumor necrosis factor (TNF)- α , and IL-18 are considered to be Th1 cytokines whereas IL-4, IL-5, and IL-6 are Th2. Exposing uncommitted T cells to IFN- γ or IL-12 promotes their development along the Th1 lineage and diminishes their Th2 response, whereas exposure to IL-4 or IL-13 has the opposite effect. CD28, the T cell ligand for CD80 and CD86, is important for an intact Th2 response in mice.⁵⁵

T-lymphocytes accumulate in the lungs 24 to 72 hours after airway challenge. CD4⁺ cells outnumber CD8⁺ cells two to four times.^{56,57} Almost all the T cells have high levels of CD44 and low CD45RB (activated/memory phenotype); the adhesion molecules expressed are: lymphocyte function-associated antigen-1 (LFA-1), intercellular adhesion molecule-1 (ICAM-1), and very late antigen-4 (VLA-4).⁵⁶ There are ten times more T-cell receptor (TCR) $\alpha\beta$ cells than TCR $\gamma\delta$ cells.⁵⁸ Prevailing conditions in the lungs, including mast cell Th2-cytokine secretion and antigen presentation by imma-

ture dendritic cells, encourage the Th2 expression.⁵⁹

Both anti-CD4 neutralizing antibody^{2,57,60} and CD4 gene deletion⁴⁹ can abolish the asthma response. The putative CD4⁺ T helper cells secrete IL-5, so allergic asthma is considered a Th2-predominant disease.⁶¹ In fact, only 1,200 of these cells per animal is sufficient to cause asthma.⁶² Nevertheless, the cooperation of CD4⁺ Th1 cells and CD8⁺ cells is needed for mounting a vigorous allergic response.^{63,64}

Simultaneous inactivation of CD80 and CD86 results in a reduction of bronchial and blood eosinophilia and OVA-specific IgE, whereas selective inhibition of CD80 only diminished the bronchial eosinophilia.⁶⁵ In contrast, when neutralizing antibodies were used, only the anti-CD86 antibody ameliorated asthma expression whereas anti-CD80 did not.^{66,67} Mathur et al⁵⁵ found that antibodies against CD80 or CD86 alone partially ameliorated asthma development and only concurrent blockade of both could abolish the condition. Recently, CD80 and CD86 knock-out animals have been generated, and only those that are deficient both in CD80 and CD86 failed to develop either airway inflammation or AHR. Selective deficiency of either leads to absent AHR and diminution, but not complete abrogation, of the cellular changes.⁶⁸

Therefore, CD4⁺ Th2 cells, MHC class II molecules, and CD28 are crucial for this mouse asthma model. Th1 and CD8⁺ cells have important supportive roles. The simultaneous presence of CD80 and CD86 are vital for the model, but their relative importance is not fully clarified. We shall see later that T cells could mediate AHR even in the absence of eosinophils, mast cells, antibodies, and Th2 cytokines.

B lymphocytes, immunoglobulins, CD40/CD40L interaction, and mast cells. In some mouse strains, B lymphocytes, immunoglobulins, CD40 and CD40 ligand interaction, or mast cells are not required for airway eosinophilia or AHR.

IgE-deficient mice (129/SVEV mice with disrupted C ϵ exons) and IL-4-deficient mice (therefore lacking IgE as well) can both develop asthma.^{69,70} IgE uptake by its low-affinity receptor (Fc ϵ RII or CD23) enhances the ability of APCs to present peptides to T cells. CD23 contributes to eosinophilic infiltration⁷¹ and allergen-induced AHR, but not nonspecific AHR.³⁵ Therefore, although IgE is not a requisite for the asthma model in some strains, it augments the inflammatory airway response by interacting with CD23.⁶ However, CD23 acts also as a negative regulatory signal.⁷²

B cell-deficient mice of C57BL/6 background can develop asthma but their eosinophils do not become activated.^{73,74} CD40-deficient mice (C57BL/6/129Sv) cannot produce allergen-specific IgE, IgA, or IgG but they could develop allergic asthma.⁷⁰ When B cell-deficient mice (B10.BR strain with μ Mt deletion) were sensitized via the airways, no AHR was detected. When the allergen was administered systemically, they did develop AHR, indicating that a modification in the experimental protocol can produce a radically different outcome.^{75,76}

Mice harboring the spontaneous W/W^v mutation are deficient in mast cells as the W gene product is necessary for fibroblast-dependent mast cell growth.⁷⁷ Bruselle et al⁵² and Takeda et al⁷⁸ have shown that these mice develop airway inflammation and late-phase AHR when sensitized and challenged. By inference, early-phase AHR should be absent in these animals.

