

Commentary

Respiratory Virus and Asthma: The Role of Immunoglobulin E

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ABSTRACT

Background: Atopic diseases, including asthma, have increased to epidemic proportions in the westernized world. The reasons for this increase are not known, nor are the mechanisms behind the development of these diseases. An interesting aspect of atopic disease is the role of respiratory viruses in the development of asthma and atopy. In fact, severe respiratory viral infection in infancy has been associated with a greatly increased risk of asthma.

Objective: This paper explores potential mechanisms through which viruses impart an increased risk of asthma, focusing on new pathways in mouse models of atopy.

Methods: A search of MEDLINE (1950–March 2008) was conducted using terms that included *viral-induced wheeze, respiratory virus, asthma, IgE, and dendritic cells*.

Results: A total of 1643 publications were identified that contained ≥ 1 of the search terms; however, only 7 of these focused on immunoglobulin E (IgE) and the viral risk of asthma, and only 1 of the 7 explored the role of dendritic cells in this process. The latter study suggested a mechanistic link between lung dendritic cells and the development of postviral atopic disease. Important in this pathway is the generation of IgE, its high-affinity receptor, and the T-cell chemoattractant CCL28.

Conclusions: Data from recent mouse models suggest that the development of asthma after severe respiratory viral infection may be the result of a response generated by production of antiviral IgE, which is capable of engaging dendritic cells to form a chemoattractant for interleukin-13-producing T cells. This new paradigm points to a focus for development of future therapies to prevent or at least ameliorate post-

viral atopic disease. (*Clin Ther.* 2008;30[Theme Issue]: 1017–1024) © 2008 Excerpta Medica Inc.

Key words: virus, asthma, dendritic cells, IgE, FcεRI.

INTRODUCTION

Atopic diseases, including asthma, represent a major health concern, not least because of their dramatically increasing prevalence, particularly in the westernized world.^{1,2} The incidence of allergic rhinitis and asthma—particularly the latter among children living in urban areas—has nearly doubled in the past 3 decades.¹ Some have suggested that as more countries become modernized, the prevalence of asthma and other atopic diseases will likely continue to increase.³ Why the prevalence of these diseases has increased so markedly is not known. Some authors have implicated the stricter hygiene practices of westernized countries.⁴ For instance, a link has been suggested between the widespread use of antibiotics, with the subsequent reduction in bacterial illness accompanied by an increase in atopic disease.⁴ This hypothesis, however, does not take into account the compelling evidence for a relationship between viral disease and atopic illness (although it attempts to incorporate the role of viruses by distinguishing nonatopic wheeze from viral infections and atopic wheeze).^{4–6}

Evidence for the importance of viral respiratory infections in the development of asthma comes from studies indicating that severe paramyxoviral infections early in life impart a markedly increased risk for asthma later in childhood. Respiratory syncytial virus

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(RSV) is a paramyxovirus that infects nearly all children by the age of 2 years.⁷ Although most of these infections have no known sequelae, infants requiring hospitalization for severe RSV infection in the first 6 months of life have a nearly 20-fold increased risk of developing asthma.⁸ Further, infections with rhinovirus, parainfluenza virus, and RSV are responsible for many asthma exacerbations.⁹ These observations cannot be entirely explained by the hygiene hypothesis, which suggests that infections and unhygienic contact may confer a protective effect against the development of allergic illnesses.^{10,11}

BACKGROUND—VIRUSES AND THE LUNG

Airborne viruses can easily be inhaled into the respiratory tree. Because viral particles are quite small, they can penetrate effortlessly into the airways, although their small size also means that they are often just as quickly exhaled from the respiratory tree. Once a virus has entered the airways, it lands on an epithelial cell. With appropriate ligand–receptor interaction, the virus may be internalized by the cell. In the case of rhinovirus, for example, intercellular adhesion molecule (ICAM)–1 must be expressed by the epithelial cell to allow viral internalization.¹² Once internalized, the virus begins to replicate and can spread to surrounding cells, expanding the infection.

The early response to viral infection depends on innate immune cells, such as natural killer (NK) cells, neutrophils, macrophages, and dendritic cells. These cells (and the epithelial barrier) form the primary initial defense against infection.¹³ NK cells and neutrophils kill infected cells in an attempt to limit the spread of the viral infection. Macrophages produce antiviral cytokines and help remove debris such as cellular corpses.¹⁴ In contrast to these cells that work directly to contain the viral infection, dendritic cells function by initiating the adaptive immune response.