Adhesion molecules. Adhesion molecules control leukocyte trafficking. The two pairs relevant to this model are vascular cell adhesion molecule 1 (VCAM-1), VLA-4, ICAM-1, and LFA-1. In the presence of antigen, IL-4 and IL-13 mediate the upregulation of VCAM-1 expression.^{21,79,80}

Antibodies to VLA-4 and VCAM-1, either singly or in combination, markedly reduced eosinophilic and lymphocytic infiltration in the murine trachea. Blocking ICAM-1 and/or LFA-1 had minimal effect on the eosinophilia but

reduced the T cell infiltration by half. Simultaneous neutralization of ICAM-1 and VCAM-1 most effectively inhibited cellular infiltration.²¹ Antibody against CD49d, a subunit of VLA-4, also effectively prevented the formation of the asthma model.⁸¹

Therefore, the migration of eosinophils is dependent on VLA-4/VCAM-1 whereas the migration of T cells is dependent on VLA-4/VCAM-1 and, to a lesser extent, ICAM-1 and LFA-1. ICAM-1 and LFA-1 seem to be most important during the early phase of asthma induction probably because of their role in APC and T cell interaction rather than cellular trafficking.⁸²⁻⁸⁴

Leukotrienes. Activated mast cells and leukocytes release leukotrienes which mediate bronchospasm, leukocyte chemoattraction, mucus production, and vasoconstriction.⁸⁵ Inhibiting 5-lipoxygenase with zileuton markedly reduced levels of LTB₄ and LTC₄ in the BAL, specific IgE in the serum, eosinophil infiltration, and mucus production in the airways but not the AHR.⁸⁶ LT receptor antagonists have not been studied in murine asthma, but in the mouse model of peritoneal eosinophilia, pranlukast did not alter cytokine production or tissue eosinophilia.⁸⁷ In contrast, arachidonic acid metabolites derived from the cyclooxygenase pathway seem to protect against airway inflammation and AHR.⁸⁸

Cytokines. The effects of cytokines may be studied by direct administration of the agents, by neutralizing them with antibody, and with gene knock-out and transgenic animals. A useful technique is to introduce the cytokine transgene downstream of the Clara cell secretory protein promoter gene, ensuring that increased expression of the protein is limited to the lungs. In knock-out animals, an unresolved concern is that the deprivation of important proteins from the embryonic stage may lead to the establishment of compensatory mechanisms that reduce the impact of their absence. Table 2 summarizes our knowledge of the cytokines in our mouse model.

Table 2. Cytokines and Murine Asthma

Cytokine administration		Transgene	Antibody administration	Gene knock-out
IL-4	Not reported	Epithelial cell hypertrophy and leukocyte-rich pulmonary infiltration without AHR. ¹³⁵	Monoclonal anti-IL-4 during systemic sensitization partially reduced the AHR, without affecting airway eosinophilia (BALB/c mice). ⁴⁸	IL-4 deficient C57BL/6 mice have reduced peribronchial inflammation and eosinophil infiltration in the BAL. ⁵²
IL-5	Not reported	Demonstrates the pathognomonic features of murine asthma without allergen sensitization. ¹³⁶	Most studies reported that it successfully prevented murine asthma, ¹²⁸⁻¹³⁰ except for one that found that it did not affect AHR though eosinophilia was reduced by 99% (BALB/c mice). ⁴⁸	Sensitized IL-5-deficient C57BL/6 mice do not have AHR or eosinophilia ³³ unlike sensitized IL-5-deficient BALB/c mice that developed AHR exactly as sensitized wild-type ones. ⁴⁵
IL-6	Not reported	Displays augmented CD4+ lymphocytic infiltrate but reduced AHR compared to wild-type animals ¹³⁷ due to dilatation of bronchiolar diameter with only moderate wall thickening). ³²	Not reported	Not reported
IL-8	Not reported	Not reported	Not reported	Sensitized IL-8 receptor-deficient BALB/cJ mice display similar pulmonary eosinophilic inflammation as wild-type, but have reduced neutrophil and increased B cell airway infiltration, as well as increased IgE production. AHR is diminished in knockout animals. ¹³⁸
IL-9	Intratracheal administration induces airway eosinophil recruitment and elevated serum IgE levels. ¹³⁹	Reduced mast cell accumulation, mucus production, eosinophil accumulation and AHR. ^{140, 141}	Not reported IL-9 is mainly responsible for mucin production in dogs. ¹⁴²	Not reported
IL-10	Inhibits neutrophilic and eosinophilic infiltration in a dose-dependent manner when it is administered topically together with allergen. ¹⁴³	Not reported	Not reported	IL-10-deficient mice do not develop AHR. ¹⁴⁴ They also demonstrate reduced IL-5 production, eosinophilic inflammation and mucus production without notable changes in IL-4 and IgE. ¹⁴⁵
IL-11	Not reported	Increases mononuclear cell infiltrate and subepithelial fibrosis. ¹⁴⁶ Airway wall thickening is disproportionate with bronchiole dilatation, resulting in AHR. ³²	Not reported	Not reported
IL-13	Not reported	Increases subepithelial fibrosis, mononuclear and eosinophilic infiltration, mucus cell metaplasia, deposition of Charcot-Leyden-like crystals, eotaxin production, and AHR. ¹⁵⁰	Reduces mucus production and AHR (but not pulmonary eosinophilia) and decreases the expression of eotaxin (not IL-4, IL-5, GM-CSF, or MCP-5). ^{90, 91}	Not reported
IL-16	Not reported	Not reported	Reduces AHR and antigen-specific IgE levels, but not tissue eosinophilia. ^{147, 148} An IL-16 blocking protein has a similar effect. ¹⁴⁹	Not reported
IL-18	Enhances IFN- γ and TNF- α production in sensitized mice but also increased eosinophilic infiltration of the trachea and BAL. No effect on AHR. ⁹⁴	Not reported	Not reported	Not reported

Initially, there was confusion about the relative importance of IL-4 and IL-5 in the pathogenesis of AHR. IL-4 promotes B cells to switch to IgE production. IL-5 has the dual roles of eosinophil activation (encompassing

maturation, proliferation, and immortalization) and eosinophil chemoattraction.⁸⁹ Anti-IL-4 antibody reduced the AHR in sensitized BALB/c mice without affecting airway eosinophilia, whereas an anti-IL-5 antibody did not

alter the AHR.⁴⁸ In contrast, deleting the IL-5 gene in C57BL/6 mice abolished their ability to generate AHR and tissue and blood eosinophilia.³³

Drazen et al⁴² reasoned that there must be two distinct pathways leading

to AHR after T-lymphocyte activation. In the first pathway, IgE-primed mast cells discharge mediators such as histamine and LTs that cause AHR after they encounter antigen. In the second, the antigen-activated T-lymphocytes release IL-5 that promotes eosinophil-mediated respiratory epithelial damage and AHR. Because C56BL/6 mice naturally favor the first pathway and BALB/c mice the second, it was the fortuitous choice of mouse strains that allowed these pathways to be distinguished. Later, a third pathway that is IL-4- and IL-5-independent was described in IL-5-deficient BALB/c mice.⁴⁵

IL-13 enhances mucus production, AHR, and eotaxin expression.^{90,91} The receptors for IL-13 and IL-4 share a common α chain,⁹² but IL-13 is important during antigen challenge, whereas IL-4 is useful during sensitization only.⁹¹ Wills-Karp et al^{7,91} contend that the major cytokine in murine asthma is IL-13 as it can cause AHR independent of IL-4 and IL-5. IL-13 also has a cytokine-modulating role: high level of IL-13 suppresses nuclear factor (NF)- κ B, thereby reducing IL-5 transcription and favoring the development of IL-4-dependent AHR, whereas a low level of IL-13 favors IL-5-dependent AHR.⁹³

Administering recombinant IL-18 (a Th1 cytokine) to sensitized mice enhanced IFN- γ and TNF- α production and, unexpectedly, also increased eosinophilic infiltration of the trachea and BAL without affecting AHR.⁹⁴ The action of IL-18 is time-sensitive. When given during allergic sensitization, it increased BAL eosinophilia and lung expression of IL-5 and IFN- γ ; when it was administered only during allergen challenge, it decreased BAL eosinophilia and increased lung IFN- γ expression, and lung expression of IL-5 remained unchanged.⁹⁵ This role of IL-18 may explain why Th1 cells are necessary for the expression of asthma in mice.