There are 2 broad types of dendritic cells: plasmacytoid dendritic cells (pDCs) and conventional dendritic cells (cDCs).¹⁵ When stimulated, pDCs produce large quantities of type I interferon (IFN) and work to contain the viral infection through the pleotropic effects of this cytokine.^{6,16,17} On the other hand, cDCs take up viral particles (and other antigens), process them into small peptides, and present them to T cells in the draining lymph node.¹⁵

It has been observed during respiratory viral infection in mice that cDCs ingest antigen and migrate

back to the draining lymph node only in the first 24 to 30 hours.^{18,19} Beyond this time, regardless of what additional stimuli are applied, cDCs appear to be incapable of migration for up to 5 days. This unresponsive state may explain the risk for bacterial superinfection during viral illnesses. The cDCs that do migrate to the draining lymph nodes present antigen to T cells, leading to proliferation of virus-specific T and B cells in the node. Several days later, the virus-specific T cells migrate to the lung. The arrival of these cells and antiviral antibodies (from the B cells) usually heralds the subsequent clearance of virus and resolution of the illness. Therefore, cDCs are critical for a productive antiviral immune response.

Of further interest, the CD4⁺ T cells produced during an antiviral response are of the T-helper 1 (Th1) subtype and primarily produce IFN- γ and interleukin (IL)-12.²⁰ The atopic/asthmatic response, however, depends on the T-helper 2 (Th2) cytokines IL-4 and IL-13.²¹ Therefore, viral infections would be expected to be protective against atopic diseases rather than acting as a risk factor. However, in severe viral infections, a phenomenon has been observed in which an antiviral Th1-biased response may lead to a proatopic Th2 response.⁵ The mechanism of this link between virus and atopy appears to be through production of immunoglobulin (Ig) E.

The major antiviral antibody produced during a viral infection is neutralizing IgG, but other antibody classes are produced as well. In particular, it has been found that IgE is produced against a large array of human viral pathogens.^{22–29} The etiology of IgE production during viral infections is not yet clearly understood, as IgE production is normally a result of a Th2-biased response.³ The fact that IgE is produced in this setting suggests that it may have an important role in linking viral disease with asthma and atopy.

REVIEW OF THE LITERATURE

This review examines the role of respiratory viruses in atopic diseases and asthma, explores potential mechanisms through which viruses impart an increased risk for asthma, and highlights recent data from mouse models that may provide new targets for future therapeutic interventions. A search of MEDLINE (1950–March 2008) was performed using the terms *viral-induced wheeze*, *respiratory virus*, *asthma*, *IgE*, and *dendritic cells*. Clinical studies of therapeutic interventions or epidemiologic studies indicating a risk

for asthma in association with viral infection were excluded.

The literature search identified 1643 publications that included at least 1 of the search terms. After application of the exclusion criteria, it was decided to focus on 7 publications that related specifically to IgE and the viral risk of asthma.^{5,8,30–34} Of these publications, only 1 discussed dendritic cells.⁵

Human Studies

Of the 3 human studies identified,^{8,30,31} 2 examined the effect of RSV infection in infants and young children.^{8,30} As early as 1980, Welliver et al³⁰ investigated the appearance of IgE in the upper respiratory tract in 42 infants and young children with various types of respiratory illness after infection with RSV and found that exfoliated nasopharyngeal epithelial cells had cell-bound IgE during the acute phase of RSV infection. The continued presence of cell-associated IgE (from 7–34 days the onset of illness) was more common in subjects who developed RSV-induced asthma compared with those who did not (proportion with cell-associated IgE: 73% vs 27%, respectively; $P < 0.05$). These findings suggested that severe viral infection altered the IgE response in the infants who developed postviral asthma. Further support for this IgE–virus axis was provided by a prospective cohort study in 47 infants hospitalized for RSV infection and 93 nonhospitalized controls matched by age, sex, and residence.⁸ A follow-up evaluation of these children was performed at the ages of 1 and 3 years, and levels of specific IgE against a panel of allergens (egg white, cat, birch, and dust mite) were determined. The infants who had been hospitalized for RSV were more likely to have developed asthma compared with controls (23% vs 1%, respectively; $P < 0.001$). Severe viral infection significantly increased the likelihood of having IgE against any of the tested allergens (32% of the RSV group vs 9% of controls; $P = 0.002$). Taken together, the results of these studies support the hypothesis that a severe viral infection early in life increases the risk for developing atopic disease, as measured by production of IgE.