B6/129 mice deficient in signal transducers and activators of transcription-6 (STAT6), which is important for IL-4 signaling,⁹⁶ do not develop AHR or eosinophil infiltration.⁹⁷ Although

IL-4 is not involved in eosinophil trafficking, it is important for the development of a Th2 response. In these mice, AHR and airway eosinophilia could be restored with IL-5 administration.⁹⁸ Because one of the main roles of IL-4 in the model is to enable the Th2 response, this explains why neutralizing IL-4 prevents asthma only when it is administered during the induction phase and not later.⁶

Mice lacking the p50 subunit of NF- κ B did not produce airway eosinophilia because of the absence of IL-5 and eotaxin production.⁹⁹ The transcription factor GATA-3 controls the expression of the Th2 cytokines and mice with double mutation of this gene only developed minimal airway inflammation.¹⁰⁰

Chemokines. The individual actions of chemokines, or chemotactic cytokines, are not clearly delineated because they engage their receptors promiscuously.¹⁰¹

Soon after the airway challenge, monocytes and macrophages accumulate in the airways (together with maximal messenger RNA [mRNA] expression), followed by T cells and eosinophils (with maximal eotaxin and RANTES expression).¹⁰²

Eotaxin, a specific eosinophil chemoattractant, is produced by type I alveolar epithelial cells, as well as the endothelium, T cells, fibroblasts, and macrophages.¹⁰³ This may explain the peribronchial and perivascular predilection of eosinophils. Anti-eotaxin antibody ameliorated the features of asthma only if it was administered after the last nasal challenge; it was ineffective even if it was administered after every challenge but the last.^{104,105} Anti-macrophage inflammatory protein-1 or anti-RANTES antibodies did not have any effect on the model.¹⁰⁵

Eotaxin and IL-5 cause tissue eosinophilia via different mechanisms. IL-5 mobilizes eosinophils from the marrow whereas eotaxin targets their accumulation at specific sites. IL-5-deficient mice did not develop localized tissue eosinophilia with subcutaneous injections of eotaxin, but this ability was restored with exogenous IL-5 or adop-

tive eosinophil transfer, suggesting that IL-5 is needed for eotaxin-induced tissue eosinophilia both by stimulating eosinophil egress from marrow and by increasing eosinophil sensitivity to eotaxin.¹⁰⁶

Under the experimental regime, eotaxin-deficient mice developed lung eosinophilia at half the level of wild-type animals, demonstrating that this cytokine is but one of many signals for eosinophil chemoattraction.¹⁰⁷

Eosinophils. Eosinophils are the key effector cells in asthma both in humans and animals.^{10,79,108,109} They possess the granule enzymes major basic protein, eosinophil peroxidase, and eosinophilic cationic protein, as well as cytokines and lipid mediators.

It is hypothesized that activated eosinophils release granule enzymes, damaging the respiratory epithelium, leading to alteration of mucosal surface osmolarity and exposure of the underlying sensory nerves, resulting in increased sensitivity of bronchial smooth muscles to nonspecific bronchoconstrictors.¹¹⁰ The eosinophil count in the peripheral blood and the amount of eosinophilic cationic protein recovered from BAL correlate with asthma severity in humans.¹¹¹

Eosinophil activation is necessary before tissue damage occurs.¹⁰⁹ In the asthma model, C3a, CC chemokines (eotaxin, MCP-3, MCP-4, RANTES) and cytokines (IL-3, IL-5, granulocyte-macrophage colony-stimulating factor) can provide this activating signal.¹¹² The IL-5-transgenic mouse (with massive eosinophilic accumulation, widespread damage, and early mortality) illustrates the destructiveness of cytokine-activated eosinophils.¹¹³