If severe RSV infection is associated with a predisposition to the development of asthma and atopic disease, then a therapy that could reduce the severity of viral infection would be expected to decrease the development of asthma and atopy. A recent age-matched control study evaluated the effect of treatment with ribavirin on the subsequent development of wheeze

and specific IgE production.³¹ One hundred seventy-five children who were hospitalized for RSV infection were evaluated retrospectively. Of these, 84 were considered high-risk children (ie, had congenital heart disease or chronic lung disease). In this high-risk group, 40 received ribavirin treatment and 44 did not. The study included 2 groups of otherwise healthy controls hospitalized for RSV and matched by age and date of hospitalization to the subjects treated and not treated with ribavirin ($n = 42$ and $n = 49$, respectively). The authors found a significantly reduced rate of asthma in the ribavirin-treated group compared with the other groups (8%, 21%, 33%, and 36%, respectively; $P = 0.004$). Furthermore, the presence of allergen-specific IgE against *Dermatophagoides pteronyssinus*, *Dermatophagoides farinae*, or *Blomia tropicalis* was significantly reduced in the ribavirin-treated group compared with controls (26% vs 75%, respectively; $P = 0.002$).

Thus, the results of studies in humans supported the contention that a severe RSV infection imparts a risk for both asthma and the production of allergen-specific IgE. However, these studies provided no insight into the mechanisms underlying this risk.

Mouse Models

Potential mechanisms linking virus and atopy have been explored in rodent studies. A 1998 study noted that exposure of mice to aerosolized antigen (ovalbumin) 3 days after inoculation with influenza led to increased airway hyperresponsiveness and antigen-specific IgE compared with either exposure alone, but suggested no mechanistic link.³² Another study found that RSV infection in mice did not protect against antigen-induced airway disease, including the expression of Th2 cytokines in the lung.³³

Another study examined the role of IgE in allergen-induced pulmonary eosinophilic inflammation using a depleting anti-IgE antibody.³⁴ Mice were given aerosolized or intraperitoneal dust mite extract with or without RSV infection, and the effect of anti-IgE on subsequent lung inflammation was observed. It was found that RSV infection significantly enhanced allergen-induced airway pathology ($P < 0.05$), and that only with aerosolized antigen did anti-IgE reduce the pathology. These data suggested that viral infection coupled with airway exposure to antigen may mediate lung disease through an IgE-dependent process. The specific pathways and cells involved, however, remain to be elucidated.

A recent study employing a mouse model of severe viral infection–induced airway disease pointed toward a potential pathway that may be important in the development of postviral asthma and atopic diseases.⁵ In the model used in that study, mice are inoculated with Sendai virus, a mouse paramyxovirus that has the ability to induce serious infections, with appropriate inoculums leading to a 20% weight loss.^{35,36} Once the mice clear the virus (~10–12 days after inoculation), they are left with airway hyperreactivity and mucous cell metaplasia that lasts at least 1 year after the initial infection.³⁵ In this model, CD4⁺ T cells are recruited to the lung just before viral clearance. While there is considerable Th1 cytokine production, some of the cells produce IL-13 and express the Th2 transcription factor Gata3.³⁶ The recent study found that, in a sequence similar to that noted in humans, mice infected with Sendai virus produced antiviral IgE at around the same time as the appearance of the neutralizing antiviral IgG.⁵ In that study, mice with a genetic deficiency in the high-affinity receptor for IgE (FcεRI) were infected and the response examined. Surprisingly, these mice did not develop postviral mucous cell metaplasia ($P < 0.05$), and IL-13–producing Th2 cells were not recruited to the lungs ($P < 0.05$). The authors of the study therefore concluded that FcεRI was crucial for the development of postviral atopic disease.

In another study using this model, the specific cell type that expressed FcεRI was further evaluated, with a focus on the substantial proportion of cDCs that did not migrate back to the draining lymph node early in the antiviral response.¹⁸ These cells appeared to have matured and were expressing antigen-presenting proteins in the lung parenchyma, contrary to the standard cDC paradigm that mature antigen-presenting cDCs exist only in lymph nodes. Of further interest was that these same cells expressed FcεRI, a response not seen in resting mouse cDCs.⁵ Subsequent experiments confirmed that expression of FcεRI on cDCs was necessary to recruit IL-13–producing T cells to the lung ($P < 0.05$).⁵

Expression of FcεRI on lung cDCs depends on both a severe viral infection and the production of type I IFNs.⁵ In this model, FcεRI expression appeared several days before antiviral IgE production. Furthermore, it was found that when FcεRI on cDCs was crosslinked by antigen, the cells produced the T-cell chemoattractant CCL28, a chemokine that has been found to be elevated in the lungs of patients with asthma.^{5,37} In 2 mouse models of asthma, CCL28 was

induced and was associated with recruitment of eosinophils, whereas blockade of CCL28 abrogated both eosinophil infiltration and airway hyperreactivity.^{38,39} CCL28 has been found to be capable of binding chemokine receptors CCR3 and CCR10 and to be chemotactic for resting CD4⁺ and CD8⁺ T cells.³⁷ The chemokine receptors that bind CCL28 are also expressed on eosinophils, as well as on Th2 cells, regulatory T cells, and NK T cells.^{38,40} It is interesting that all of these cell types have been reported to be important in the pathogenesis of atopic disease.^{3,41,42} Therefore, CCL28 may potentially influence critical cell populations associated with atopic disease.

Taken together, these studies point to a novel pathway linking severe respiratory viral infection to the recruitment of IL-13–producing Th2 cells via induction of antiviral IgE, cDC FcεRI, and CCL28. This recently delineated pathway suggests numerous potential avenues for therapeutic intervention. However, questions remain, in particular why a normal response to severe viral infection includes generation of antiviral IgE and recruitment of Th2 cells to the lung.⁵ Until further elucidation of the mechanisms becomes available, a prudent approach should be taken to the clinical application of these data.

POTENTIAL THERAPEUTIC STRATEGIES FOR INHIBITING VIRUS-INDUCED ASTHMA

An understanding of the mechanisms of a virus-initiated Th2 proatopic response would lay the groundwork for new therapeutic strategies to inhibit the development of asthma and atopic diatheses. As represented graphically in the **figure**, there are numerous points at which interventions might be beneficial in preventing virus-induced asthma. It should be noted that these potential avenues are based on mouse models; further work toward clarifying the pathway and the roles of each of the intermediates, including IgE and its receptor, is necessary before any extension can be made to therapeutic strategies for the inhibition of human pathways of atopy.

An obvious point of intervention is to reduce or even eliminate exposure to and transmission of viral pathogens through public health measures. This concept is similar to the approach taken by a specialist treating allergic disease—the first and most important recommendation is that patients avoid the allergens to which they are sensitive. Reducing viral transmission between individuals has the potential to greatly re-

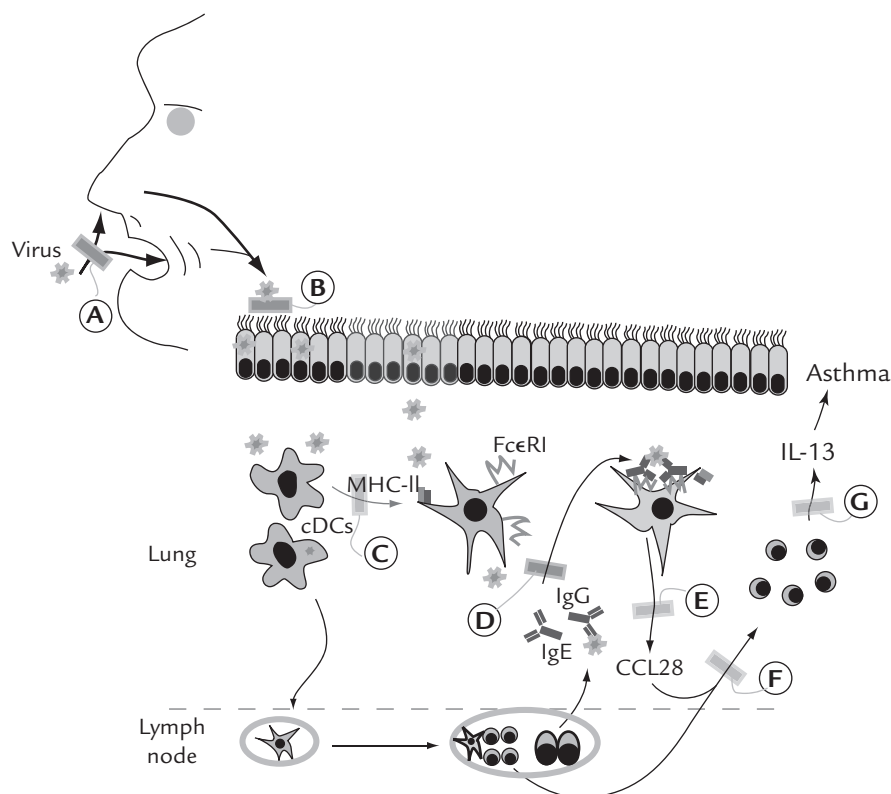


Figure. Potential points of intervention in preventing virus-induced asthma: (A) public health measures to further reduce viral transmission; (B) blockade of cofactors required for viral entry into target cells, such as the respiratory epithelium; (C) prevention of expression of the high-affinity receptor (FcεRI) for immunoglobulin (Ig) E on conventional dendritic cells (cDCs) in the lung parenchyma; (D) removal of IgE; (E) neutralization of CCL28, a chemoattractant that recruits IL (interleukin)-13, producing T-helper type 2 (Th2) cells, or prevention of its release; (F) interference with Th2-cell recruitment by blockade of Th2-specific adhesion molecules (should any be identified); and (G) blocking the release or function of IL-13 produced by Th2 cells. MHC-II = major histocompatibility class II.