The eosinophil-depleted mouse is a direct example of eosinophils in asthma.¹¹⁴ However, an attempt to establish a causal link between major basic protein and AHR has been unsuccessful.¹¹⁵

Other factors. Matrix metalloproteinases (MMPs) enable eosinophils and lymphocytes to migrate into the lung epithelium. MMP-2 and MMP-9 levels are raised in the BAL after allergen inhalation, and inhibiting

MMPs reduced the airway inflammation and AHR.¹¹⁶

Nerve growth factor is also elevated in the serum and BAL of sensitized mice and it seems to augment the Th2 response. It is suggested that nerve growth factor acts as an intermediary between the nervous and immune systems.¹¹⁷ Platelet-activating factor receptor-transgenic mice exhibited features of asthma¹¹⁸ and the enzymatic degradation of platelet-activating factor seems to alleviate allergic asthma.¹¹⁹

De Sanctis et al¹²⁰ studied the contribution of each of the three isoforms of the nitric oxide synthase (NOS) in the murine asthma model. Deleting the genes for the constitutive isoforms NOS1 and NOS3 led to decreased and increased AHR, respectively, in sensitized mice. The inducible NOS2 had no effect on murine asthma, contrary to data from human experiments.

Current View on the Pathogenesis of Airway Hyperresponsiveness

It is now widely accepted that airway allergic inflammation is the basis for AHR.^{1,121} The precise elucidation of the pathogenesis of AHR proved elusive.

From our discussion, we learned that up to three partly overlapping cellular pathways are implicated to lead to AHR (Fig 1). The existence of multiple mechanisms helps to explain why reducing eosinophilic inflammation may not lead to reduction in AHR, why AHR can occur in the absence of eosinophils, and why eosinophils alone may not be sufficient to cause AHR, which are questions raised in human asthma research.^{122,123} Airway inflammation orchestrated by T-lymphocytes is ultimately the cause of AHR, but the intermediaries could be eosinophils, mast cells or, apparently, solely IL-13. Nevertheless, eosinophils are probably the most important cellular mediator of AHR (Table 3).

Current and Potential Therapeutic Strategies

The preceding discussion has highlighted the areas of new knowledge the mouse model has provided. It is fortunate that the same model is also the

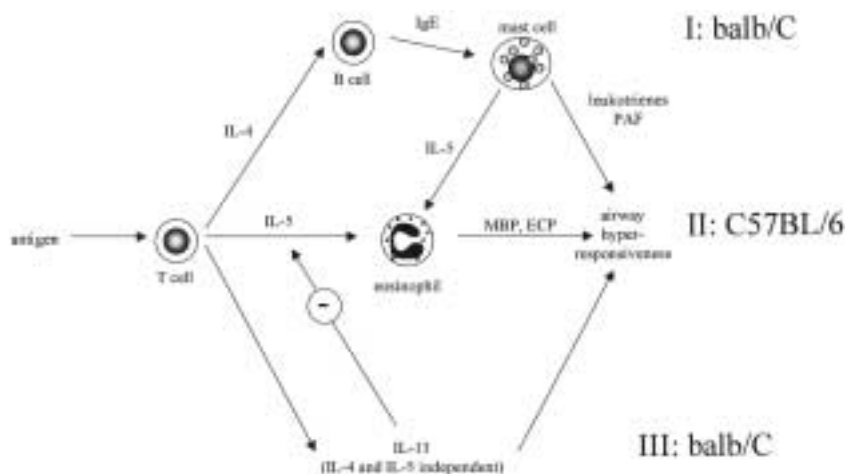


Figure 1. Three independent but interrelated pathways are postulated to be important for the development of airway hyperresponsiveness in mice. The first pathway is dependent on IL-4 and mast cells, the second on IL-5 and eosinophils, and the third is independent of IL-4 and IL-5, and is likely to be mediated by IL-13. IL-13 also has an inhibitory effect on the action of IL-5. The mouse strains on the right indicate those whose development of AHR was shown to use the corresponding mechanism.

testing ground for new (and old) therapies, to establish proof of principle before embarking on human trials.

Corticosteroids are powerful anti-asthmatic drugs. Administering betamethasone to mice before airway challenge leads to a marked decrease in eosinophil infiltration and IL-4, IL-5, and IFN- γ mRNA transcription, with minimal effect on lymphocyte numbers.⁵⁷ Betamethasone blocks the release of eosinophils from bone marrow.¹²⁴ Inhaled corticosteroid has a similar anti-inflammatory effect.¹²⁵ Correspondingly, reducing endogenous cortisol production with metyrapone enhanced the inflammatory response.¹²⁶ In the chronic asthma model

using *Schistosoma*, dexamethasone was more effective than an anti-IL-5 antibody in reducing airway eosinophilia, mucoid cell hyperplasia, and AHR, prompting the authors to suggest that anti-IL-5 antibody alone may not be effective for treating chronic disease.¹²

Inhibition of phosphodiesterase-4 also leads to downregulation of the immune system. In the mouse model, the administration of the specific phosphodiesterase-4-inhibitor, rolipram, hindered the establishment of AHR, the accumulation of eosinophils, neutrophils, and lymphocytes, as well as the production of IL-4 and IL-5.¹⁵

IL-5 is an obvious target for asthma therapy because it is important for eosinophilia (Table 4). Monoclonal anti-IL-5 antibody is effective in preventing the development of respiratory eosinophilia and AHR when administered either topically¹²⁷ or systemically.^{128–130} Its major effect is the inhibition of eosinophil egress from bone marrow.¹²⁴ Its action lasts as long as 12 weeks because it persists in the serum.¹³¹ An important property of some IL-5 inhibitors is their synergism with corticosteroid. However, an anti-IL-5 antibody administered to 24 patients with mild asthma did not lead to im-

Table 3. Eosinophils are Likely to Be the Most Important Cellular Mediator of AHR

Eosinophils are ubiquitous in lung biopsies and BAL of human asthma patients
Eosinophilic granule proteins are capable of damaging respiratory epithelium
Such granules are demonstrated to be discharged into pulmonary parenchyma
Eosinophil infiltration almost invariably precedes the development of late-phase AHR ^{8, 151}
Abolishing pulmonary eosinophilia (with an anti-IL-5 antibody, for example) prevents AHR in some murine models

Table 4. Approaches to Modify the Effects of IL-5 in Allergic Asthma

Drug or technique	Function	Effect in mouse model	Reference
Systemic anti-IL-5 antibody	Antagonizes the systemic effects of IL-5	Prevents development of asthma	128–130
Intranasal anti-IL-5 antibody	Antagonizes the local pulmonary effects of IL-5; systemic effects not excluded	Prevents development of asthma	127
Mutant IL-5	Binds IL-5 receptor without stimulating post-receptor events	Not studied in mice	152
Cyclosporin A	Reduces IFN- γ , IL-4 and IL-5 messenger RNA	Reduces eosinophilia; useful in human asthmatics	153, 154
Lidocaine	Abrogates IL-5-induced eosinophil survival	Not studied in mice; useful in steroid-resistant human asthmatics	155–157
Lyn-binding peptide inhibitor	Prevents Lyn from binding to the β -chain of IL-5r receptor during IL-5 engagement	Reduces eosinophilia	158
YY1, Oct1 and octamer-like factors	Modifies IL-5 production at the genetic level	Not studied in mice	159
RE-II BP	Represses IL-5 transcription by binding to promoter region of IL-5 gene	Not studied in mice	160
PNU-142731A	Inhibits the production of the entire host of Th2 cytokines	Reduces eosinophilic infiltration, mucus production, BAL IgE concentration and Th2-cytokine message	161

provement in allergen-induced bronchospasm despite the marked reduction in eosinophil number.¹³² As discussed, there are alternative pathways causing bronchospasm independent of IL-5 and eosinophils in the mouse model and this study suggests that they are operative in humans as well.

LT modifiers are useful in the treatment of human asthma. In the mouse, 5-lipoxygenase inhibition did not effect the AHR, but did attenuate airway inflammation.⁸⁶ This finding is consistent in human experiments, where improvement in forced expiratory volume in 1 second is modest, but pulmonary inflammation seems to be reduced as deduced from measuring urinary LTE₄.⁸⁵ F-1322 possesses activity against thromboxane A2 synthetase, 5-lipoxygenase, and the histamine receptor. Oral administration of F-1322 to sensitized mice immediately before airway challenge reduced the eosinophilic inflammation.¹³³

The T cell is an obvious target for therapeutic intervention. Antibodies against the TCR CD3¹ and costimulatory molecule CD28 can prevent the development of murine asthma, but the resultant T cell depletion poses a significant risk of opportunistic infections.¹³⁴

Because allergic asthma is mediated by lymphocytes of Th2 lineage, an attractive option is to change the T cell polarity to Th1 without actually eliminating them.⁵⁹ Table 5 lists the approaches, including the use of Th1 cytokines, bacterial DNA sequences, immunotherapy, and drugs.