duce the incidence of viral infections, as well as asthma exacerbations. However, some viral pathogens, such as RSV, are not likely to be easily eliminated from the environment. In fact, although one study reported that children in a “clean” day care center had lower rates of viral infection than those in standard day care, the frequency of viral infections was still 52.5% greater than the rate in children who were not in day care.^{43,44} Furthermore, in a follow-up study 12 years later, no difference in rates of atopic illness was found between the 2 groups.⁴⁵ The clean day care center in the original study enforced hand washing and personal hygiene in an attempt to reduce transmission of viral disease.⁴³ One criticism of this study is the in-

ability to determine how clean the day care environment actually was, limiting the ability to draw strong conclusions from these negative results.

The next potential point of intervention is at the level of infectivity. As mentioned earlier, some viruses must bind proteins expressed on epithelial cells to gain entry to the cell. As a result, efforts directed at blocking this interaction may be beneficial. However, initial exposure to a viral pathogen is asymptomatic, and treatment (eg, with an ICAM-inhibiting drug) would require constant daily dosing throughout the viral season. Clearly, future research to identify new ways of inhibiting epithelial-cell entry is necessary to make this approach feasible.

Receptor expression may be a potential pathway for limited modulation of the response to viral presentation. The findings concerning the role of cDCs and IgE from the mouse study reported earlier support the rationale for attempting to block FcεRI expression on lung cDCs during a viral response.⁵ This therapeutic approach would be expected to prevent recruitment of Th2 cells to the lung, subsequently limiting development of postviral atopic disease. For this type of therapy to be effective, the cDCs migrating back to the draining lymph nodes would need to remain unaffected; otherwise, there would be too great a risk of inhibiting or modulating the adaptive immune response and viral clearance. Conventional dendritic-cell FcεRI is an appealing target, as it is expressed after the onset of viral symptoms, and, because only a limited subset of cells express FcεRI, targeting this molecule would be likely to affect only a limited number of cells. This approach, however, assumes that the virus-IgE-cDC-CCL28 pathway is intact not only in mouse models, but in humans. Further study of this potential pathway is clearly necessary.

Anti-IgE is a currently available treatment that binds and removes IgE from the circulation.^{46–48} The potential of a single injection of anti-IgE during a severe viral infection to protect against the development of subsequent asthma is intriguing. As IgE is produced toward the end of the viral infection, symptoms could be used as an indicator for the timing of therapy. However, further research on the downstream effects of IgE production during viral infection is warranted before such an approach can be recommended for viral infections. If the role of IgE is to suppress the immune response, administration of anti-IgE may have the potential to worsen the inflammation. Based on initial studies in our laboratory, no evidence of this or of increased disease in FcεRI- or IgE-deficient animals has been noted. Therefore, in our opinion, anti-IgE may be beneficial in preventing RSV-induced asthma; however, further studies are needed in mice and humans before this intervention can be recommended.

An additional potential intervention would involve blocking the function of Th2 cells in the lung. This approach could focus on inhibition of the release of CCL28, thereby curbing subsequent recruitment of Th2 cells. Finally, it appears that the development of atopic disease is related to the production by Th2 cells of Th2 cytokines such as IL-13, and the use of drugs that block the IL-13 pathway could be both easily timed,

particularly as atopic disease is a late response after the development of symptoms, and of short duration, as T-cell recruitment was limited to only a few days in animal models.^{36,49} Thus, inhibition of IL-13 may have utility in disconnecting the virus-to-atopy pathway, and additional studies are warranted.

CONCLUSIONS

Viral respiratory disease appears to be implicated in the development of atopy and asthma. Among recently elucidated pathways is the role of IgE and its receptor after the introduction of virus into the respiratory airways. Understanding this virus-to-atopy conduit may form the foundation for future studies in both delineation of pathways and potential points of therapeutic intervention. While the research in this area is promising, much work remains to be done to translate the findings from mouse models into new therapies for human use with the goal of potentially curbing and eliminating the rise of atopy and asthma in the general population.

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