CONCLUSION

The mouse model has advanced our understanding of asthma in the last decade. It has proven that the immune system, in particular the T cell and its associates, the dendritic cell, MHC class II molecule, and costimulatory molecules, are crucial to the development of airway eosinophilia and AHR.

Table 5. Approaches to Augment Th1 and Reduce Th2 Expression in Allergic Asthma

Drug or technique	Effect in mouse model	Reference
Intraperitoneal IFN- α	Prevents Th2 inflammatory response	162
Nebulized IFN- α	More effective than intraperitoneal IFN- α (in mice receiving nasal sensitization)	163
IL-12	Prevents and reverses Th2 inflammatory response	164, 165
Attenuated <i>Mycobacterium tuberculosis</i> (BCG)	Skews the lymphocyte response towards Th1 thereby diminishing airway eosinophilia	166, 167
CpG-motif oligodeoxynucleotides (CpG ODNs)	Induces a Th1 expression, with diminished OVA-specific IgE and IgG1 production and prevention of AHR, lasting as long as 6 weeks	168–170
Subcutaneous immunotherapy	Converts the Th2 response to Th1	171, 172
Oral immunotherapy M50367	Converts the Th2 response to Th1 Significantly decreases OVA-specific IgE, AHR, eosinophil, IL-4, and IL-5 levels in BAL	172–176 87

IL-5 and eosinophils are major mediators of AHR, but other cells and molecules have important permissive or cooperative roles. Other questions, such as the interplay of the various cytokines and the molecular and cellular pathways of AHR, await further work. Radical and promising methods of treating asthma have been carried out on these animal models and their applicability in humans is under trial.

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CME Examination

1–5, Leong KP and Huston DP. 2001;87:96–110.

CME Test Questions

1. Murine asthma is different from human disease because:
 - a. There is less experimental support of eosinophilic degranulation in the mouse.
 - b. Neutrophils, not eosinophils, are the predominant cells found in the trachea of animals that have been sensitized and challenged with antigen.
 - c. There are two phases of airway hyperresponsiveness.
 - d. The inflammatory infiltrate is concentrated around the peribronchial and perivascular regions.
 - e. Drugs used for treating people are ineffective in mice.
2. The characteristics of the mouse model of allergic asthma are dependent on the experimental protocol. One of the following is not true:
 - a. A more intense airway allergen challenge leads to greater inflammatory cellular infiltration.
 - b. Mice sensitized and challenged entirely through the nasal route have airway hyperresponsiveness without airway eosinophilia.
 - c. The choice of the allergen has only a minor effect on the production of the model.
 - d. Evidence of airway inflammation disappears in 6 weeks after the last airway allergen challenge in most protocols.
 - e. Repeated airway challenge with high allergen doses may lead to tolerance rather than sensitization.
3. These are essential for the production of airway hyperresponsiveness in mice except:
 - a. Immune system.
 - b. T-lymphocytes.
 - c. B-lymphocytes.
 - d. Dendritic cells.
 - e. CD4 molecule.
4. These are the effects of corticosteroid in the mouse model of asthma except:
 - a. Inhibition of eosinophil release from the marrow.
 - b. Decreased eosinophil infiltration of the airways.
 - c. Reduced IL-4, IL-5, and IFN- γ mRNA transcription.
 - d. Reduced mast cell proliferation.
 - e. Decreased mucoid cell hyperplasia.
5. Therapies that antagonize the effects of IL-5 include the following except:
 - a. Monoclonal anti-IL-5 antibody.
 - b. CpG-motif oligodeoxynucleotides.
 - c. Lidocaine.
 - d. Lyn-binding peptide inhibitor.
 - e. Mutant IL-5.

Answers found on page 137.